Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

Fecal Microbiota Transplantation

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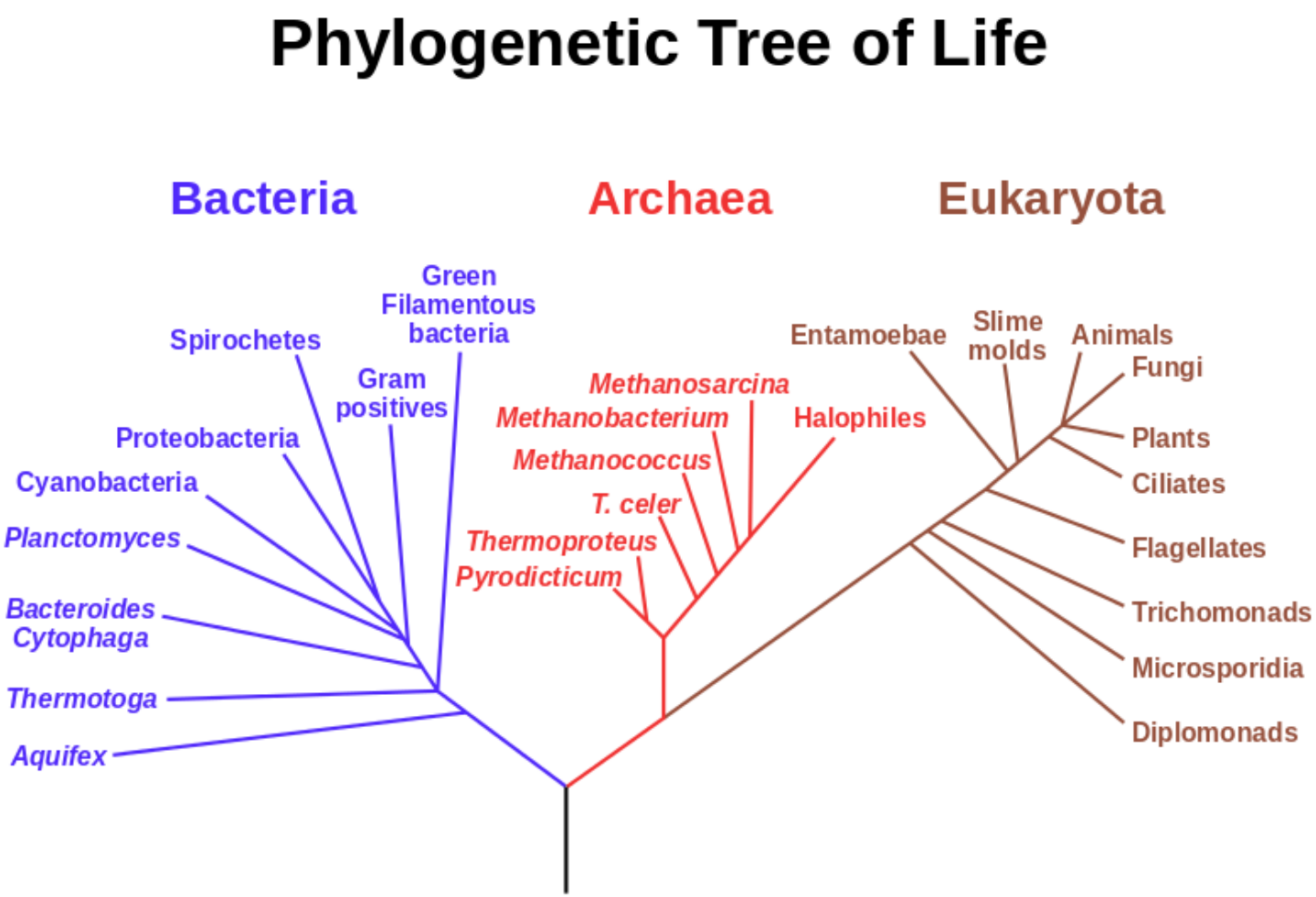
Medical Director of Epidemiology, MVH
Dayton, Ohio, USA

Objectives

- Microbiome/Microbiota
- *Clostridium difficile* infection (CDI)
- Recurrent CDI and role of microbiota
- Fecal Microbiota Transplantation (FMT)
- Local experience with FMT
- Conclusions

***Microbes*: organisms that are too small to be seen with the naked eye**



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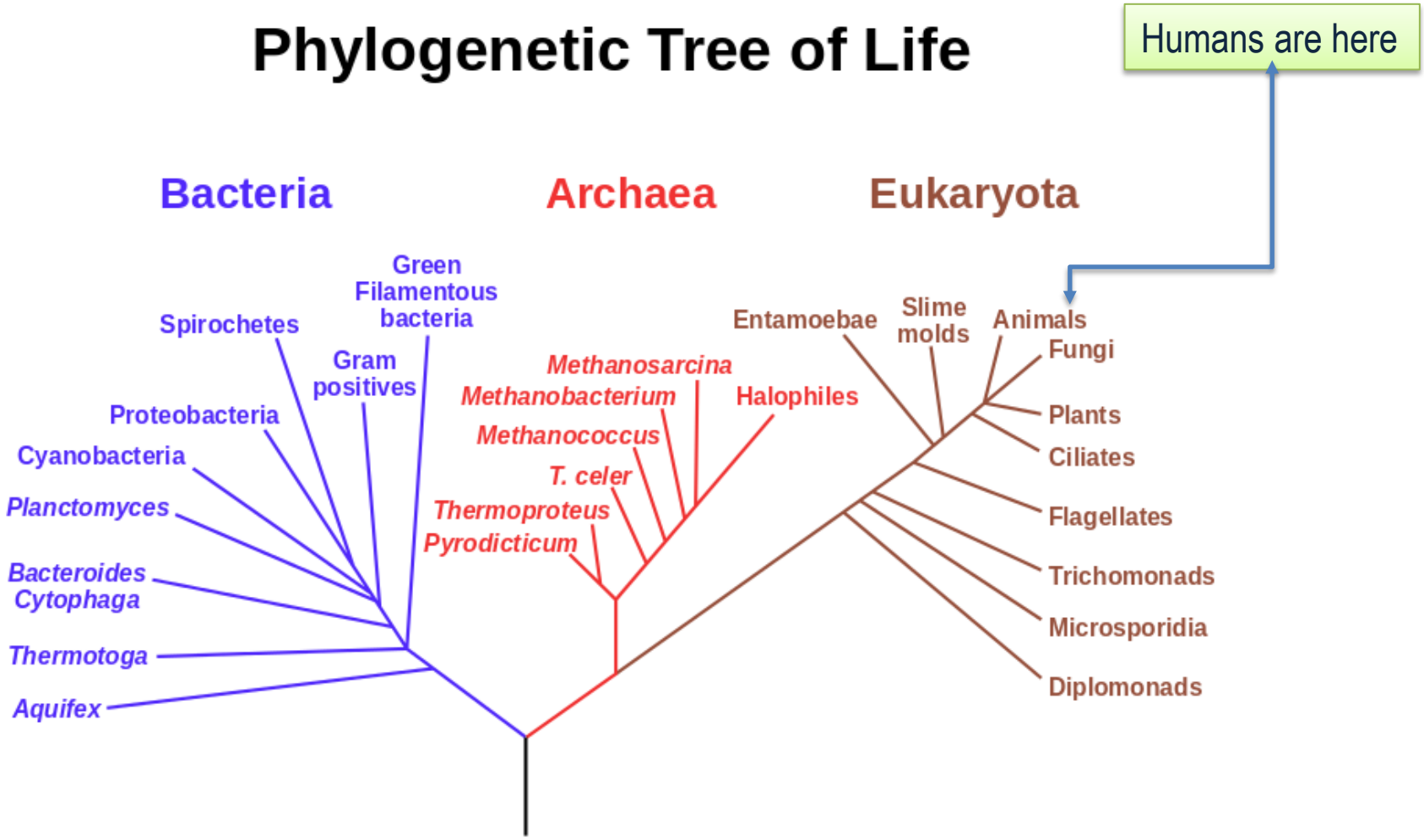


https://en.wikipedia.org/wiki/File:Phylogenetic_tree.svg

Definitions

- **Microbiome: the total microbial community, genes, and biomolecules within a defined environment.**
- **Microbiota: the total collection of microbes within a community, typically used in reference to an animal host.**
- Metagenome: the total genomic DNA of all organisms within a community.
- Metabolome: the total metabolite pool of a community.
- Metaproteome: the total proteome of all organisms within a community.
- Metatranscriptome: the total transcribed RNA pool of all organisms within a community.
- **Dysbiosis: changes to the structure of a microbial community that are detrimental to its host.**

Kjersti Aagaard, Ruth Ann Luna, and James Versalovic. **The Human Microbiome of Local Body Sites and Their Unique Biology.** *Chapter 2*. In Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 2015.

100 TRILLION

The human microbiome is made up of more than 100 trillion bacteria, fungi, protozoa, and viruses that live on and inside the body.

10X

We have 10 times more microbial cells in our body than human cells and the majority live in our guts—especially the large intestine, or colon.

The bacteria in our microbiomes are essential to human health and aid in biological processes such as:

$E=mc^2$

Extracting energy from food

RETINOL FOLATE RIBOFLAVIN BIOTIN NIACIN

Producing essential vitamins

Regulating our immune system

Regulating our glucose levels and metabolism

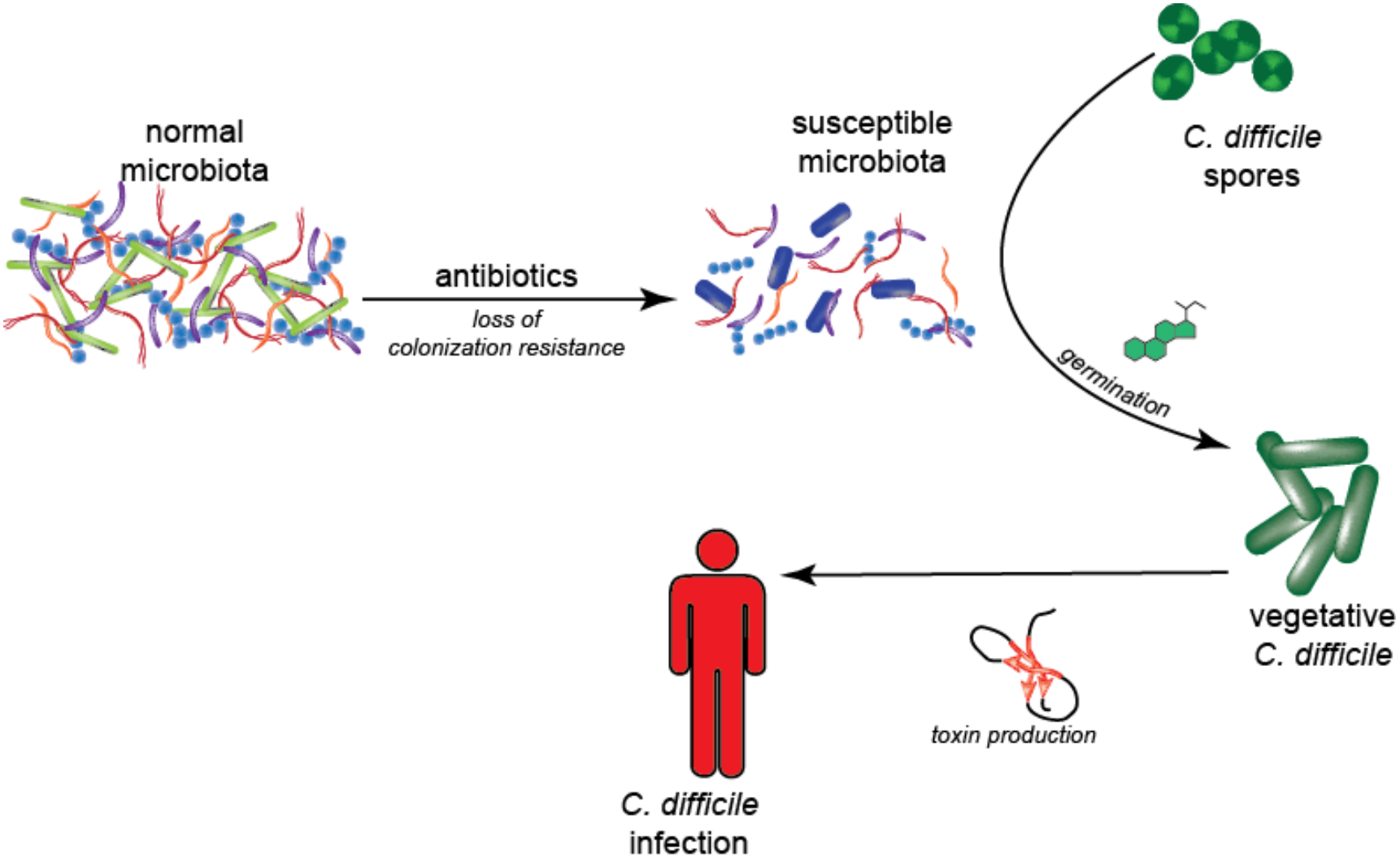
Protecting us against disease-causing microbes

SYMBIOTIC

The beneficial and symbiotic relationship between humans

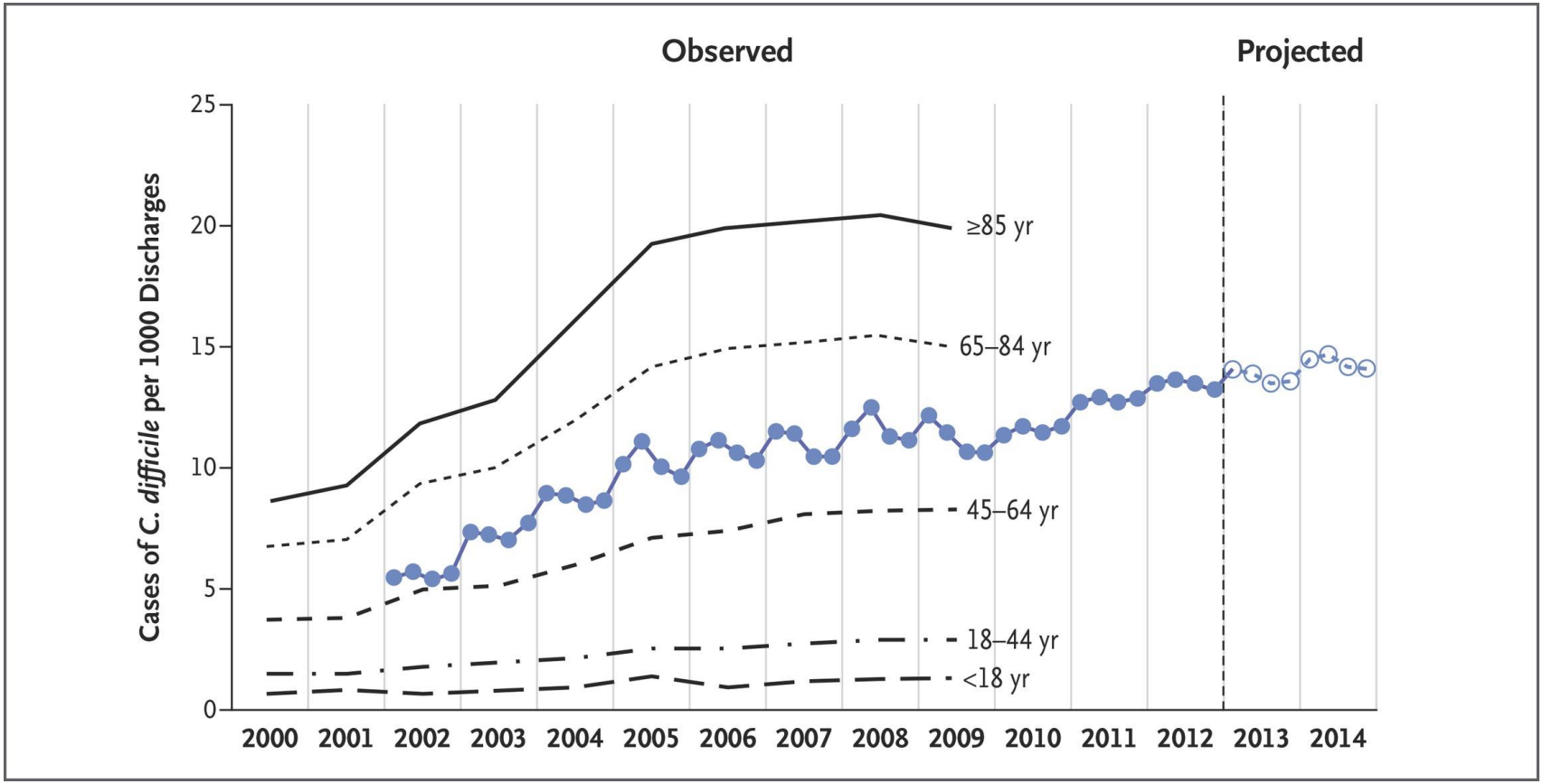
Personal microbial communities shift throughout a person's life and are influenced by diet, exercise, medications such as antibiotics, pathogens, and other environmental factors.

http://www.serestherapeutics.com/our-science/microbiome-101



https://sites.google.com/a/umich.edu/younglab/research-interests

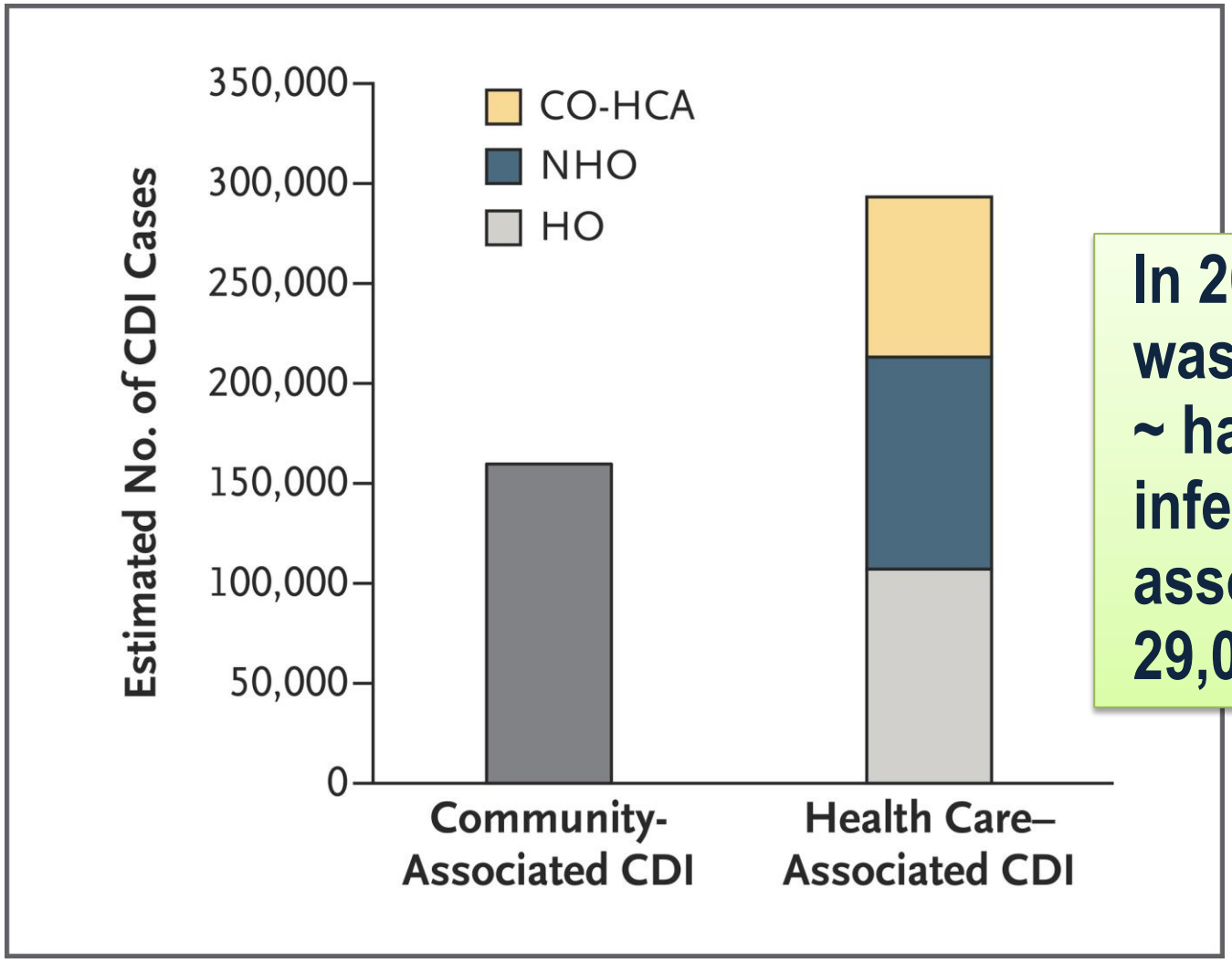
Incidence of Nosocomial *C difficile* Infection



The overall incidence of nosocomial *C. difficile* infection is shown by year (blue), as is the incidence according to patient age (black).

Leffler DA, Lamont JT. N Engl J Med 2015;372:1539

Estimated U.S. Burden of CDI, According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.



In 2011, *C. difficile* was responsible for ~ half a million infections and was associated with ~ 29,000 deaths.

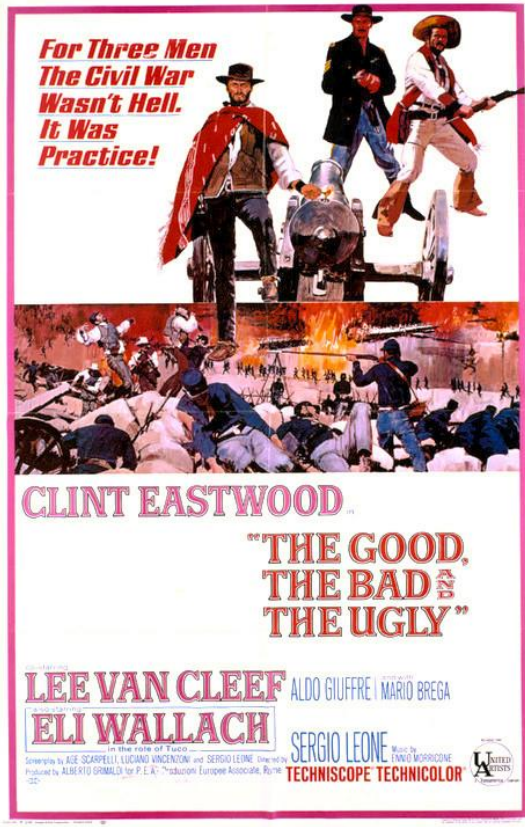
CO-HCA: community-onset health care–associated infection,
HO hospital onset,
NHO nursing home onset.

Lessa FC et al. N Engl J Med 2015;372:825

Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

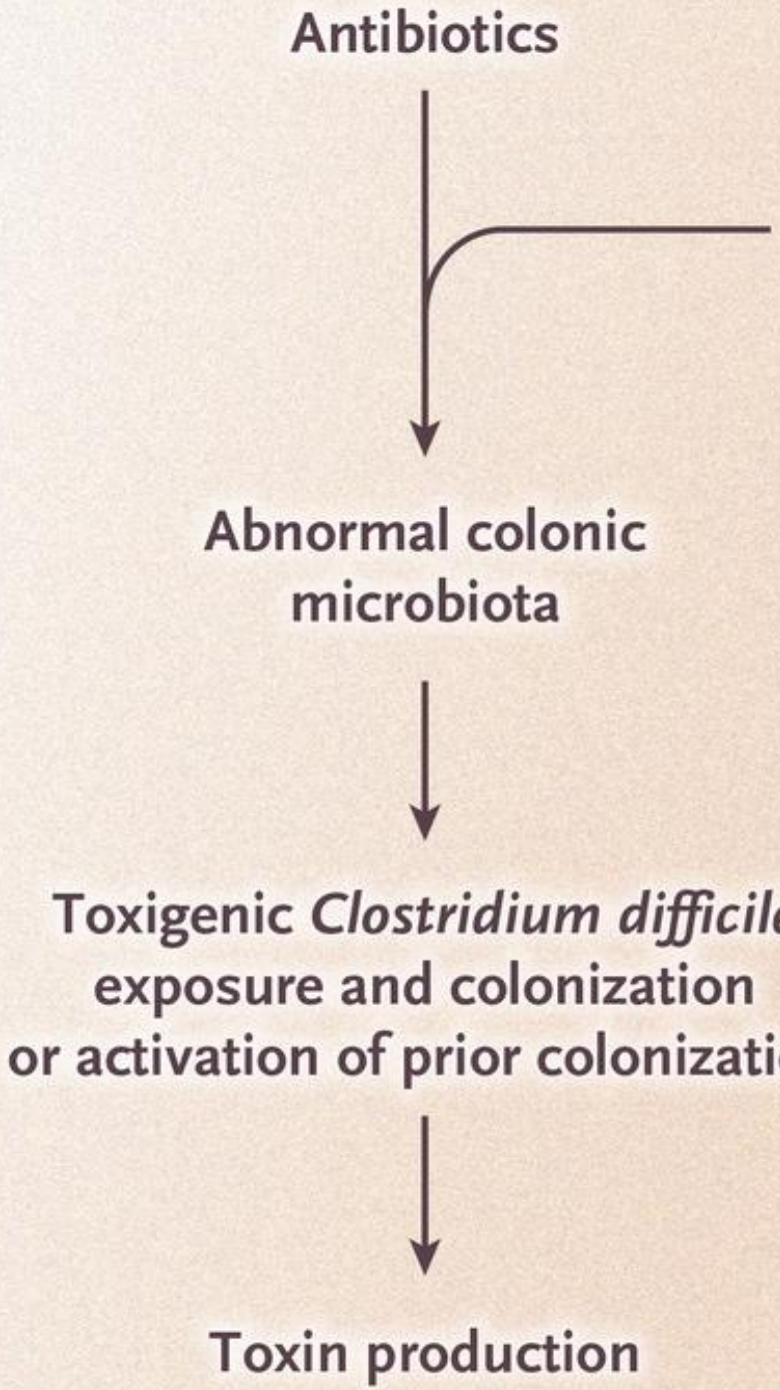
Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common
Macrolides	Somewhat common
Aminoglycosides	Uncommon
Bacitracin	Uncommon
Metronidazole	Uncommon
Teicoplanin	Uncommon
Rifampin	Uncommon
Chloramphenicol	Uncommon
Tetracyclines	Uncommon
Carbapenems	Uncommon
Daptomycin	Uncommon
Tigecycline	Uncommon

* Specific antibiotics are listed if their association with *C. difficile* infection differs from that of most other antibiotics in their class.



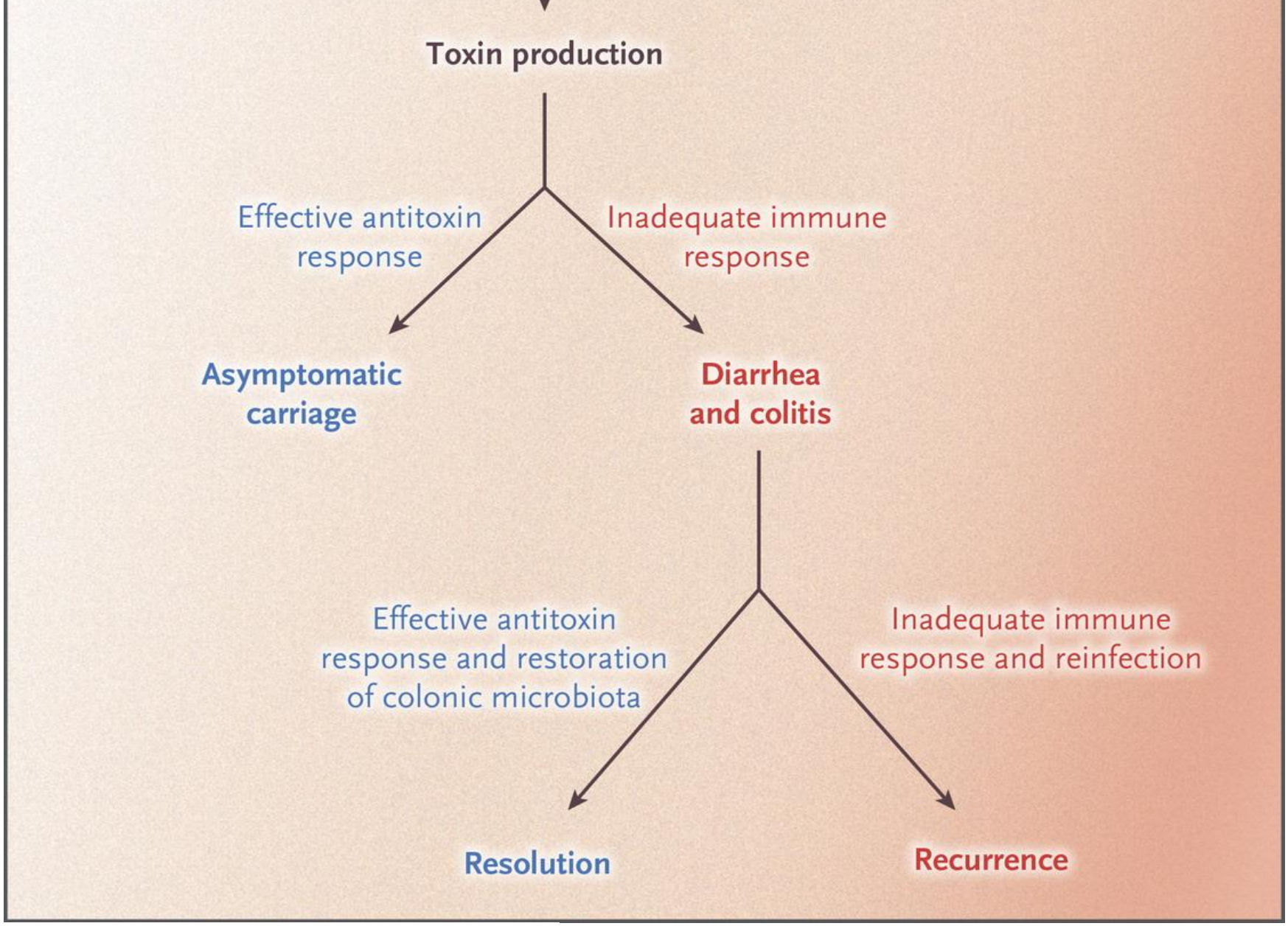
Antibiotic Classes and Their Association with *C difficile* Infection

Leffler DA, Lamont JT. N Engl J Med 2015;372:1539-1548



Pathogenesis of *Clostridium difficile* Infection

Leffler DA, Lamont JT. N Engl J Med 2015



CDI Pathogenesis

Leffler DA, Lamont JT. N Engl J Med 2015;372:1539.

Table 2. Treatment of *Clostridium difficile* Infection.*

Severity	Clinical Manifestations	Treatment
Asymptomatic carrier	No symptoms or signs	No treatment indicated
Mild†	Mild diarrhea (3 to 5 unformed bowel movements per day), afebrile status, mild abdominal discomfort or tenderness, and no notable laboratory abnormalities	Predisposing antibiotic cessation, hydration, monitoring of clinical status, and either administration of metronidazole (500 mg three times per day) or close outpatient monitoring without the administration of antibiotics
Moderate	Moderate nonbloody diarrhea, moderate abdominal discomfort or tenderness, nausea with occasional vomiting, dehydration, white-cell count >15,000/mm^3, and blood urea nitrogen or creatinine levels above baseline	Consideration of hospitalization and cessation of predisposing antibiotics; hydration, monitoring of clinical status, and either administration of oral metronidazole (500 mg three times per day) or first-line therapy with oral vancomycin (125 mg four times per day for 14 days)
Severe	Severe or bloody diarrhea, pseudomembranous colitis, severe abdominal pain, vomiting, ileus, temperature >38.9°C, white-cell count >20,000/mm^3, albumin level <2.5 mg/dl, and acute kidney injury	Hospitalization; oral or nasogastric vancomycin (500 mg four times per day) with or without intravenous metronidazole (500 mg three times per day), or oral fidaxomicin (200 mg twice a day for 10 days) instead of vancomycin if the risk of recurrence is high
Complicated	Toxic megacolon, peritonitis, respiratory distress, and hemodynamic instability	Antibiotics as for severe infection, and surgical consultation for subtotal colectomy or a diverting ileostomy with vancomycin colonic lavage; consideration of fecal microbial transplantation or additional antibiotics
First recurrence		Oral vancomycin (125 mg four times per day for 14 days) or oral fidaxomicin (200 mg twice a day for 10 days)
Second or further recurrence		Vancomycin in a tapered and pulsed regimen‡, fecal microbial transplantation, or fidaxomicin (200 mg twice a day for 10 days)

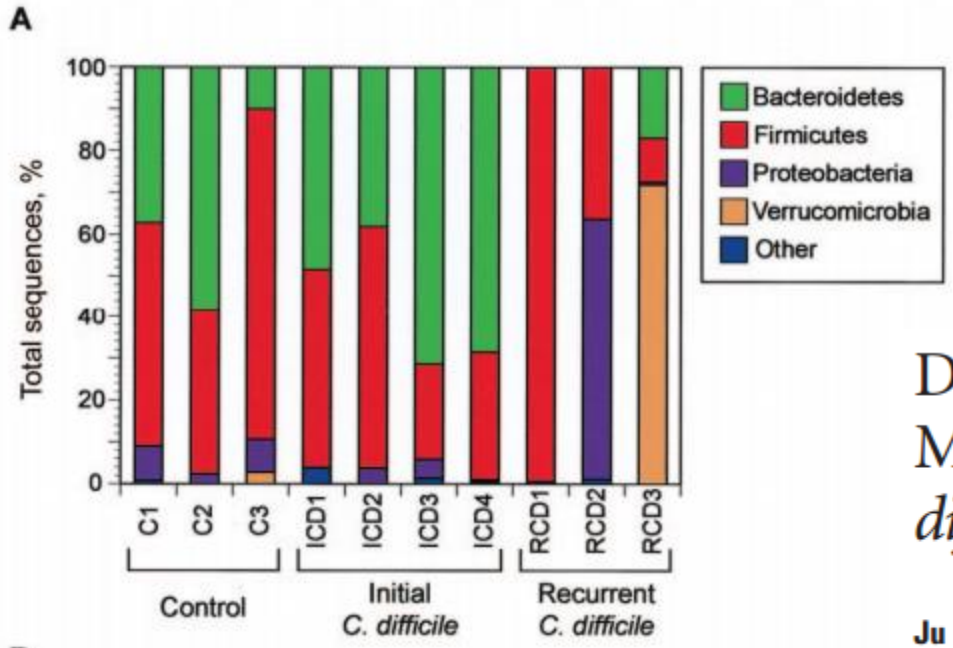
* Some data are from Debast et al.[54] and Cohen et al.[55]
† *C. difficile* infection should be considered mild only if it occurs in outpatients.
‡ A tapered and pulsed regimen involves the administration of vancomycin as follows: 125 mg four times a day for 1 week, 125 mg three times a day for 1 week, 125 mg twice a day for 1 week, 125 mg daily for 1 week, 125 mg once every other day for 1 week, and 125 mg every 3 days for 1 week.

Approximately 25% of CDI patients will have at least one recurrence !

Leffler DA, Lamont JT. N Engl J Med 2015;372:1539

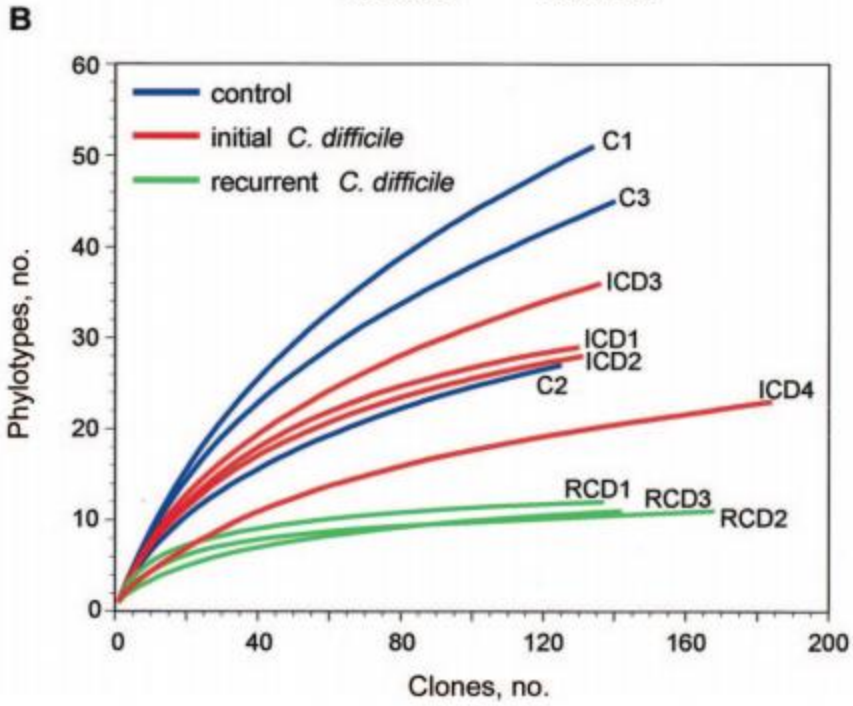
Recurrent *C.difficile* Infection

- Approximately 25% of CDI patients will have another episode of CDI that year
  - Relapse vs re-infection
- After 2nd recurrence the risk is further increased
  - 2^{nd} : 30-45%
  - 3^{rd} : 45-60%
- Each recurrence is *more* difficult to treat
  - May continue for years
  - No clear treatment recommendations



Decreased Diversity of the Fecal Microbiome in Recurrent *Clostridium difficile*–Associated Diarrhea

Ju Young Chang,[1,a] Dionysios A. Antonopoulos,[1,a] Apoorv Kalra,[3] Adriano Tonelli,[3] Walid T. Khalife,[2] Thomas M. Schmidt,[1] and Vincent B. Young[1,3,4,a]

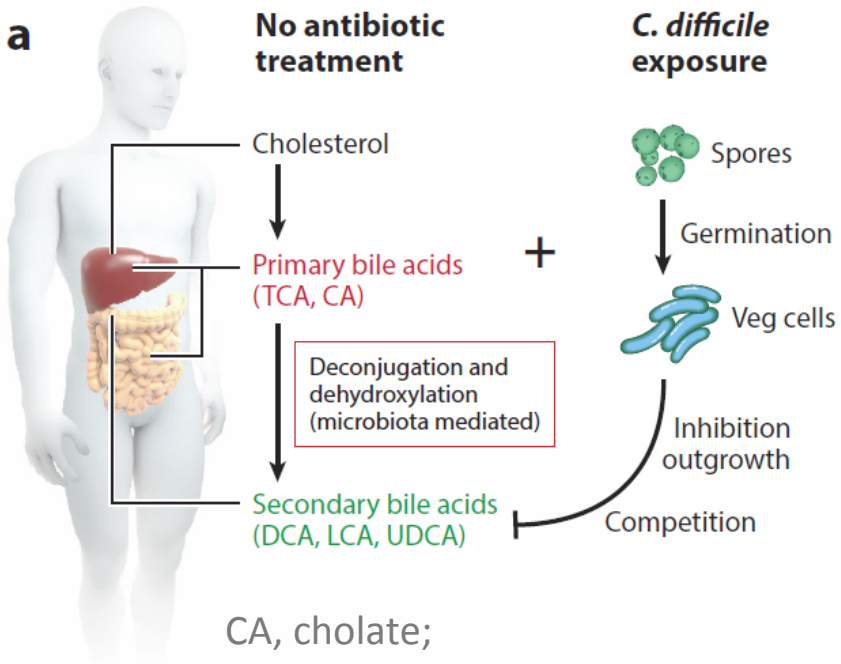


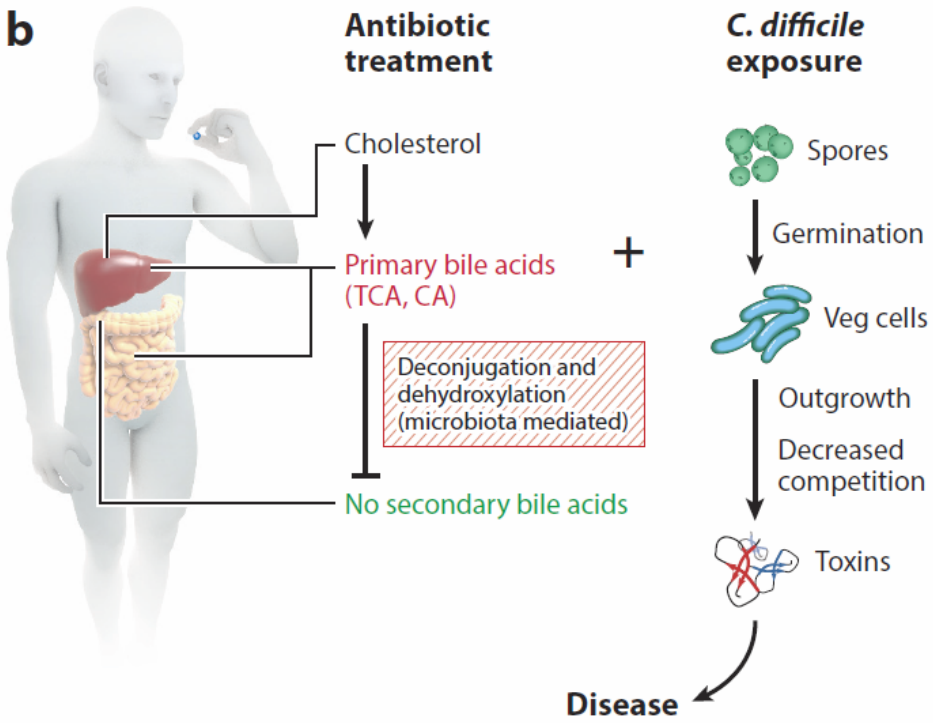
Gut microbiota structure changes:

- decrease in **bacterial diversity**
- increase in **Proteobacteria**
- decrease in Bacteroidetes

J Infect Dis 2008:197;435-8

Antibiotic-induced alterations in gut microbial metabolism decrease colonization resistance against *C. difficile*





CA, cholate;
DCA, deoxycholate;
LCA, lithocholate;
TCA, taurocholate;
UDCA, ursodeoxycholate

CM Theriot & VB Young. Annu. Rev. Microbiol. 2015. 69:445–61

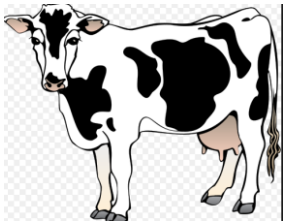
FMT

- Fecal microbiota transplant (FMT) is the term used when stool is taken from a healthy individual and instilled into a sick person to cure a certain disease

Bakken JS, Borody T, Brandt LJ et al. Fecal Microbiota Transplantation (FMT) Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol 2011;9:1044

History of FMT

- Ancient China
  - Oral use of human fecal material for food poisoning or severe diarrhea
- Veterinary medicine (17c)
  - transfaunation (transfer of fresh feces) from healthy horses to treat horses with diarrhea
  - rumen transfaunation: cows
- **1958: Dr. Eismann:** FMT enema for 4 pts with pseudomembranous colitis
  - ***All recovered***



Original Article

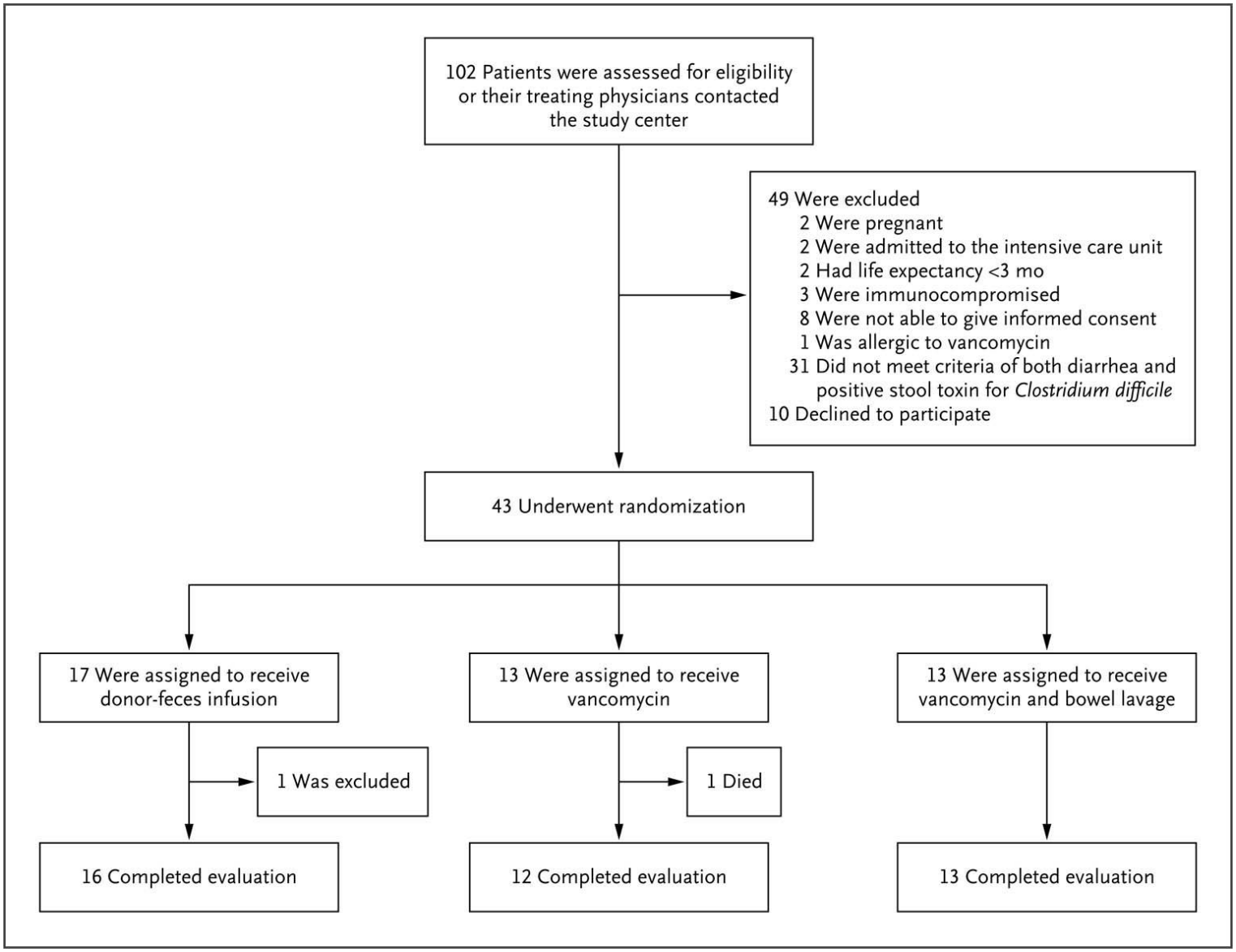
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

N Engl J Med
Volume 368(5):407-415
January 31, 2013

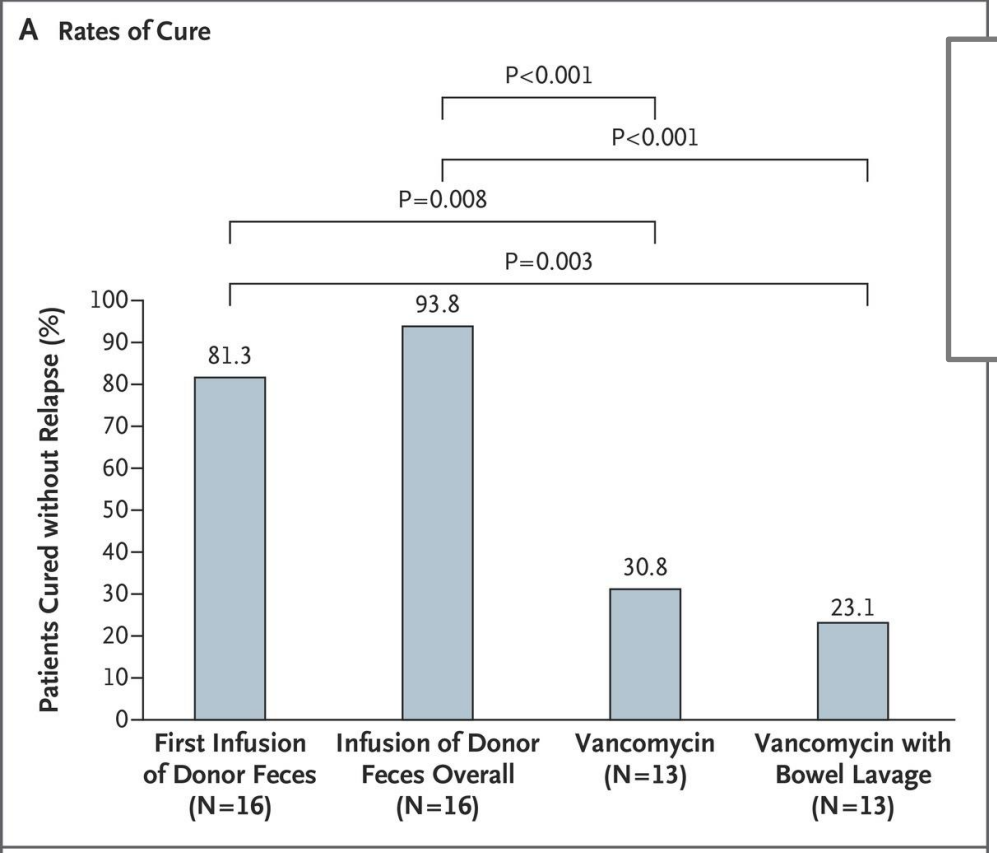
The NEW ENGLAND JOURNAL of MEDICINE

Enrollment and Outcomes

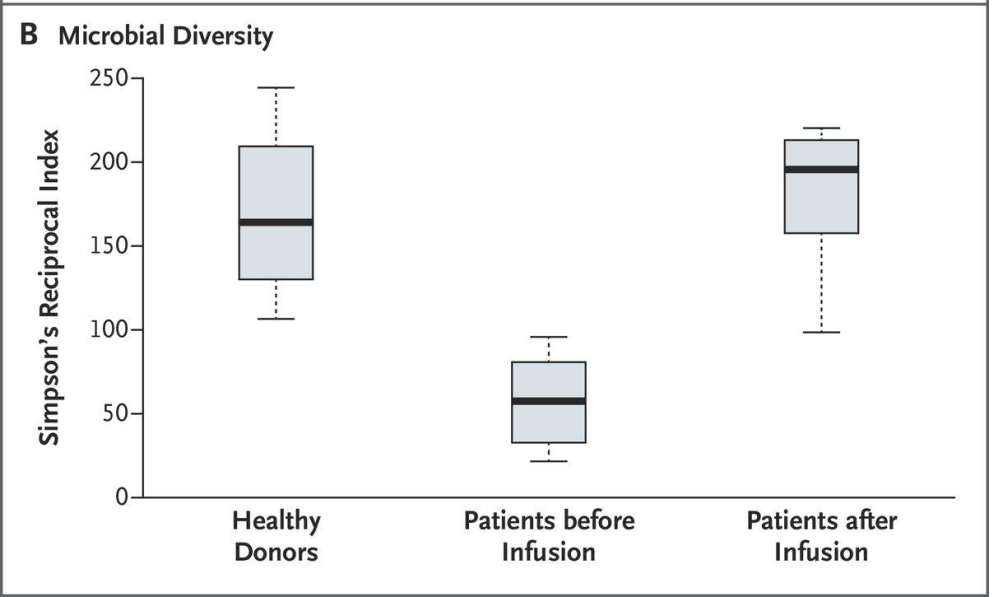


van Nood E et al. N Engl J Med 2013;368:407

FMT for Recurrent *C difficile* Infection



Rates of Cure



Changes to the Microbiota after FMT

van Nood E et al. N Engl J Med 2013;368:407

FMT Effects in CDI

- FMT results in normalization of microbial diversity and community structure in patients being treated for CDI, with high rates of clinical cure
- The restored colon microbial community could inhibit *C. difficile* by many mechanisms:
  - competition for nutrients
  - direct suppression by antimicrobial peptides
  - bile-acid-mediated inhibition of spore germination and vegetative growth
  - activation of immune-mediated colonization resistance

Khoruts & Sadowsky. Nature Reviews Gastroenterology & Hepatology 2016

FMT Regulatory Issues 1.0

- May 2013 FDA announced to the public that FMT were to be regulated as a **drug**
  - Needed an Investigational New Drug (IND) application to use
    - Use of FMT and clinical studies to evaluate its safety and effectiveness are subject to regulation by FDA, and that the complex nature of FMT products presents specific scientific and regulatory challenges…

FMT Regulatory Issues 2.0

- In July 2013, FDA issued a guidance announcing **enforcement discretion** for CDI when used by licensed physicians to treat patients with CDI that does not respond to standard therapies.
  - FDA will not enforce its own requirement that FMT be performed under an IND as long as providers obtain informed consent, detail risks around the procedure, and explain that FMT is considered an investigational therapy.

US Food and Drug Adminstration. Guidance for industry: enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium diffcile* infection not responsive to standard therapies. July 2013. Available at:

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf.

FMT Clinical Studies: 133 studies as of 9/2016

1	Enrolling by invitation	FMT for Multidrug Resistant Organism Reversal	**Condition:** Infection With Multi-drug Resistant Organisms
2	Not yet recruiting	Fecal Microbiota Transplantation for the Treatment of Obesity	**Condition:** Obesity
3	Not yet recruiting	Safety and Efficacy of Fecal Microbiome Transplantation (FMT) in the Treatment of Antibiotic Dependent Pouchitis (ADP)	**Condition:** Pouchitis
4	Completed	Fecal Microbiota Transplantation (FMT) for Treatment of Ulcerative Colitis in Children	**Condition:** Ulcerative Colitis
5	Recruiting	Fecal Microbiota Transplantation After HSCT	**Condition:** Bone Marrow Transplantation
6	Recruiting	Manipulating the Microbiome in IBD by Antibiotics and FMT	**Conditions:** Exacerbation of Ulcerative Colitis; Ulcerative Colitis, Active Severe; Crohn's Colitis
7	Recruiting	Fecal Microbiota Transplantation in Irritable Bowel Syndrome With Bloating	**Condition:** Irritable Bowel Syndrome
8	Recruiting	Prevention of Recurrence of Crohn's Disease by Fecal Microbiota Therapy (FMT)	**Condition:** Crohn's Disease
9	Active, not recruiting	Fecal Microbiota Transplantation in Pediatric Patients	**Conditions:** Inflammatory Bowel Diseases (IBD); Crohn's Disease (CD); Ulcerative Colitis (UC)

https://clinicaltrials.gov/

FMT Clinical Studies: 133 studies as of 9/2016

Conditions

1 Enrolling by invitation — FMT for Multidrug Resistant Organism Reversal
Condition: Infection With Multi-drug Resistant Organisms

2 Not
3 Not
4 C
5 F
6 F
7 F
8 F
9 A

Crohn's Disease
Ulcerative Colitis
Antibiotic Dependent Pouchitis (ADP)
Pancreatitis
Irritable Bowel Syndrome
Chronic intestinal pseudo obstruction
Nonalcoholic Steatohepatitis(NASH)
Hepatic Encephalopathy

Obesity
Metabolic Syndrome
Type 2 Diabetes Mellitus

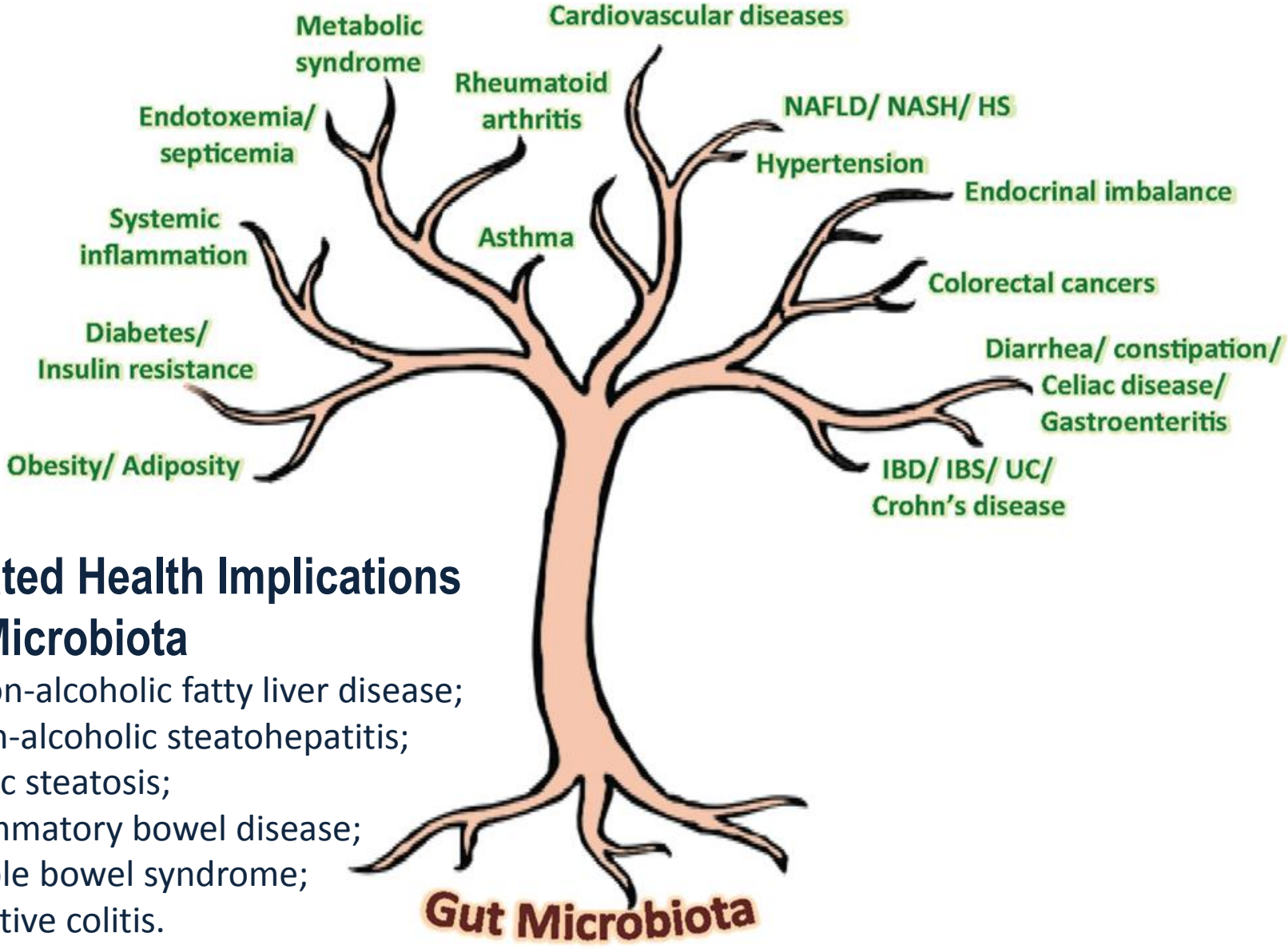
Multidrug Resistant Organism Reversal

Epilepsy

biotic Dependent

e; Crohn's Colitis

https://clinicaltrials.gov/

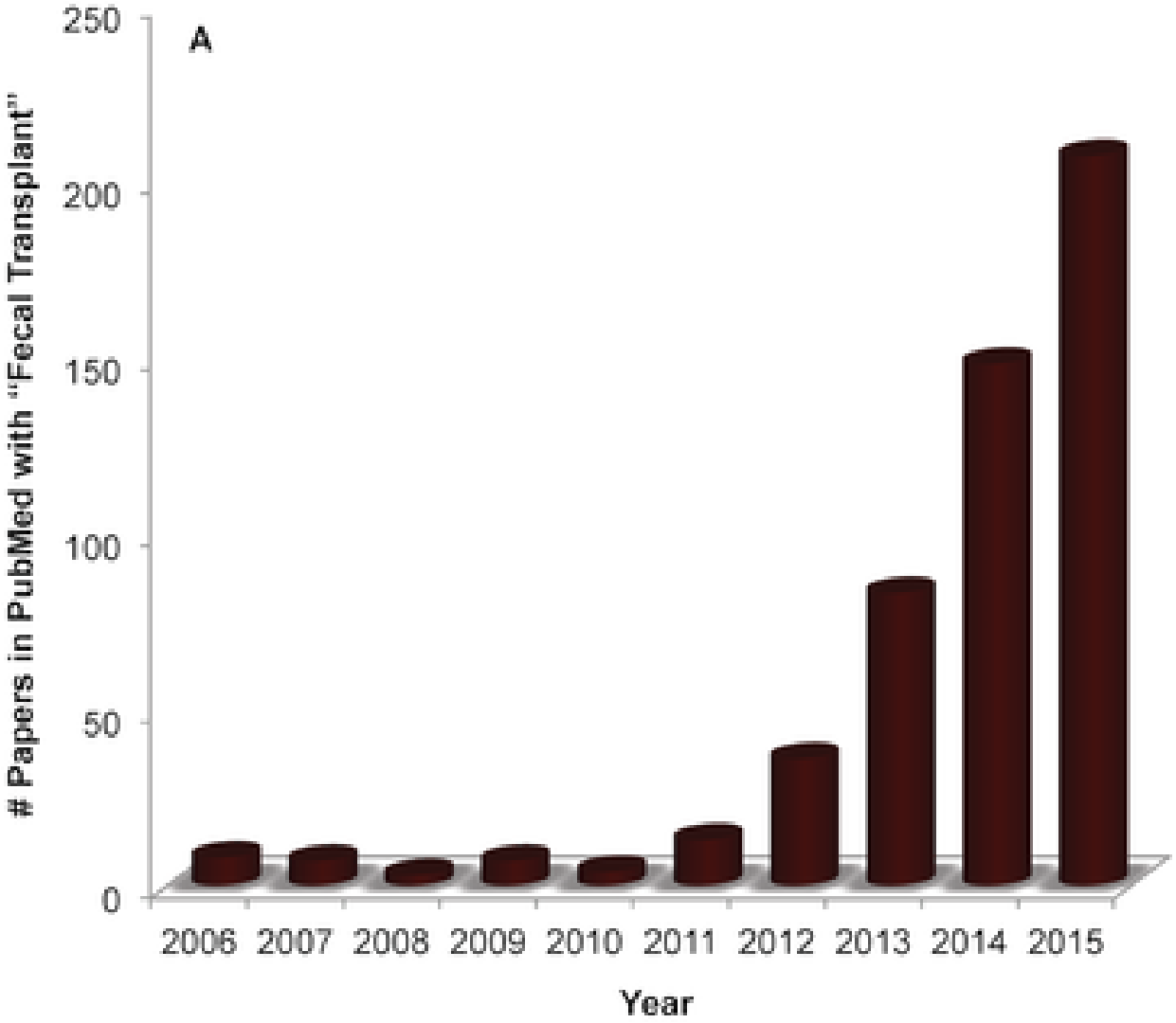


Speculated Health Implications of Gut Microbiota

NAFLD, non-alcoholic fatty liver disease;
NASH, non-alcoholic steatohepatitis;
HS, hepatic steatosis;
IBD, inflammatory bowel disease;
IBS, irritable bowel syndrome;
UC, ulcerative colitis.

Front. Med., 23 June 2014 | http://dx.doi.org/10.3389/fmed.2014.00015

The growth of fecal transplants as reflected in references in PubMed



Bojanova DP, Bordenstein SR (2016) Fecal Transplants: What Is Being Transferred?. PLoS Biol 14(7): e1002503. doi:10.1371/journal.pbio.1002503
http://journals.plos.org/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002503

PLOS | BIOLOGY

One man's poop is another's medicine

By John Bonifield and Elizabeth Cohen, CNN Health

Updated 12:02 PM ET, Thu August 27, 2015

Source: CNN

One man's poop is another's medicine 02:52

Focus on Health


Back to school: What kids a most anxious about is ...


Mutant lice are probably coming! But first, the hype


5 myths about 'female Viagr busted


Study: Happy friends could help teenagers beat depression

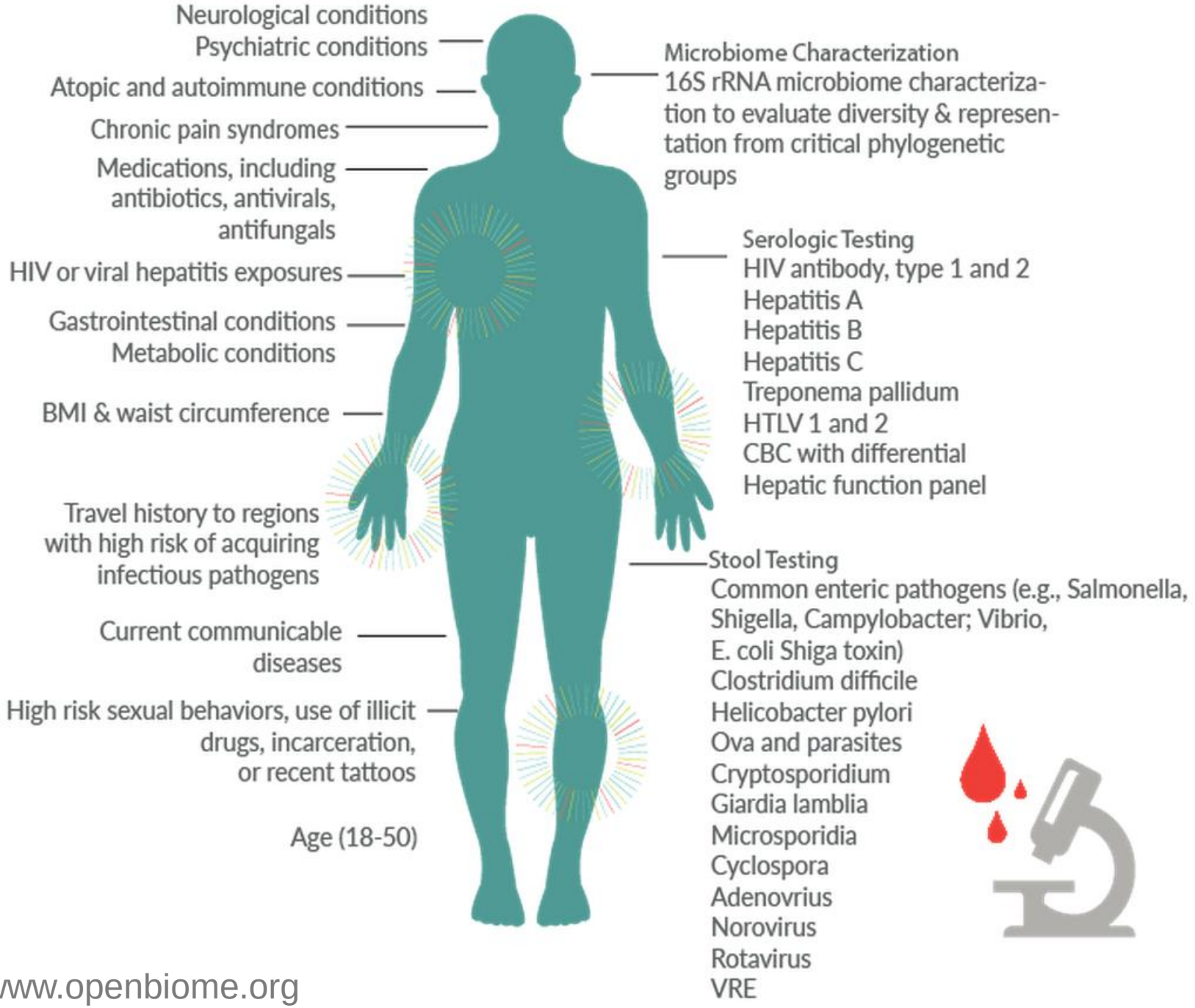

Way into a woman's heart a through her stomach

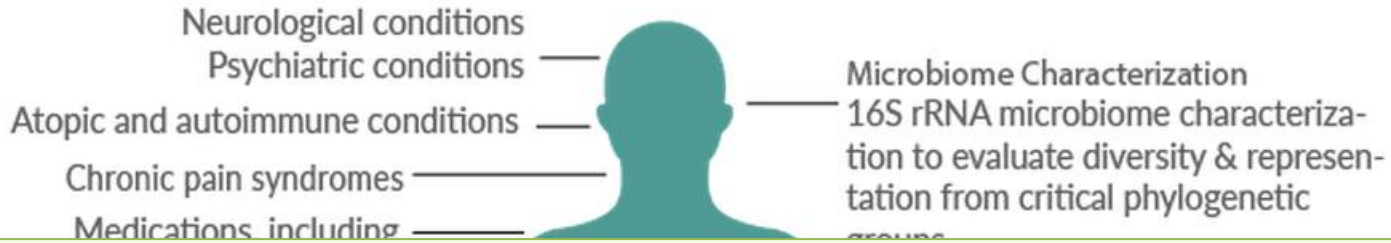

The science of a happy marriage

Donor – Opinion on FMT

- "*It's unreal. I never thought I would be staring at my poop frozen in a freezer destined to help people across the country. It's really cool."*
- But did he do it for the money? The easy money?
- *"Not at all," he says. "It's a nice perk, of course."*
  - If you're inspired to donate like Eric, you have to live in the Boston area. And you may have to wait. Some 6,000 people have already signed up. OpenBiome usually invites about 50 people for interviews every week.
- *"It's easier to get into MIT and Harvard than it is to get enrolled as one of our donors,*" Smith says. "A lot of our donors are pretty excited to take something they do every day otherwise and save people's lives with it."

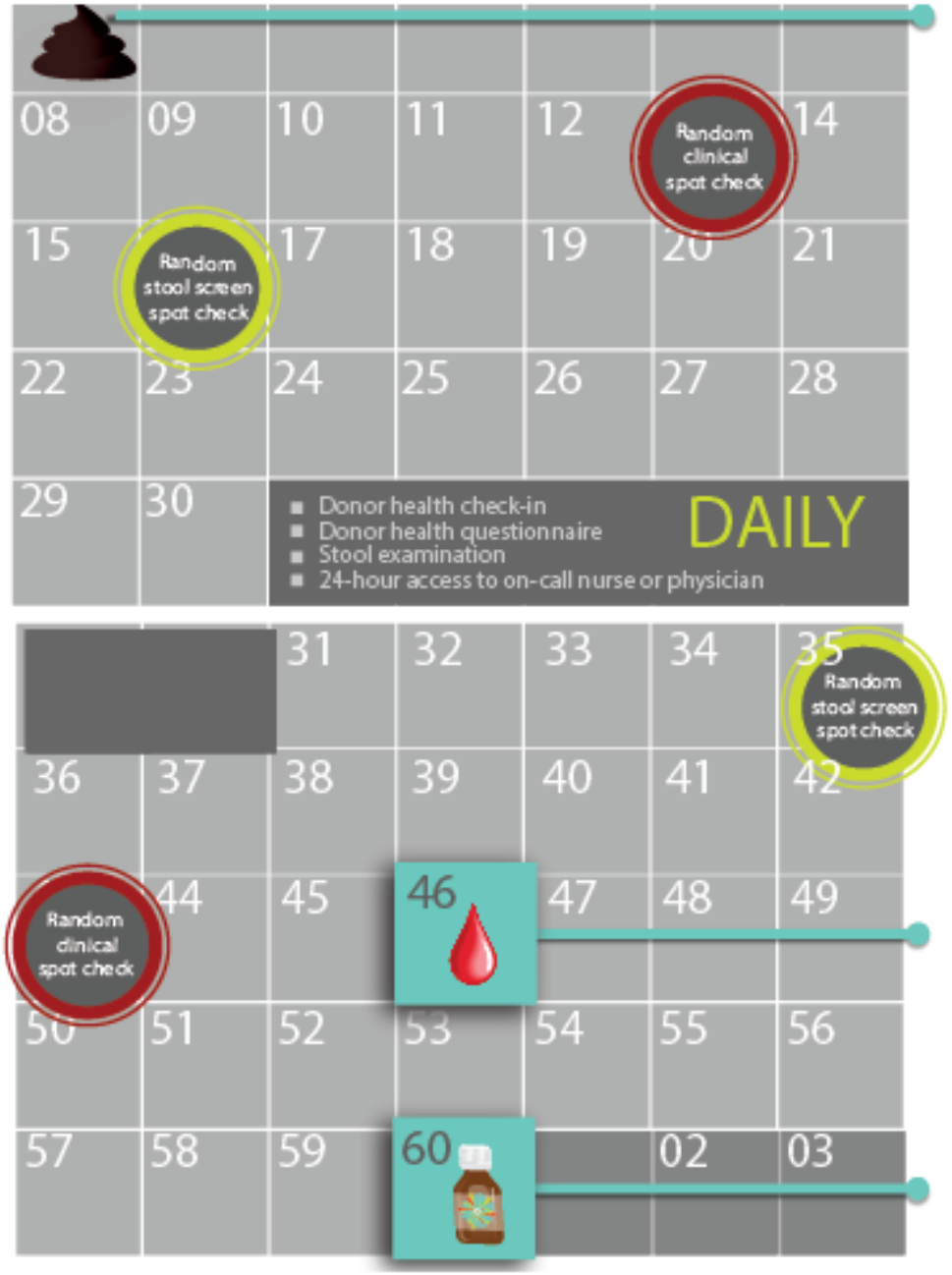
CNN Health Aug 27,2015


Neurological conditions
Psychiatric conditions
Atopic and autoimmune conditions
Chronic pain syndromes
Medications, including antibiotics, antivirals, antifungals
HIV or viral hepatitis exposures
Gastrointestinal conditions
Metabolic conditions
BMI & waist circumference
Travel history to regions with high risk of acquiring infectious pathogens
Current communicable diseases
High risk sexual behaviors, use of illicit drugs, incarceration, or recent tattoos
Age (18-50)
Microbiome Characterization
16S rRNA microbiome characterization to evaluate diversity & representation from critical phylogenetic groups
Serologic Testing
HIV antibody, type 1 and 2
Hepatitis A
Hepatitis B
Hepatitis C
Treponema pallidum
HTLV 1 and 2
CBC with differential
Hepatic function panel
Stool Testing
Common enteric pathogens (e.g., Salmonella, Shigella, Campylobacter; Vibrio, E. coli Shiga toxin)
Clostridium difficile
Helicobacter pylori
Ova and parasites
Cryptosporidium
Giardia lamblia
Microsporidia
Cyclospora
Adenovrius
Norovirus
Rotavirus
VRE



Prospective donors undergo a **rigorous** screening process:

- 109-Question Clinical Evaluation
- Battery of serological and stool-based assays to screen for infectious pathogens
  - Less than 3% of prospective donors pass the screens to become active OpenBiome donors.
  - Once active, donors contribute material for a min of 60 days and must fully re-qualify at the end of the collection window



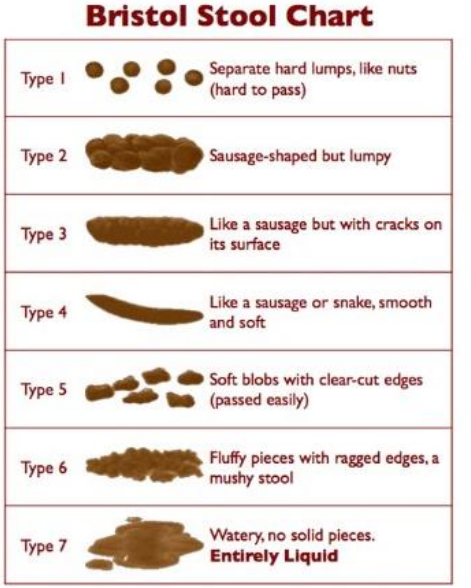
Collection Period Start
Stool collection begins. FMPs are placed in quarantine.

Seroconversion Window
From Day 46 on, stool stays in quarantine until donor screen at end of next collection period to account for seroconversion windows.

Donor Rescreening
If passes, FMPs from Day 1-45 are released for clinical use.

OpenBiome

Not all poop is acceptable!



Standardized Stool Examination

Our lab technicians evaluate every stool sample based on Bristol type and stool pathology.

Filtering & Homogenization

Stool specimens are filtered for particulates and homogenized in a glycerol buffer.

Processing, Storage & Shipping Controls

All samples are processed under a Class II BSC that is UV-sterilized and cleaned with a sporicidal agent. Samples are stored in a glycerol buffer at -80 degrees C, sealed with tamper-evident bands, and transported on dry ice with temperature verification.

OpenBiome

Microbiota Preparations

Lower Delivery
microbiota preparation

We offer a 250mL fecal microbiota preparation for lower gastrointestinal delivery (e.g. colonoscopy or enema)

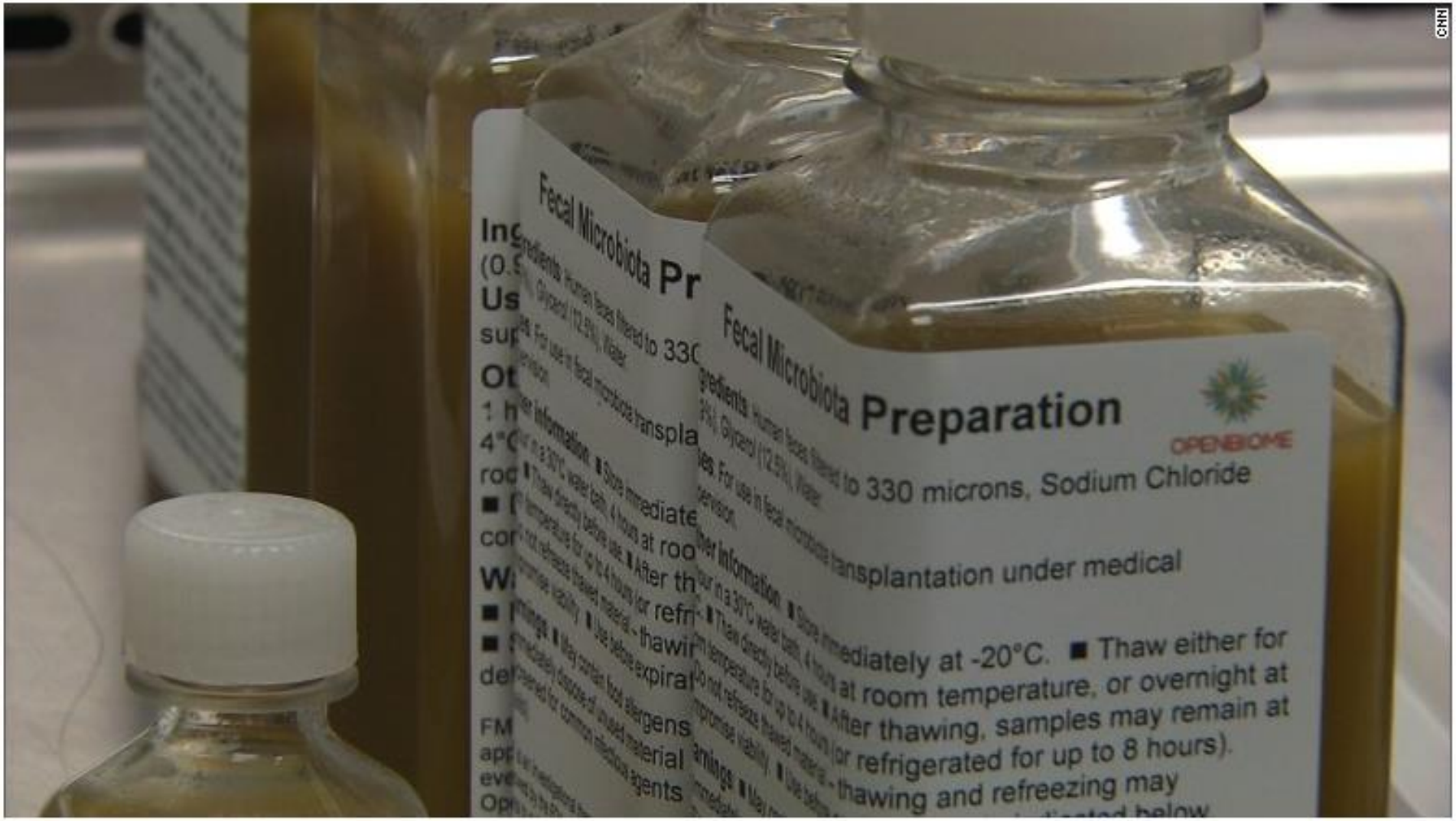
Upper Delivery
microbiota preparation

We offer a 30mL fecal microbiota preparation for upper gastrointestinal delivery (e.g. enteric naso-gastric tube)

Capsule G3
microbiota preparation with MEM technology

We have developed orally administered capsules for FMT. Capsules are currently available under OpenBiome's compassionate care program and for research purposes.

http://www.openbiome.org


Fecal Microbiota Preparation
OPENBIOME
Fecal Microbiota Pr
330 microns, Sodium Chloride
transplantation under medical
-20°C. ■ Thaw either for
room temperature, or overnight at
thawing, samples may remain at
refrigerated for up to 8 hours).
thawing and refreezing may
CNN

OpenBiome
Patient Preparation

- Informed consent:
  - Discuss R/B/A of procedure & microbiota transfer
  - MD must let the patient know that the use of FMT products to treat CDI is *investigational*
- Discontinue oral vancomycin or fidaxomicin 48 hours prior to FMT
    - large volume bowel lavage ?
  - Naso-enteric delivery
    - PPI for 24 to 48 h prior FMT

OpenBiome
Administration of FMT Material

- Upper delivery
  - ND/NJ tube → confirm placement by radiogaph
  - Endoscopic → install under direct visualization
    - 30 mL FMT* material (More concentrated less volume; less risk for aspiration
- Lower delivery:
  - C-scope
    - 250 mL FMT* material infusion of all material in the cecum or most proximal aspect
  - Retention Enema → less effective

* FMT should be thawed 1-4 hours prior to the procedure

OpenBiome
Patient Discharge & Follow-Up

- Assess patient at the following time points:
  - 1 week post FMT administration (phone)
    - Most common time that FMT non-response occurs
  - 4 weeks post FMT (phone)
  - 8 weeks post FMT (phone/clinic)

OpenBiome
Cost

Order Information

E. ORDER INFORMATION				
ITEM	**DESCRIPTION**	**UNIT PRICE**	**QUANTITY**	**TOTAL**
FMP250	250 mL Fecal Microbiota Preparation for lower administration	$385		
FMP30	30 mL Fecal Microbiota Preparation for upper administration	$385		
Standard S&H	Flat Shipping & Handling fee per shipment, waived on orders of 15 units or more	$250		
Same-day Shipping	Order must be received before 3pm ET Mon-Thur. Availability not guaranteed	Additional $50		
First Overnight	Approximate 8am local delivery time, compared to approximate 10:30am Standard delivery time	Additional $100		

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Web: www.openbiome.org

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: Fecal Microbiota Transplantation for *Clostridium difficile* Infection: A Systematic Review

Drekonja et al. Ann Intern Med. 2015;162(9):630-638. doi:10.7326/M14-2693

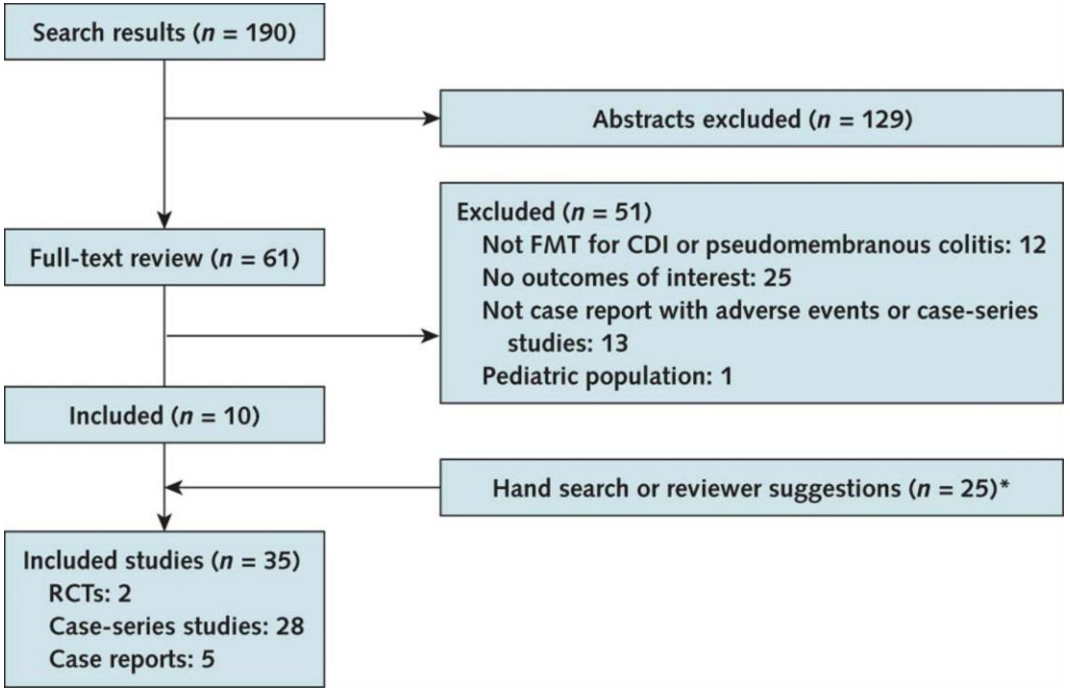


Figure Legend:

Summary of evidence search and selection.
CDI = Clostridium difficile infection; FMT = fecal microbiota transplantation; RCT = randomized, controlled trial.
* Included 1 RCT.

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review

Drekonja et al. Ann Intern Med. 2015;162(9):630-638. doi:10.7326/M14-2693

Table 2. Summary Results for Reported Resolution of Symptoms After Initial FMT for Recurrent CDI, Overall and by FMT Method

FMT Method	Patients With Resolution of Symptoms Without Recurrence, %*	Studies/Total Studies Analyzed, *n/N*
Upper GI tract	77	7/187†
Colonoscopy	90	11/257†
Enema	78	5/45
Upper GI tract and colonoscopy	100	1/27
All methods	85	23/516‡

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal.

* Because of small sample sizes and the abundance of data from case-series studies, 95% CIs were considered to be unreliable and were not calculated.

† Includes 10 patients from reference 18.

‡ Total number of studies is 1 less than the sum of individual rows.

Kettering Medical Center - FMT Data

- Program started July 2016
- Total 7 FMTs performed to date
- Success in 6
- Failure in 1
  - 2nd FMT via upper GI delivery: success

Premier Health - FMT Data

- Program started June 2015
- Total 49 FMTs performed in 13 months
- Success: 40 (81%) (86%)
- Unknown: 2 (lost to f/u)
- Failures in 7 (14%) (4 →Ulcerative colitis)
  - 2nd FMT via upper GI delivery: success in 2 pts
- Adverse events:
  - GI upset; diarrhea
  - Acute renal failure; MSSA bacteremia…

Case

- 77 yo WF with COPD; 3 courses of antibiotics for RTI in the past 6 months
- Admitted with lower abdominal discomfort and diarrhea … *C diff* toxin positive
- IV metronidazole and PO Vancomycin
- Not getting better… **progressive abdo-distention, tachycardia, leukocytosis, acidosis … colon distention by CT scan**

Recent Labs

	11/24/15 0449	11/23/15 0546	11/22/15 0943
WBC	53.5*	48.8*	38.9*
HEMOGLOBIN	14.6	14.7	14.6
HEMATOCRIT	42.4	43.1	43.4
PLATELETS	293	296	265
NA	128*	133*	135*
POTASSIUM	4.1	4.7	4.3
CL	103	107	106
CO2	21*	22	23
BUN	22*	19	11
CREATININE	0.4	0.4	0.3*
GLUCOSE	123*	123*	124*

CT abdo-pelvis: Diffuse wall enhancement of the colon, with colonic distention to 8 cm maximum involving transverse colon… colonic thumbprinting from wall edema …diffuse mesenteric edema and some ascites…

Case cont.

- Severe CDI non-responsive to standard therapy with signs concerning for toxic megacolon
- Options for management
  - Cont same + add IV tigecycline, IVIg
  - FMT
  - Surgery: subtotal colectomy or diverting loop ileostomy with colonic lavage

Case Cont.

- C scope with FMT performed
- The next day: Abdomen less distended, less firm

	11/27/15 0553	11/26/15 0512	11/25/15 0511
WBC	21.3*	39.6*	60.1*

Medical Staff Progress Note

Date of Service: 11/29/15

Manis, Ronal D Jr., MD
Internal Medicine

ID

Cont impressive response to fecal transplant noted.

Safety of FMT

- Short-term events
  - Procedural-based on method of FMT delivery (eg, colonoscopy, sedation)
    - Perforation of colon
    - Aspiration pneumonia
  - Intrinsic to FMT itself
    - GI upset
- Long-term

CR Kelly et al. Gastroenterology. 2015;149:223

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

* Adverse events that were reported on the day of donor-feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.
† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.
‡ On day 56, one patient was hospitalized for symptomatic choledocholithiasis, for which endoscopic retrograde cholangiopancreatography and stone extraction were performed.
§ One patient with autonomic dysfunction had dizziness combined with diarrhea after donor-feces infusion.

Duodenal Infusion of Donor Feces for Recurrent CDI

Adverse Events in 16 Patients in the Infusion Group

van Nood E et al. N Engl J Med 2013;368:407

PLOS | ONE

RESEARCH ARTICLE

Systematic Review: Adverse Events of Fecal Microbiota Transplantation

Sinan Wang[1☯], Mengque Xu[1☯], Weiqiang Wang[1], Xiaocang Cao[1], Meiyu Piao[1], Samiullah Khan[1], Fang Yan[1,2], Hailong Cao[1,2]*, Bangmao Wang[1]*

1 Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin, China, **2** Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232, United States of America

Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. (2016) Systematic Review: Adverse Events of Fecal Microbiota Transplantation. PLoS ONE 11(8): e0161174. doi:10.1371/journal.pone.0161174

RESEARCH ARTICLE

Systematic Review: Adverse Events of Fecal Microbiota Transplantation

Sinan Wang[1☯], Mengque Xu[1☯], Weiqiang Wang[1], Xiaocang Cao[1], Meiyu Piao[1], Samiullah Khan[1], Fang Yan[1,2], Hailong Cao[1,2*], Bangmao Wang[1*]

1 Department of Gastroenterology and Hepatology, General Hospital, Tianjin Medical University, Tianjin, China, **2** Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232, United States of America

- 78 kinds of AEs were revealed ; incidence rate 28.5%.
- 5→ definitely and 38 → probably related to FMT.
- The commonest FMT- AE was abdominal discomfort.
- Upper GI delivery 43.6% vs 17.7% for lower ;
- Serious AE 2.0% for upper and 6.1% lower ;
- Death (3.5%); infection (2.5%) (*not attributed to FMT)*

Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. (2016) Systematic Review: Adverse Events of Fecal Microbiota Transplantation. PLoS ONE 11(8): e0161174. doi:10.1371/journal.pone.0161174

Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

Colleen R. Kelly, MD, FACG[1], Chioma Ihunnah, MD, MPH[1], Monika Fischer, MD, MSCR[2], Alexander Khoruts, MD[3], Christina Surawicz, MD, MACG[4], Anita Afzali, MD, MPH[4], Olga Aroniadis, MD[5], Amy Barto, MD[6], Thomas Borody, MD, PhD, FACG[7], Andrea Giovanelli, BS[8], Shelley Gordon, MD, PhD[9], Michael Gluck, MD[10], Elizabeth L. Hohmann, MD[11], Dina Kao, MD[12], John Y. Kao, MD[13], Daniel P. McQuillen, MD[6], Mark Mellow, MD, FACG[14], Kevin M. Rank, MD[3], Krishna Rao, MD[13], Arnab Ray, MD[15], Margot A. Schwartz, MD, MPH[10], Namita Singh, MD[16], Neil Stollman, MD, FACG[8], David L. Suskind, MD[16], Stephen M. Vindigni, MD, MPH[4], Ilan Youngster, MD[11] and Lawrence Brandt, MD, MACG[5]

OBJECTIVES: **Patients who are immunocompromised (IC) are at increased risk of *Clostridium difficile* infection (CDI), which has increased to epidemic proportions over the past decade. Fecal microbiota transplantation (FMT) appears effective for the treatment of CDI, although there is concern that IC patients may be at increased risk of having adverse events (AEs) related to FMT. This study describes the multicenter experience of FMT in IC patients.**

METHODS: **A multicenter retrospective series was performed on the use of FMT in IC patients with CDI that was recurrent, refractory, or severe. We aimed to describe rates of CDI cure after FMT as well as AEs experienced by IC patients after FMT. A 32-item questionnaire soliciting demographic and pre- and post-FMT data was completed for 99 patients at 16 centers, of whom 80 were eligible for inclusion. Outcomes included (i) rates of CDI cure after FMT, (ii) serious adverse events (SAEs) such as death or hospitalization within 12 weeks of FMT, (iii) infection within 12 weeks of FMT, and (iv) AEs (related and unrelated) to FMT.**

RESULTS: **Cases included adult (75) and pediatric (5) patients treated with FMT for recurrent (55%), refractory (11%), and severe and/or overlap of recurrent/refractory and severe CDI (34%). In all, 79% were outpatients at the time of FMT. The mean follow-up period between FMT and data collection was 11 months (range 3–46 months). Reasons for IC included: HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other medical conditions/medications (15). The CDI cure rate after a single FMT was 78%, with 62 patients suffering no recurrence at least 12 weeks post FMT. Twelve patients underwent repeat FMT, of whom eight had no further CDI. Thus, the overall cure rate was 89%. Twelve (15%) had any SAE within 12 weeks post FMT, of which 10 were hospitalizations. Two deaths occurred within 12 weeks of FMT, one of which was the result of aspiration during sedation for FMT administered via colonoscopy; the other was unrelated to FMT. None suffered infections definitely related to FMT, but two patients developed unrelated infections and five had self-limited diarrheal illness in which no causal organism was identified. One patient had a superficial mucosal tear caused by the colonoscopy**

Kelly CR, et al Am J Gastroenterol. 2014; 109:1065.

Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

- Multi-center retrospective review of 80 (75 adult and 5 pediatric) immunocompromised pts [HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressives for IBD; 36), other(15)].
- Cure rate after a single FMT was 78% .
- Serious adverse event within 12-weeks in 15% .
  - Two deaths: a sedation-associated aspiration during FMT by colonoscopy; and the other unrelated to FMT.
- Immunocompromised patients appear to have approximately the same rates of clinical cure

Kelly CR, et al Am J Gastroenterol. 2014; 109:1065.

Fecal Microbiota Therapy as Rescue Therapy for Life-Threatening *Clostridium difficile* Infection in the Critically Ill: A Small Case Series

---

To the Editor—A retrospective review of anonymous data obtained from patients treated with fecal microbiota therapy (FMT) was conducted as part of an antibiotic stewardship program in a Bavarian regional medical center that is part of the Network of the German Consulting Center for Infection Control and Prevention. Data handling was perfomed in accordance with German Federal Data Protection Law (Bundesdatenschutzgesetz); the analysis of anonymous routine quality assurance data does not constitute human research requiring institutional review board approval. Table 1 summarizes the descriptions of each case based on point prevalence data from antibiotic stewardship rounds.

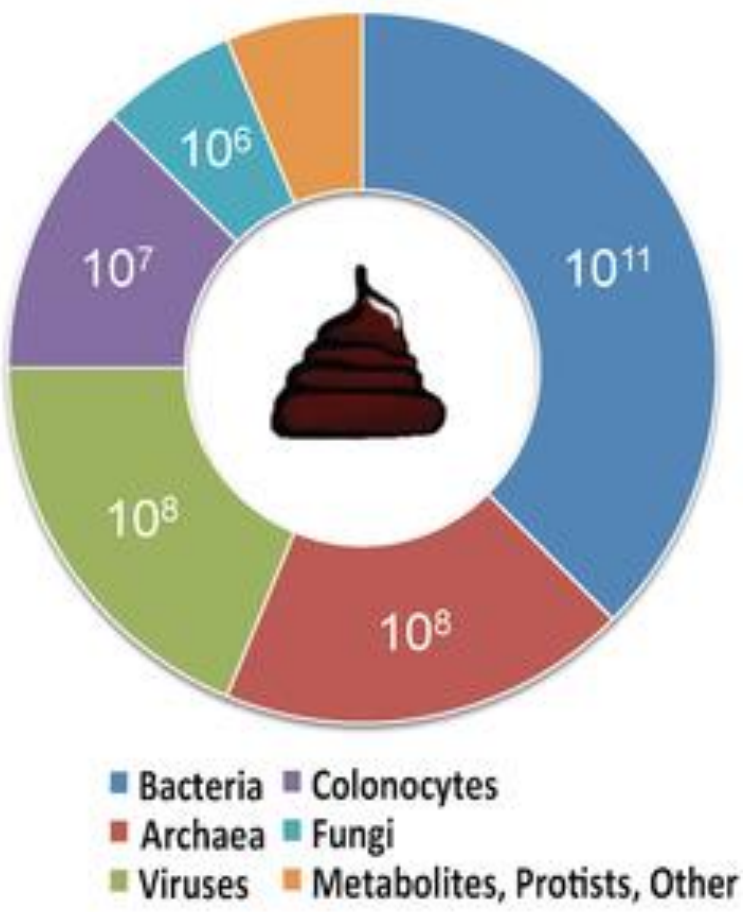
Infection Control & Hospital Epidemiology, Volume 37, Issue 9
September 2016, pp. 1129-1131
Sebastian Schulz-Stübner et al.

Potential Long-term Effects of Alterations in the Gut Microbiome

- Transmission of *novel pathogen*
- Nutritional status
  - body weight
  - diabetes risk
  - cardiovascular risk
- Fatty Liver Disease
- Autoimmune status
- Wound repair/fibrosis
- Cognition/mood
- Cancer risk
- Other?

CR Kelly et al. Gastroenterology. 2015;149:223

The estimated composition of human feces



Bojanova DP, Bordenstein SR (2016) Fecal Transplants: What Is Being Transferred?.
PLoS Biol 14(7): e1002503. doi:10.1371/journal.pbio.1002503
http://journals.plos.org/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002503

PLOS | BIOLOGY

Annals of Internal Medicine®

From: Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial

Ann Intern Med. Published online August 23, 2016. doi:10.7326/M16-0271

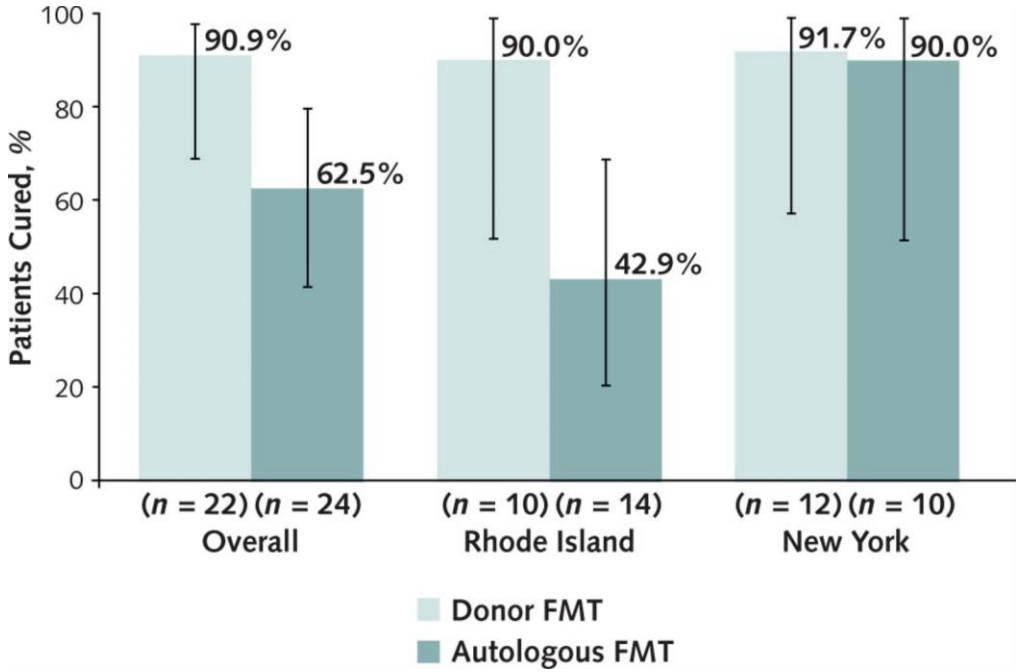


Figure Legend:

Rates of clinical cure in the intention-to-treat population, overall and by site. Error bars represent 95% CIs. FMT = fecal microbiota transplantation.

Date of download: 9/29/2016

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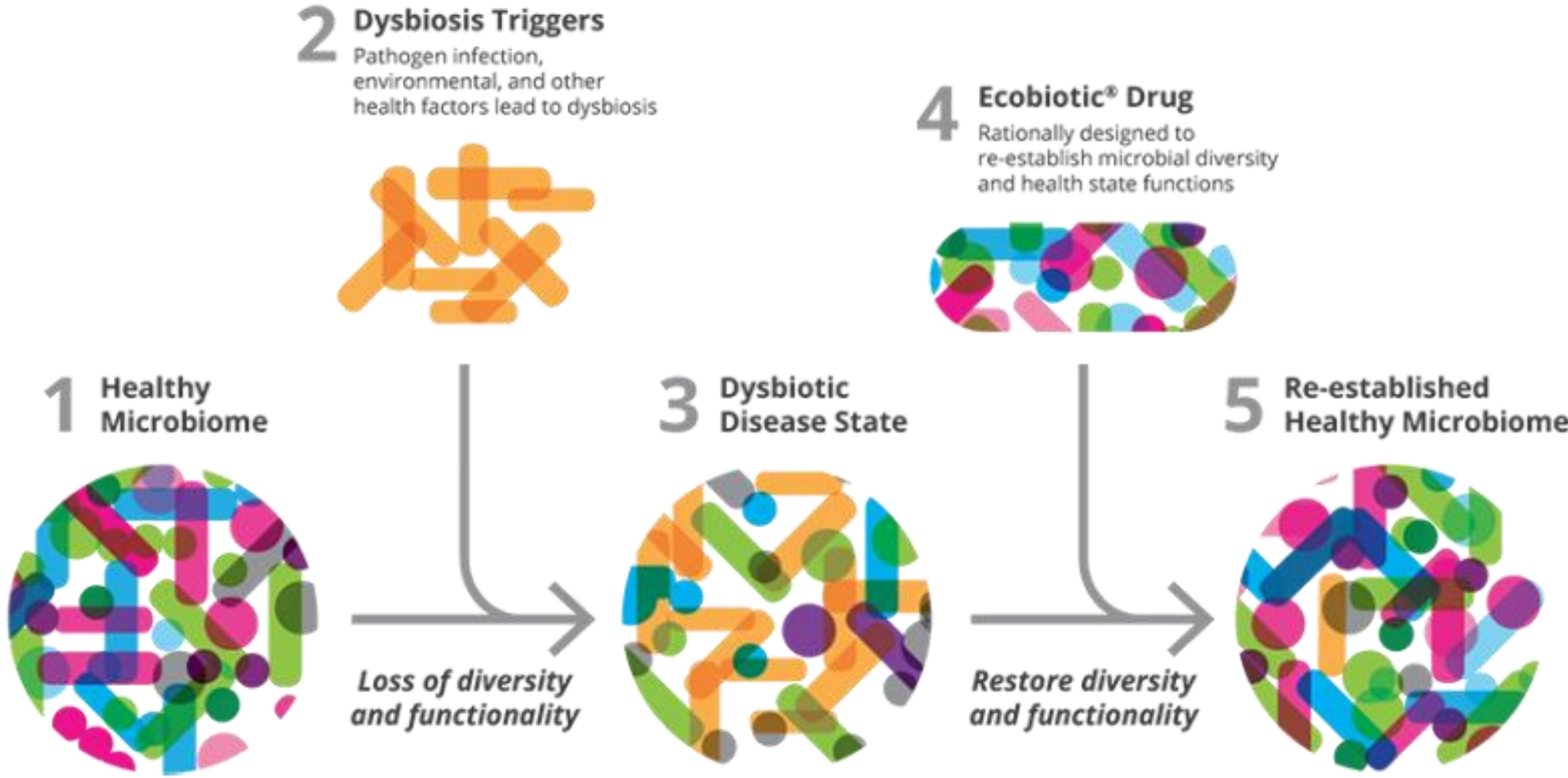
Future of FMT
FMT 2.0: Microbiome Therapeutics



http://www.serestherapeutics.com/our-science/microbiome-101

SERES THERAPEUTICS™

Aug. 21, 2015 Seres Therapeutics, Inc….announces FDA Orphan Drug Designation for SER-109 for the Prevention of Recurrent CDI Infection … also granted Breakthrough Therapy Designation by the FDA

SER-109 is the lead Ecobiotic® microbiome therapeutic in clinical testing for the treatment of recurrent CDI.

SER-109 was developed utilizing the Seres Microbiome Therapeutics™ platform that provides deep insight into the ecologies of disease and then identifies microbial compositions that can catalyze a shift to a healthier state.

Seres Therapeutics, Inc. is a leading microbiome therapeutics platform company developing a novel class of biological drugs that are designed to treat disease by restoring the function of a dysbiotic microbiome.

Phase 1b/2 study of SER-109 in 30 pts with rCDI → 97 % (29/30) efficacy

The Journal of Infectious Diseases

MAJOR ARTICLE

A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent *Clostridium difficile* Infection

Sahil Khanna,[1] Darrell S. Pardi,[1] Colleen R. Kelly,[2] Colleen S. Kraft,[3] Tanvi Dhere,[3] Matthew R. Henn,[4] Mary-Jane Lombardo,[4] Marin Vulic,[4] Toshiro Ohsumi,[4] Jonathan Winkler,[4] Christina Pindar,[5] Barbara H. McGovern,[4] Roger J. Pomerantz,[4] John G. Aunins,[4] David N. Cook,[4] and Elizabeth L. Hohmann[5]

[1]Mayo Clinic, Rochester, Minnesota; [2]Miriam Hospital, Women's Medicine Collaborative, Providence, Rhode Island; [3]Emory University School of Medicine, Atlanta, Georgia; [4]Seres Therapeutics, Cambridge, and [5]Massachusetts General Hospital, Boston, Massachusetts

(See the editorial commentary by Vehreschild and Cornely on pages 169–70.)

Background. Patients with recurrent *Clostridium difficile* infection (CDI) have a ≥60% risk of relapse, as conventional therapies do not address the underlying gastrointestinal dysbiosis. This exploratory study evaluated the safety and efficacy of bacterial spores for preventing recurrent CDI.

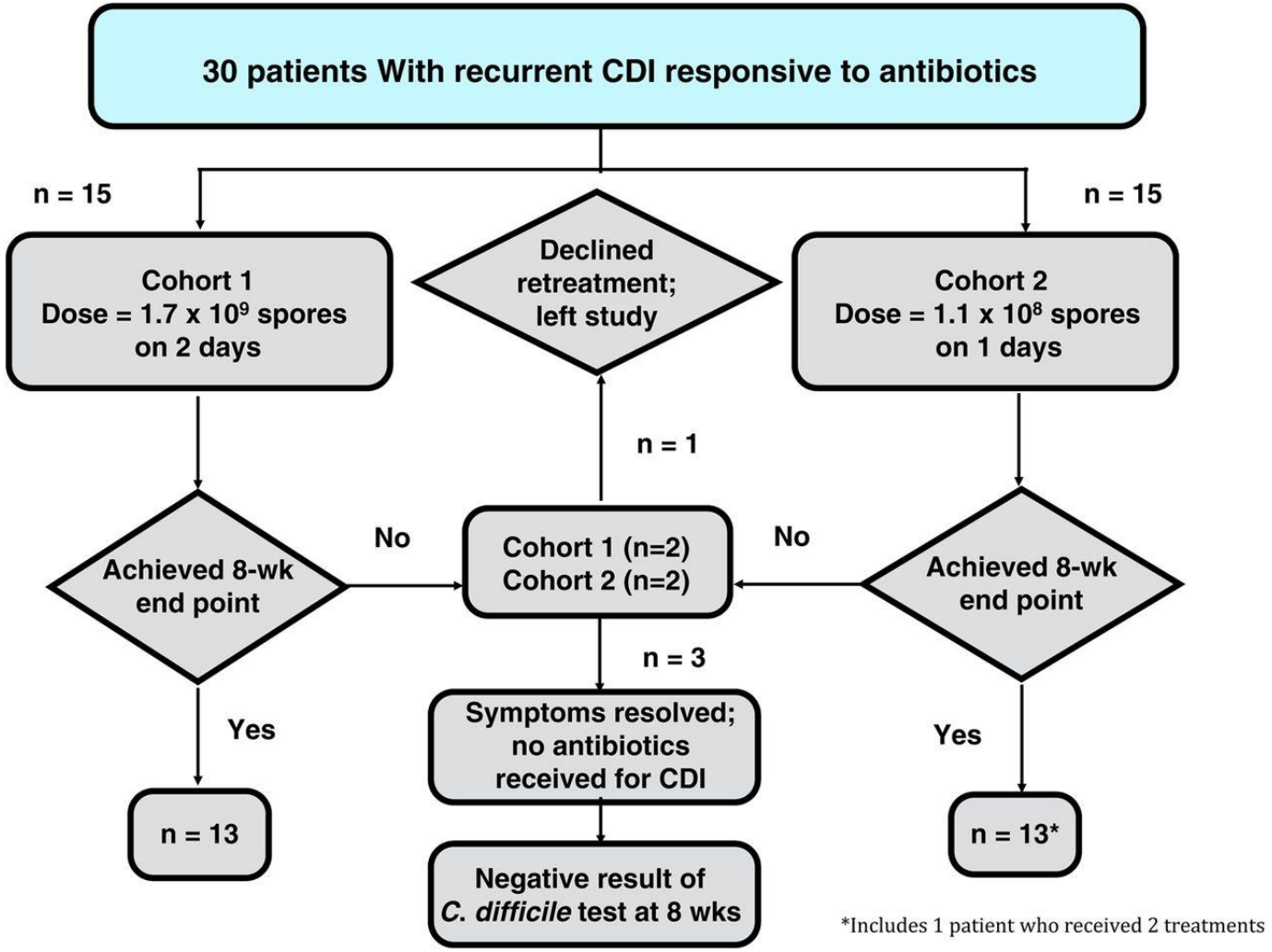
Methods. Stool specimens from healthy donors were treated with ethanol to eliminate pathogens. The resulting spores were fractionated and encapsulated for oral delivery as SER-109. Following their response to standard-of-care antibiotics, patients in cohort 1 were treated with SER-109 on 2 consecutive days (geometric mean dose, 1.7×10^9 spores), and those in cohort 2 were treated on 1 day (geometric mean dose, 1.1×10^8 spores). The primary efficacy end point was absence of *C. difficile*–positive diarrhea during an 8-week follow-up period. Microbiome alterations were assessed.

Results. Thirty patients (median age, 66.5 years; 67% female) were enrolled, and 26 (86.7%) met the primary efficacy end point. Three patients with early, self-limiting *C. difficile*–positive diarrhea did not require antibiotics and tested negative for *C. difficile* at 8 weeks; thus, 96.7% (29 of 30) achieved clinical resolution. In parallel, gut microbiota rapidly diversified, with durable engraftment of spores and no outgrowth of non–spore-forming bacteria found after SER-109 treatment. Adverse events included mild diarrhea, abdominal pain, and nausea.

Conclusions. SER-109 successfully prevented CDI and had a favorable safety profile, supporting a novel microbiome-based intervention as a potential therapy for recurrent CDI.

Keywords. *Clostridium difficile* infection; microbiome; dysbiosis; vancomycin-resistant *Enterococcus*; *Clostridium difficile* treatment.

Patient flow chart and outcomes.



Sahil Khanna et al. J Infect Dis. 2016;214:173-181

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The Journal of Infectious Diseases

Clinical Infectious Diseases

MAJOR ARTICLE

Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD Study

Robert Orenstein,[1] Erik Dubberke,[2] Robert Hardi,[3] Arnab Ray,[4] Kathleen Mullane,[5] Darrell S. Pardi,[6] and Mayur S. Ramesh[7]; for the PUNCH CD Investigators[a]

[1]Division of Infectious Diseases, Mayo Clinic–Arizona, Phoenix; [2]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; [3]Chevy Chase Clinical Research, Capital Digestive Care, Maryland; [4]Ochsner Clinic, New Orleans, Louisiana; [5]Section of Infectious Diseases and Global Health, University of Chicago Medicine, Illinois; [6]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; and [7]Henry Ford Hospital System, Detroit, Michigan

Background. Managing recurrent *Clostridium difficile* infection (CDI) presents a significant challenge for clinicians and patients. Fecal microbiota transplantation (FMT) is a highly effective therapy for recurrent CDI, yet availability of a standardized, safe, and effective product has been lacking. Our aim in this study was to assess the safety and effectiveness of RBX2660 (microbiota suspension), a commercially prepared FMT drug manufactured using standardized processes and available in a ready-to-use format.

Methods. Patients with at least 2 recurrent CDI episodes or at least 2 severe episodes resulting in hospitalization were enrolled in a prospective, multicenter open-label study of RBX2660 administered via enema. Intensive surveillance for adverse events (AEs) was conducted daily for 7 days following treatment and then at 30 days, 60 days, 3 months, and 6 months. The primary objective was product-related AEs. A secondary objective was CDI-associated diarrhea resolution at 8 weeks.

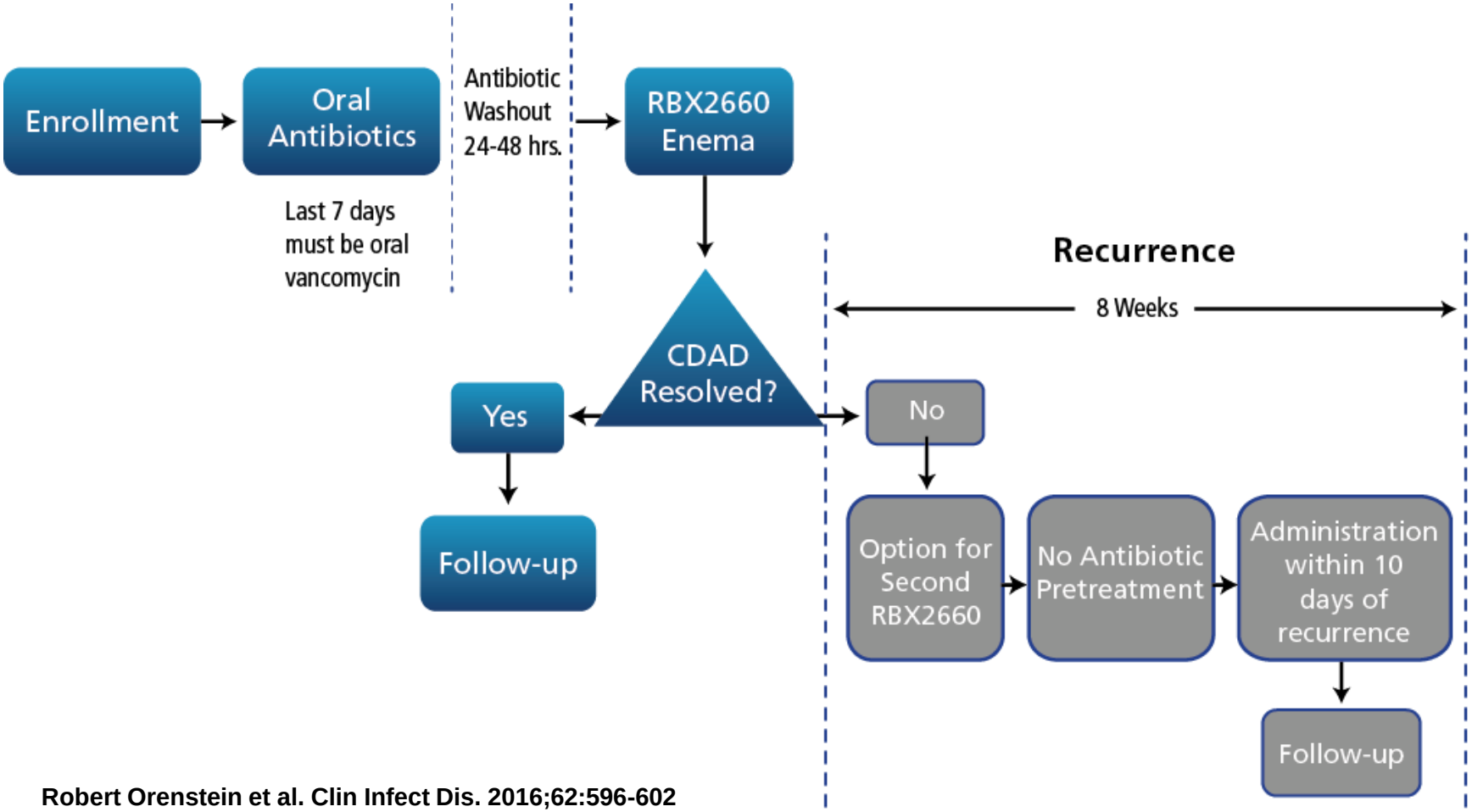
Results. Of the 40 patients enrolled at 11 centers in the United States between 15 August 2013 and 16 December 2013, 34 received at least 1 dose of RBX2660 and 31 completed 6-month follow-up. Overall efficacy was 87.1% (16 with 1 dose and 11 with 2 doses). Of 188 reported AEs, diarrhea, flatulence, abdominal pain/cramping, and constipation were most common. The frequency and severity of AEs decreased over time. Twenty serious AEs were reported in 7 patients; none were related to RBX2660 or its administration.

Conclusions. Among patients with recurrent or severe CDI, administration of RBX2660 via enema appears to be safe and effective.

Clinical Trials Registration. NCT01925417.

Keywords. fecal microbiota transplant; *Clostridium difficile*; microbiome; safety.

PUNCH CD study design- Open Label Safety Trial



Robert Orenstein et al. Clin Infect Dis. 2016;62:596-602

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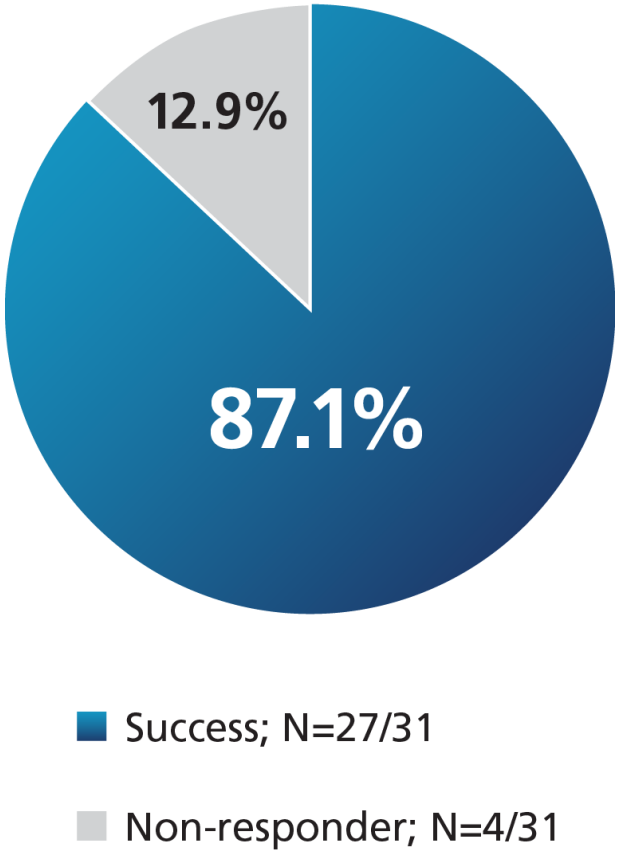
Clinical Infectious Diseases

Rebiotix
Microbiota Restoration Therapy

PUNCH™ CD: Efficacy



- 87.1% represents absence of CDI at 8 weeks
- No additional occurrences in successful patients out to 6 months with/without antibiotic treatment for other indications

Robert Orenstein et al. Clin Infect Dis. 2016;62:596-602

Rebiotix
Microbiota Restoration Therapy

PUNCH™ CD

Table 2. Types of Adverse Events

Type	n (%)
Gastrointestinal disorders include	**107 (56.9)**
Diarrhea	26 (24.3)
Flatulence	15 (14.0)
Abdominal pain	14 (13.1)
Constipation	14 (13.1)
Abdominal distention	9 (8.4)
Anorectal discomfort	6 (5.6)
Nausea	5 (4.7)
Vomiting	5 (4.7)
Proctalgia	3 (2.8)
Infections	**19 (10.1)**
Bacteremia	1
Clostridium difficile colitis	3
C. difficile infection	4
Nasopharyngitis	2
Upper respiratory infection	3
Sinusitis	1
Tooth abscess	1
Pneumonia	1
Urinary tract infection	3

Robert Orenstein et al.
Clin Infect Dis.
2016;62:596-602

Conclusions

- Nurture your own microbiota
- Think twice when prescribing antibiotics
- FMT is the most effective therapy for recurrent CDI
  - More studies (RCTs) and long-term safety data (registries) needed
  - Increased use of FMT in early CDI, complicated CDI
  - Refinements of FMT: pills
- Increasing number of microbiome therapeutics
- Increased use of FMT in the treatment of other conditions

ESSAY

Fecal Transplants: What Is Being Transferred?

Diana P. Bojanova[1], Seth R. Bordenstein[1,2]*

1 Department of Biological Sciences, Vanderbilt University, Nashville, Tennessee, United States of America, 2 Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, Tennessee, United States of America

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Abstract

Fecal transplants are increasingly utilized for treatment of recurrent infections (i.e., *Clostridium difficile*) in the human gut and as a general research tool for gain-of-function experiments (i.e., gavage of fecal pellets) in animal models. Changes observed in the recipient's biology are routinely attributed to bacterial cells in the donor feces (~10^{11} per gram of human wet stool). Here, we examine the literature and summarize findings on the composition of fecal matter in order to raise cautiously the profile of its multipart nature. In addition to viable bacteria, which may make up a small fraction of total fecal matter, other components in unprocessed human feces include colonocytes (~10^{7} per gram of wet stool), archaea (~10^{8} per gram of wet stool), viruses (~10^{8} per gram of wet stool), fungi (~10^{6} per gram of wet stool), protists, and metabolites. Thus, while speculative at this point and contingent on the transplant procedure and study system, nonbacterial matter could contribute to changes in the recipient's biology. There is a cautious need for continued reductionism to separate out the effects and interactions of each component.

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Citation: Bojanova DP, Bordenstein SR (2016) Fecal Transplants: What Is Being Transferred? PLoS Biol

Bojanova DP, Bordenstein SR (2016) Fecal Transplants: What Is Being Transferred?. PLoS Biol 14(7): e1002503. doi:10.1371/journal.pbio.1002503
http://journals.plos.org/plosbiology/article?id=info:doi/10.1371/journal.pbio.1002503

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PEARLS

A Gut Odyssey: The Impact of the Microbiota on *Clostridium difficile* Spore Formation and Germination

Aimee Shen*

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click for updates

OPEN ACCESS

Citation: Shen A (2015) A Gut Odyssey: The Impact of the Microbiota on *Clostridium difficile* Spore Formation and Germination. PLoS Pathog 11(10): e1005157. doi:10.1371/journal.ppat.1005157

Introduction

The Gram-positive, anaerobic, spore-forming bacterium *Clostridium difficile* is the leading cause of health care–associated infections and gastroenteritis-associated deaths in the United States [1]. *C. difficile*-associated disease is primarily toxin-mediated, although the organism's natural antibiotic resistance and propensity to cause disease recurrence can lead to severe clinical complications, such as pseudomembranous colitis and toxic megacolon [2]. Antibiotic exposure potentiates *C. difficile* infections (CDI) by disrupting the colonization resistance conferred by the normal gut microbiota [3–5], while spore formation allows *C. difficile* to outlast antibiotic therapies and persist in the environment.

The remarkable success of fecal microbiota transplantation (FMT) in treating severe recurrent CDI provides the most direct evidence that our gut microbiota protects us from *C. difficile* invasion [4–6]. While the most effective antibiotic-based therapies lead to an ~20% CDI recur-

Shen A (2015) A Gut Odyssey: The Impact of the Microbiota on Clostridium difficile Spore Formation and Germination. PLoS Pathog 11(10): e1005157. doi:10.1371/journal.ppat.1005157
http://journals.plos.org/plospathogens/article?id=info:doi/10.1371/journal.ppat.1005157

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Fig 1. Developmental life cycle of Clostridium difficile during infection.

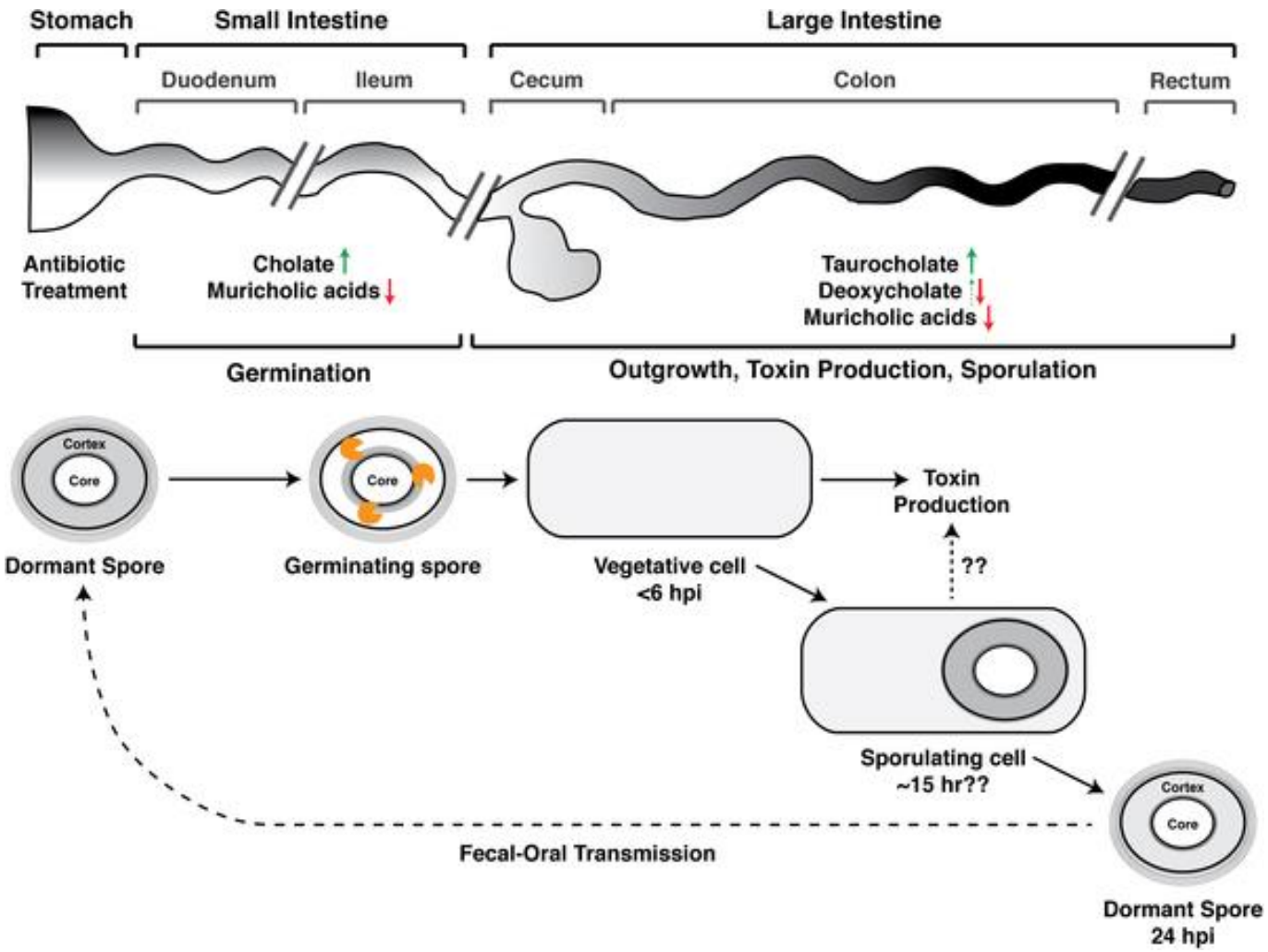

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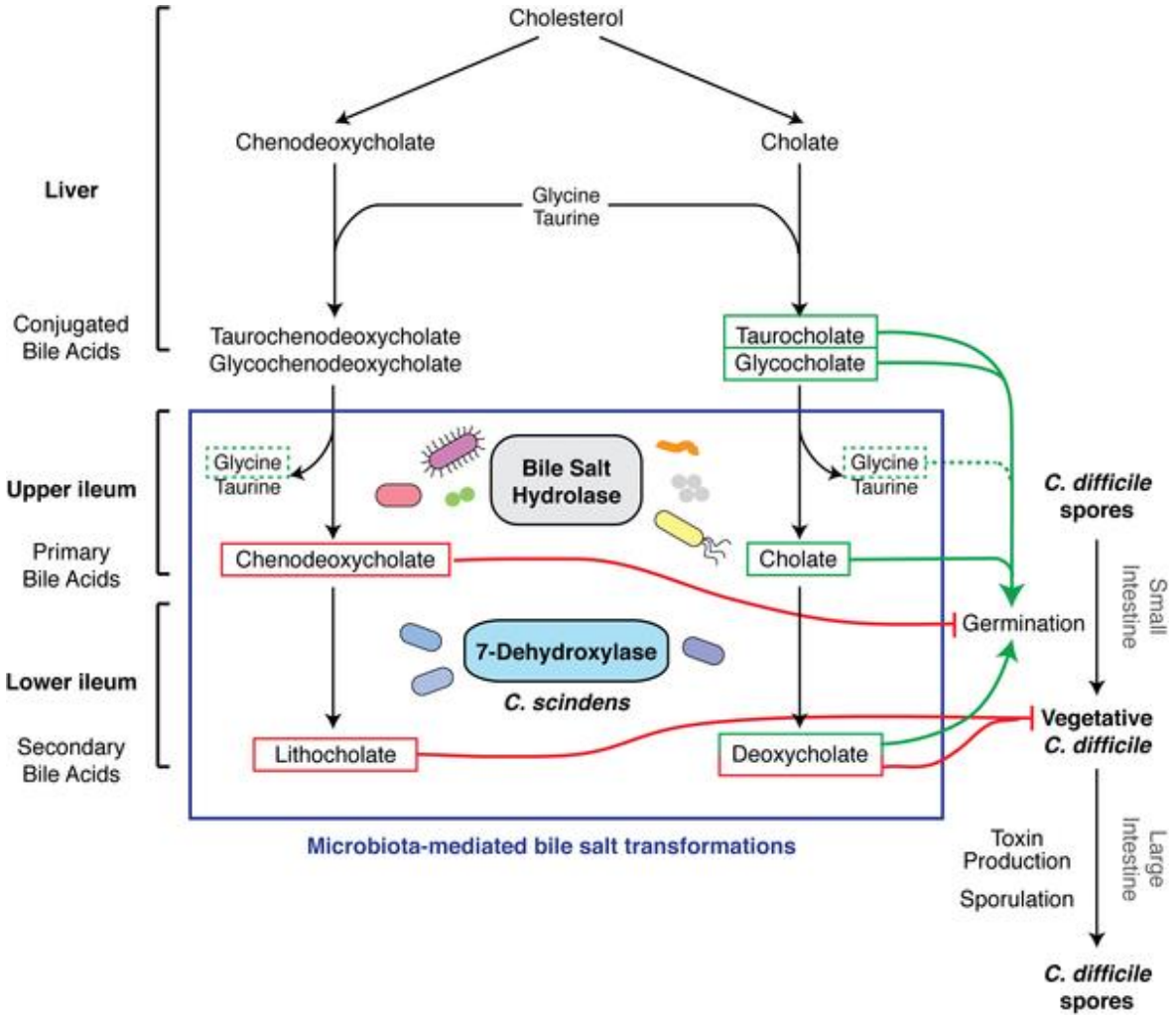
Fig 2. Effect of bile acid metabolism on the developmental life cycle of C. difficile.



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Understanding the mechanisms of faecal microbiota transplantation

Alexander Khoruts[1] and Michael J. Sadowsky[2]

Abstract | This Review summarizes mechanistic investigations in faecal microbiota transplantation (FMT), which has increasingly been adapted into clinical practice as treatment for *Clostridium difficile* infection (CDI) that cannot be eliminated with antibiotics alone. Administration of healthy donor faecal microbiota in this clinical situation results in its engraftment and restoration of normal gut microbial community structure and functionality. In this Review, we consider several main mechanisms for FMT effectiveness in treatment of CDI, including direct competition of *C. difficile* with commensal microbiota delivered by FMT, restoration of secondary bile acid metabolism in the colon and repair of the gut barrier by stimulation of the mucosal immune system. Some of these mechanistic insights suggest possibilities for developing novel, next-generation CDI therapeutics. FMT might also have potential applications for non-CDI indications. The gut can become a reservoir of other potential antibiotic-resistant pathogens under pressure of antibiotic treatments, and restoration of normal microbial community structure by FMT might be a promising approach to protect against infections with these pathogens as well. Finally, FMT could be considered for multiple chronic diseases that are associated with some form of dysbiosis. However, considerable research is

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Understanding the mechanisms of faecal microbiota transplantation

Key points

- Faecal microbiota transplantation (FMT) involves administration of the whole microbial community from healthy donor stool into the recipient's intestinal tract to normalize or modify intestinal microbiota composition and function
- Overall suppression of microbiota and disruption of its community structure in the colon, most commonly resulting from antibiotic therapies, is the fundamental problem underlying the pathogenesis of *Clostridium difficile* infection (CDI)
- FMT results in normalization of microbial diversity and community structure in patients being treated for CDI, with high rates of clinical cure
- The restored colon microbial community could inhibit *C. difficile* by multiple mechanisms: competition for nutrients; direct suppression by antimicrobial peptides; bile-acid-mediated inhibition of spore germination and vegetative growth; and activation of immune-mediated colonization resistance

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- Bile acids in the cholic acid class generally promote *C. difficile* spore germination. The primary bile salt taurocholate is typically used in laboratory *C. difficile* growth media.
- Lithocholic acid, a secondary bile acid, is an inhibitor of *C. difficile* spore germination.
- Combinations of bile acids present at physiological concentration in healthy adult faeces (lithocholic acid and deoxycholate) are inhibitory to *C. difficile*[61].
- Combinations of bile acids found in faeces of patients with refractory R-CDI before faecal microbiota transplantation (taurocholate, cholate, chenodeoxycholic acid) are stimulatory to *C. difficile*[61].

diseases that are associated with some form of dysbiosis. However, considerable research is needed to optimize the FMT protocols for such applications before their therapeutic promise can be evaluated.

Table 1 – modified from Surawicz et al. American Journal of Gastroenterology 2012[14]

CDI Severity	Criteria	Treatment
Severe CDI	Serum albumin <3g/dL plus ONE of the following: WBC ≥ 15,000 cells/mm^3 Abdominal tenderness	Vancomycin 125mg PO QID x 10 days
Severe-Complicated CDI	Any of the following attributable to CDI: Admission to ICU for CDI Hypotension with or without vasopressors Fever ≥ 38.5^{o}C Ileus or significant abdominal distension Mental status changes WBC ≥ 15,000 cells/mm^3 or <2,000 cells/mm^3 Serum lactate level >2.2mmol/L End organ failure (e.g., mechanical ventilation, renal failure)	Vancomycin 500mg PO QID and metronidazole 500mg IV q8h, and vancomycin per PR (vancomycin 500mg in 500mL saline as enema) QID AND Surgical consultation