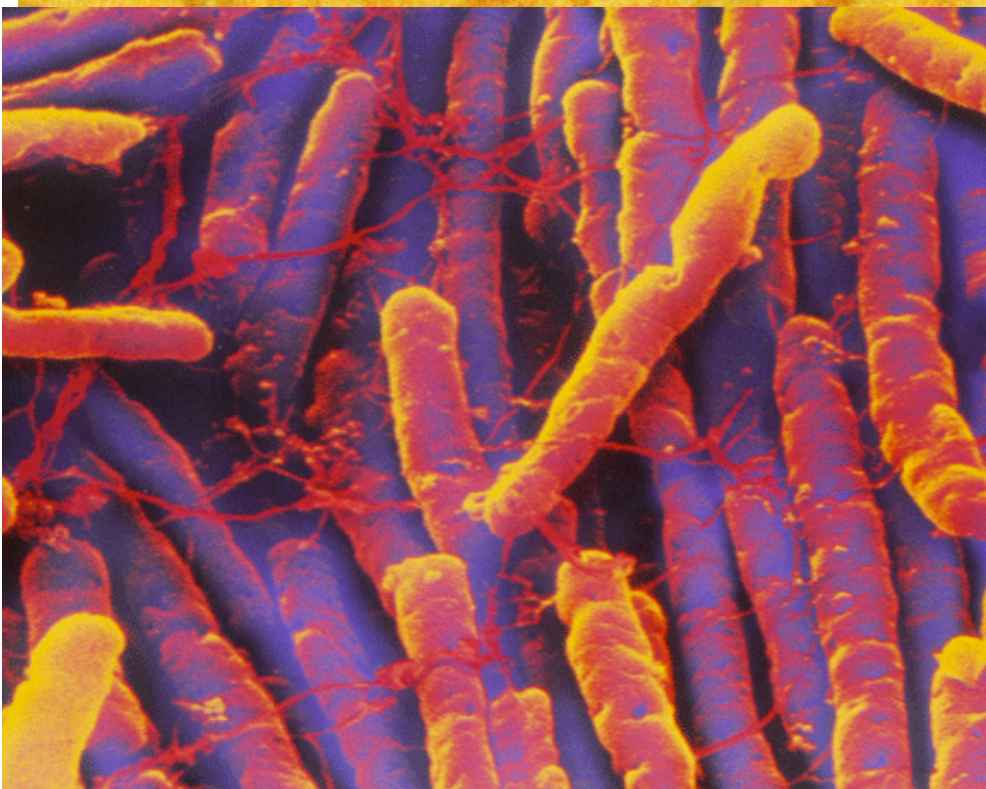


Fecal microbial transplant for *C. difficile*



Kristine Krueger MD
Professor and Chief
Division of Gastroenterology
Hepatology, and Nutrition
University of Louisville

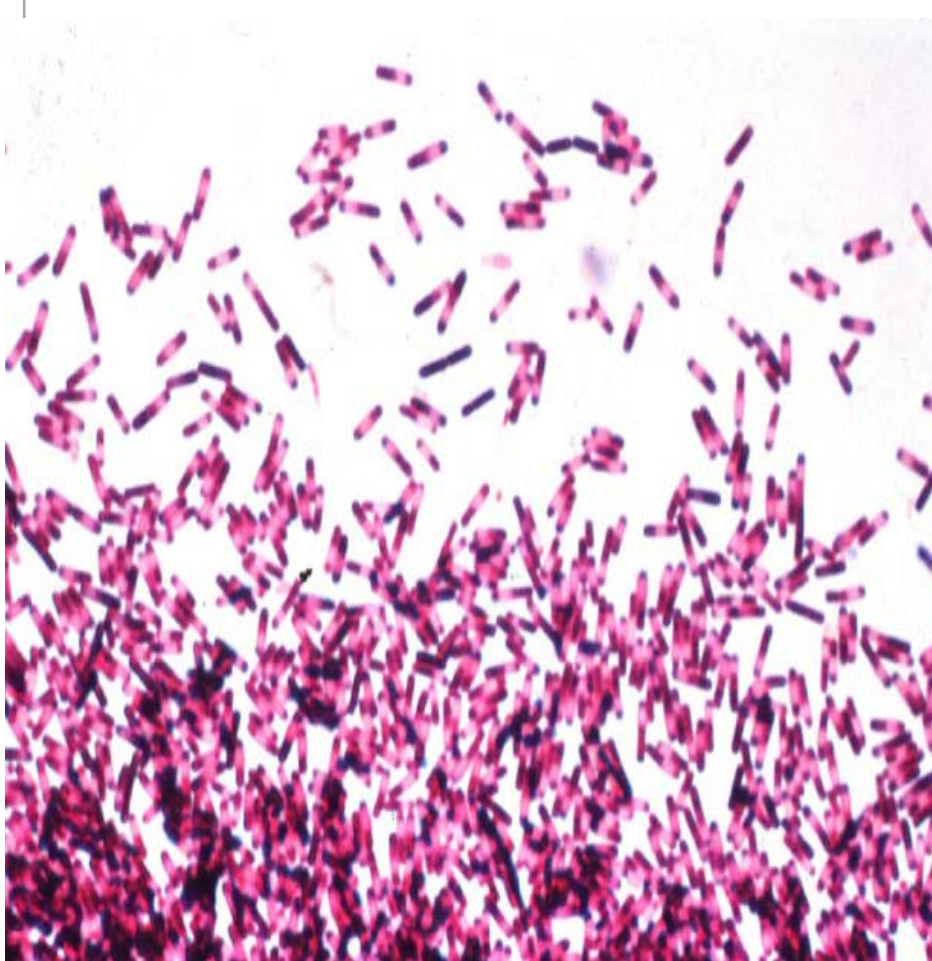
Speaker Disclosure and Acknowledgements

- Dr. Krueger has no industry disclosures
- Key References:
 - Journal of the KMA January 2013
 - AJG February 2013 (LJ Brandt)
 - NEJM January 31, 2013;368(5)
 - NEJM May 16, 2015;372
 - JAMA May 5, 2015,313(17)

Learning Objectives

- Review Epidemiology, Pathogenesis and burden of *C. difficile* infection
- Update on medical treatments, including antibiotics, probiotics, surgical treatment, and fecal microbial transplant (FMT)
- Discuss prevention strategies “medical stewardship” as well as the potential role of immunotherapy and vaccines

C. difficile

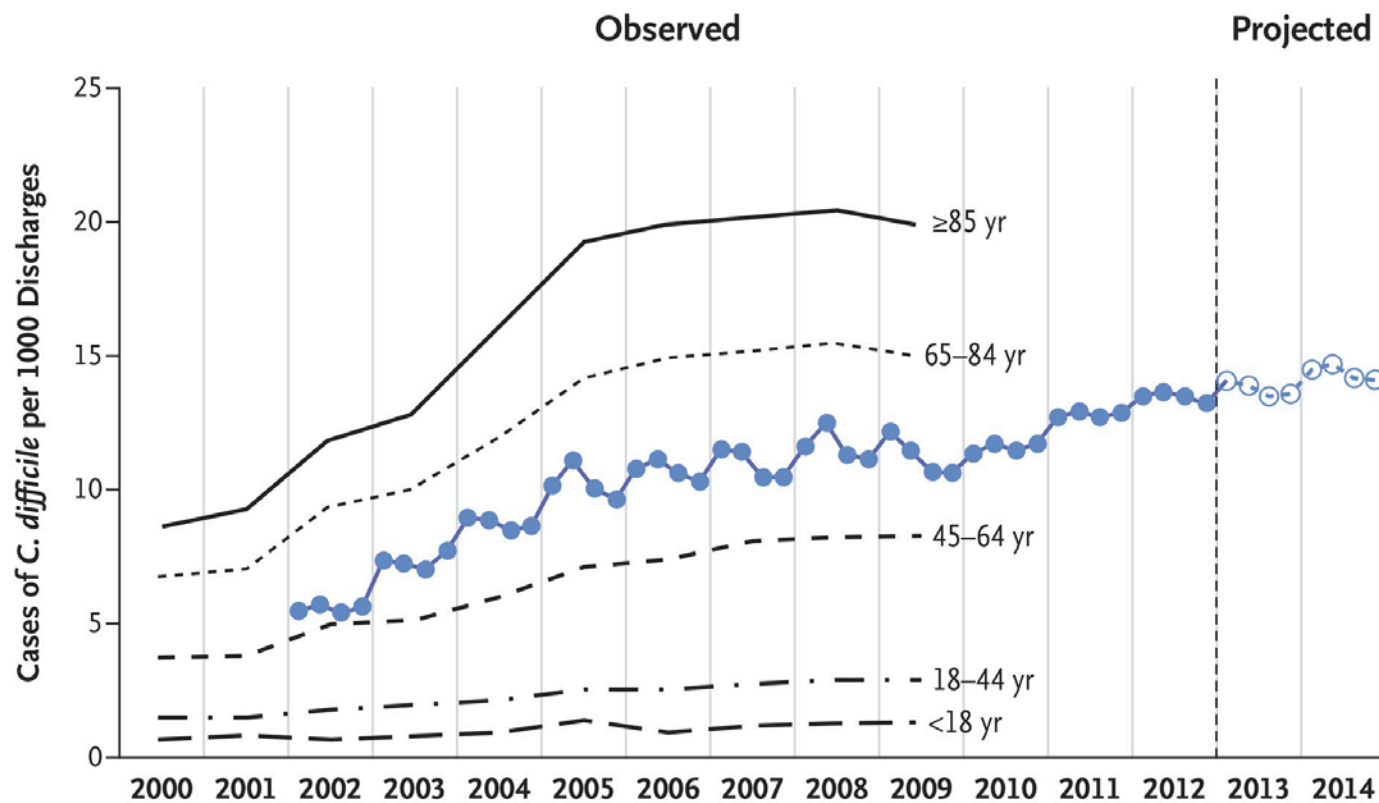


***C. difficile* Infection**

Health Burden

- Leading cause of nosocomial infection in the US, and community born outbreaks are on the rise (25%)
- Commensal bacterium in 2-5% of the population, likely much higher in health care and daycare workers
- Colonizes a majority of infants, however most are asymptomatic (?lack of toxin binding receptors)
- Rising prevalence due to broad spectrum antibiotic use, emergence of hypervirulent strains (B1/NAP-1/027) poor infection control, older patients, immunocompromised
- Not a required public health reportable disease, so we don't know actual or local incidence rates

Incidence of Nosocomial *Clostridium difficile* Infection.



***C. difficile*-Epidemiology**

- Acquired in 13% hospitalized for 2 weeks
- Acquired in 50% hospitalized for >4 wks
- After initial treatment with Metronidazole, Recurrence rate is 20-25%, this increases to 40% then > 50% with subsequent recurrences.
- PPI use doubles the risk of *C. diff* infection

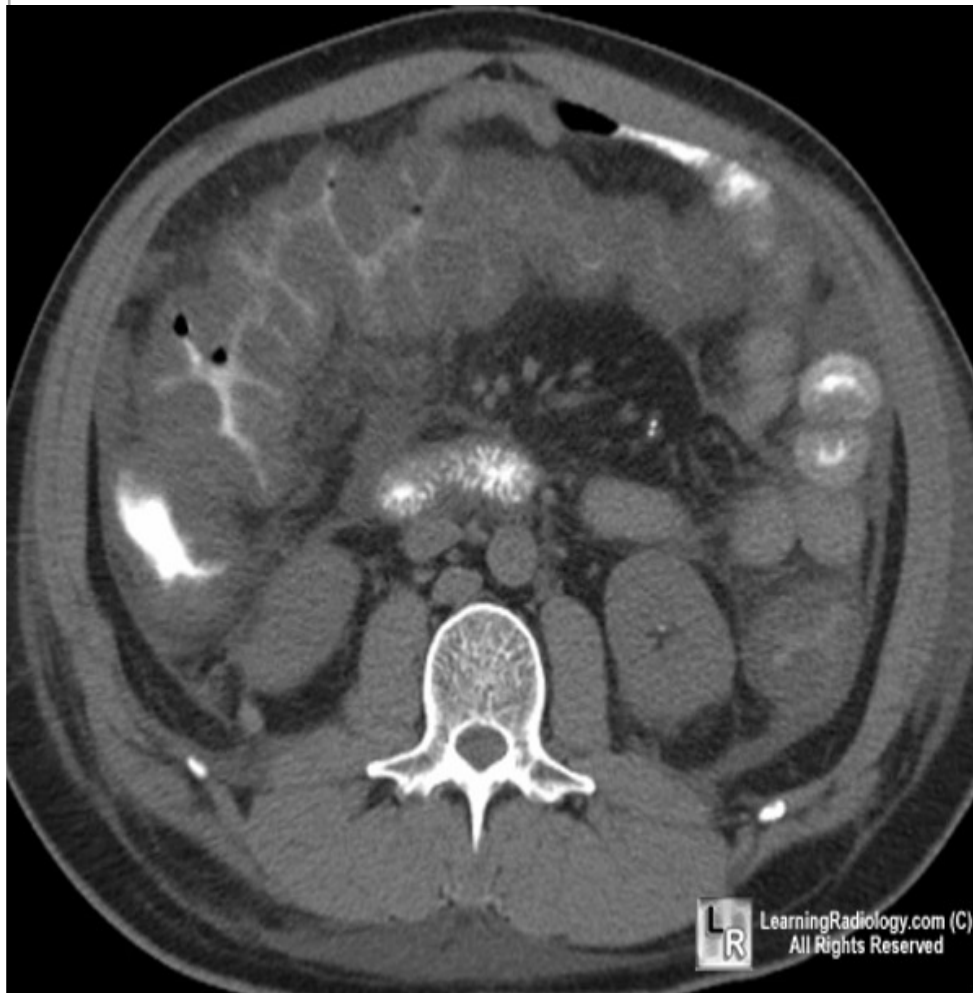
C. difficile - Spectrum of Disease

- Mortality rates have risen over 400% in recent years, at 250,000 cases/yr, and **15,000 deaths annually in US**
- Half infections occur in persons less than 65 yrs old, however, 90% deaths are in those over 65 of age
- Patients may have lingering mild diarrhea to dehydration requiring hospitalization
- Toxic megacolon is the most severe complication, incidence 1-5%; however very high mortality without surgery, about half subjects die despite subtotal colectomy

***C. Difficile* Diagnosis**

- Send stool (up to three samples) for cytotoxin A and B
- CT with hallmark bowel wall thickening $>4\text{mm}$ is 70% sensitive and 93% specific
- Distinctive stool odor that seasoned nurses recognize, and “sniffer dogs” can be trained to diagnose *c-difficile*
- Stool PCR (since 2009), now the preferred method for diagnosis

Radiographic Signs in Severe Colitis



Pseudomembranous Colitis

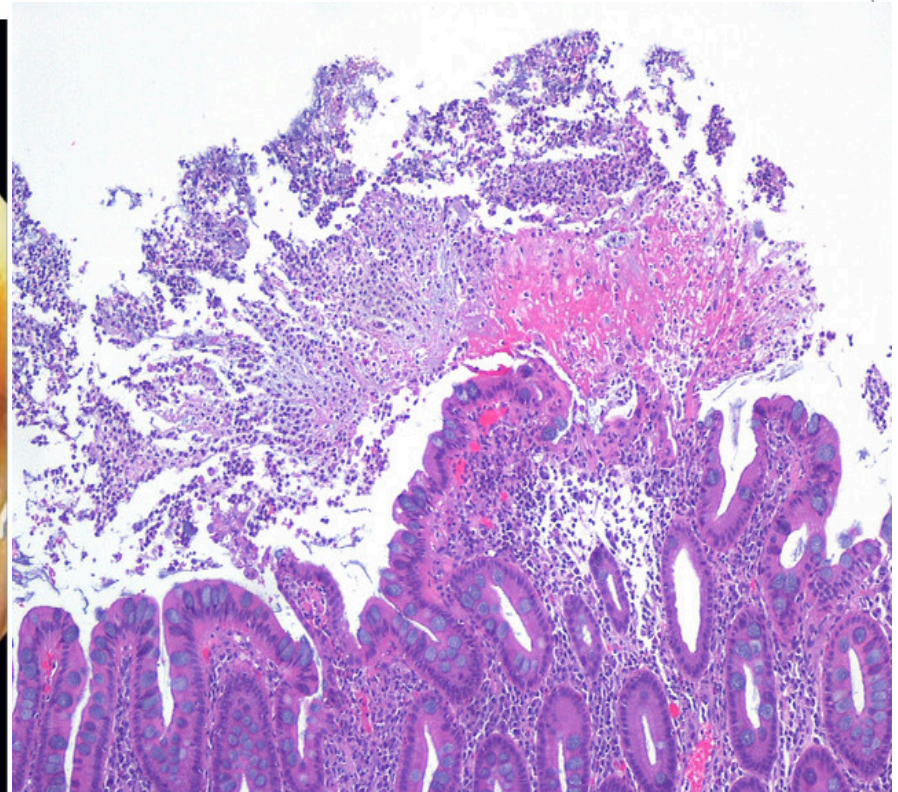
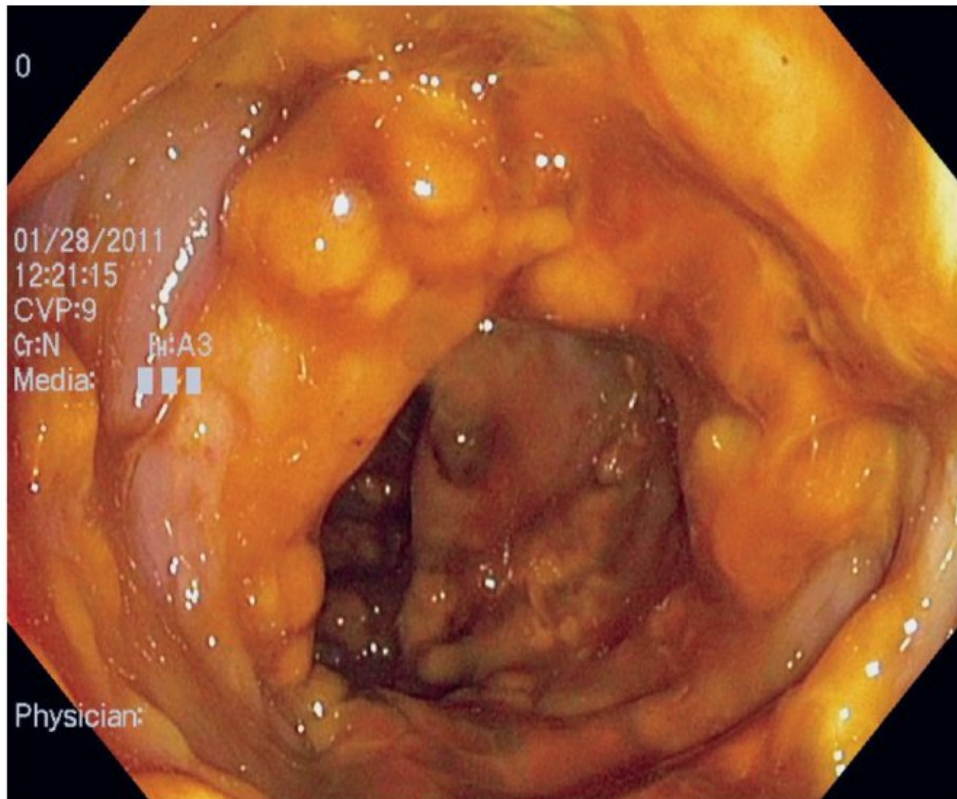


Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

Class	Association with <i>C. difficile</i> 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

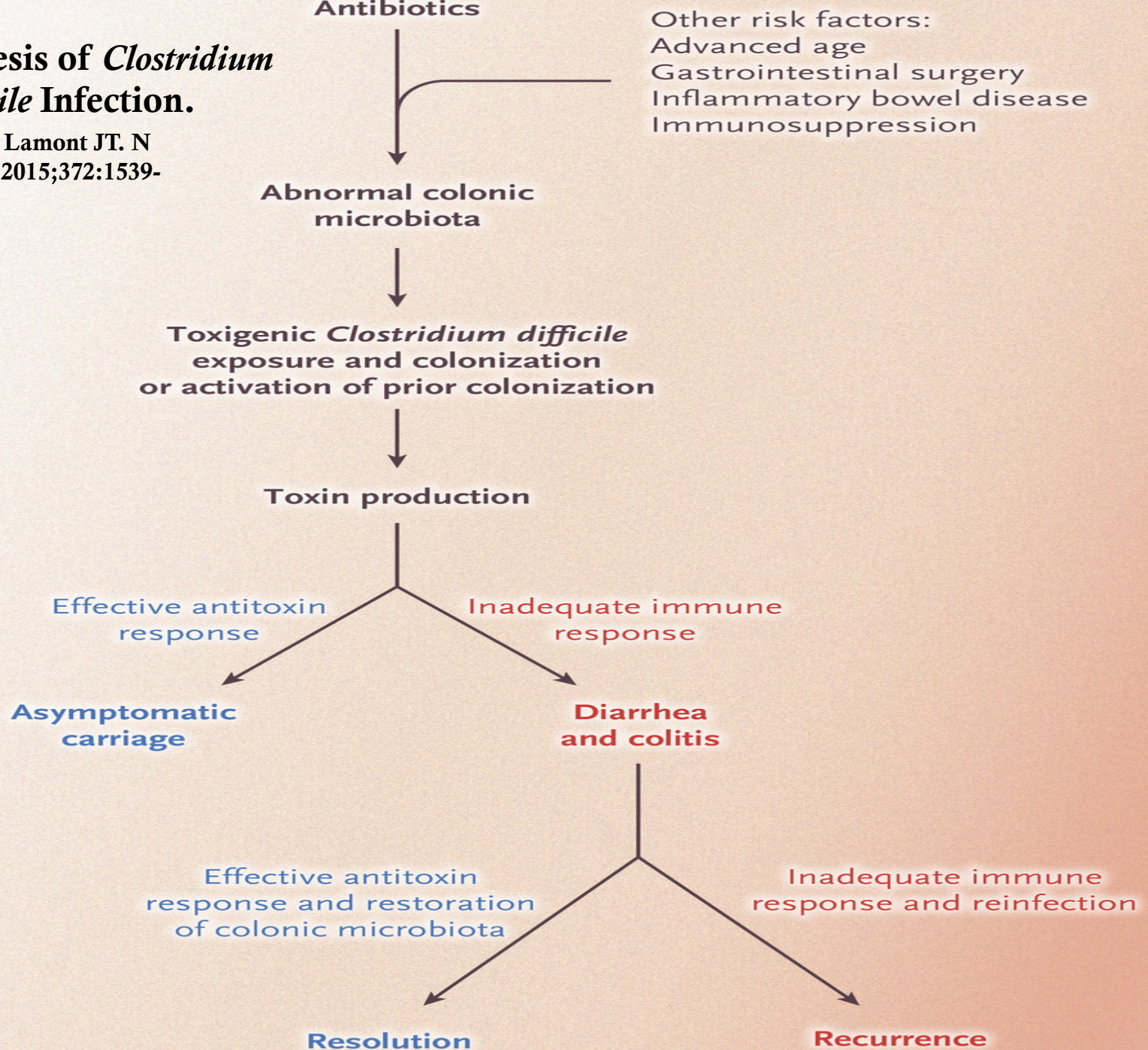
***C. difficile* Prevention Infection Control Stewardship**

- Test for *C. difficile* in patients with diarrhea
- Isolate patients with *C. diff*, notify transferring facilities
- Wear gloves and gowns then discard when you leave the patient's room before touching anything else
- **HAND SANITIZERS AND HAND WASHING IS NOT ADEQUATE**
- Clean surface with BLEACH or EPA approved spore killing disinfectant
- Pulsed xenon UV disinfection (new technique, expensive)
- Reduce antibiotic use whenever possible

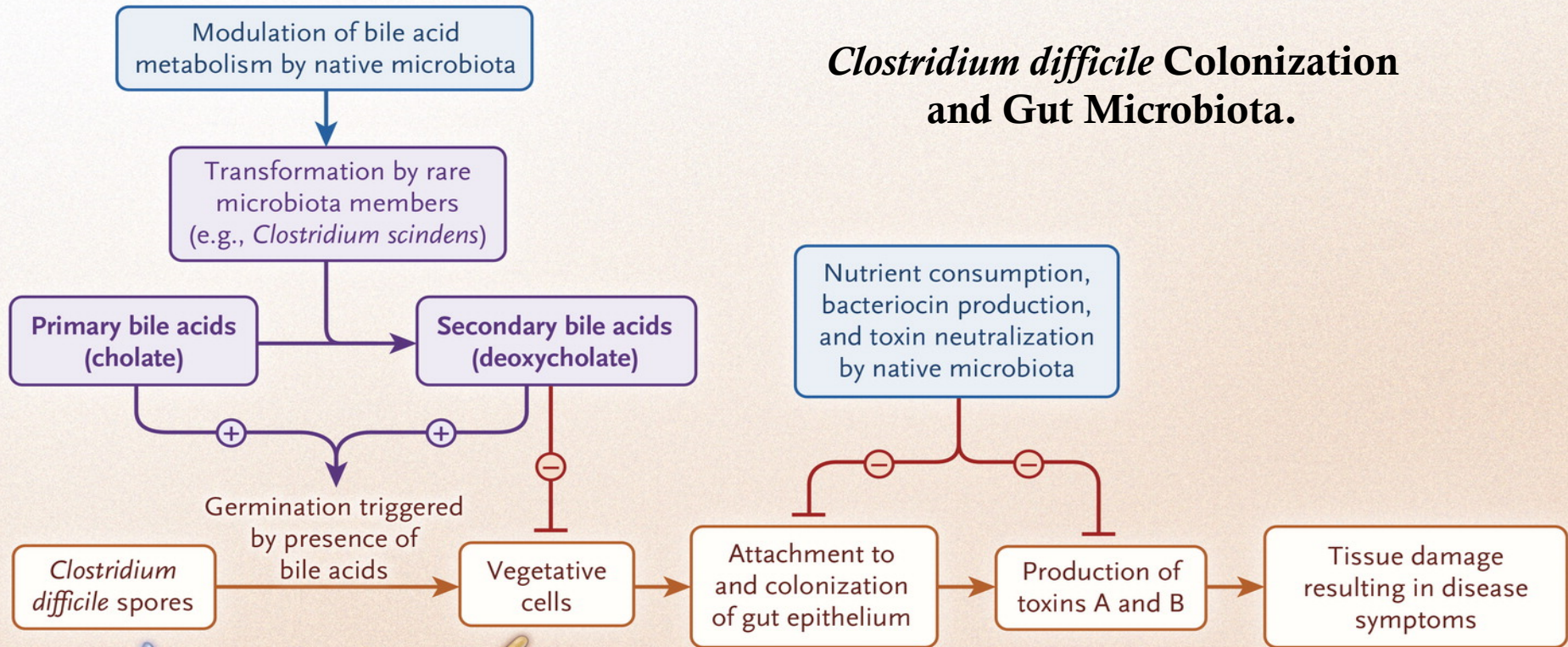
Results in 50% reduction of transmission

Pathogenesis of *Clostridium difficile* Infection.

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



Clostridium difficile Colonization and Gut Microbiota.



Human Microbiome

Project NIH-2007

Catalogue Microbial genes/species
DNA sequencing quantitative PCR

Body = 50 phyla, GI tract = 10

90% bacteroidetes and firmicutes

10% acinetobacter, proteobacteria,
fusobacteria, verrucomicrobia,
cyanobacteria, spirochetes, others

Microbiome = Ten trillion cells:
10x Eukaryotic cells in the body,
most reside in the GI tract

- **Eubiosis:** Well balanced, correct diversity and quantity for health

- **Dysbiosis:** Reduced load, lower representation of bacteroidetes and firmicutes, with higher representation of acinetobacteria and enterobacteria, also more adherent and invasive species including E.-coli, campylobacter, mycobacteria.

- **Specific diseases are associated** with reduced commensal or beneficial microbiota, and more pathogenic microbiota:

Inflammatory Bowel Disease
Obesity/ Metabolic Syndrome
Gastric and Colorectal CA

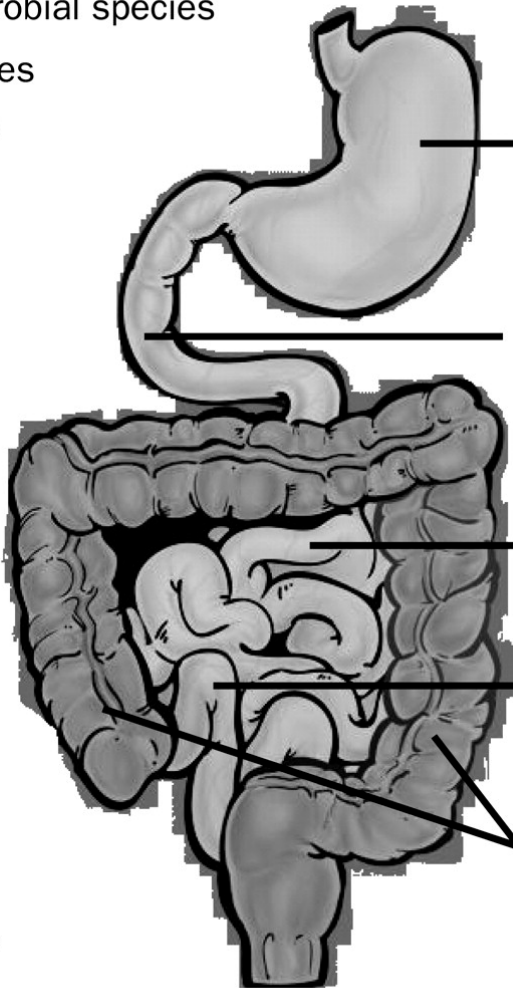
Gut Flora: Features and Functions

500-1000 Microbial species

Aerobes



Anaerobes



Stomach

$<10^2$ cfu/mL
pH, 1-2

Digestion and
acid secretion

Duodenum

10^{1-3} cfu/mL
pH, 6-7

Small
intestine

Digestion and absorption
of carbohydrates, proteins,
and fats

Jejunum

10^{3-4} cfu/mL
pH, 6-7

Ileum

10^{7-9} cfu/mL
pH, 6-7

Absorption of bile acids
and vitamin B₁₂

Colon

10^{10-12} cfu/mL
pH, 5-7

Large
intestine

Absorption of water,
electrolytes, and short-chain
fatty acids

Fecal Microbial Transfer (FMT)

Historical Perspectives

- 4th century China Ge Hong gave fecal suspension by mouth for diarrhea “yellow soup”
- 17th century veterinary medicine
- WWII Germans observed North African Bedouins ingesting camel dung for dysentery; led to use of probiotic *bacillus subtilis*
- 1958 Eiseman gave retention enema for pseudomembranous colitis
- 1981 Bowden used enemas in 16 pts
- 1983 Schwan first case *C. diff* treated with FMT



FMT outcomes show improvement or cure

GI/Metabolic Diseases

- Crohn's disease
- Metabolic Syndrome
- Irritable bowel Syndrome
- *C. difficile* infection

Non-GI Diseases

- Parkinson's disease
- Autism
- Multiple sclerosis
- Fibromyalgia/Arthritis

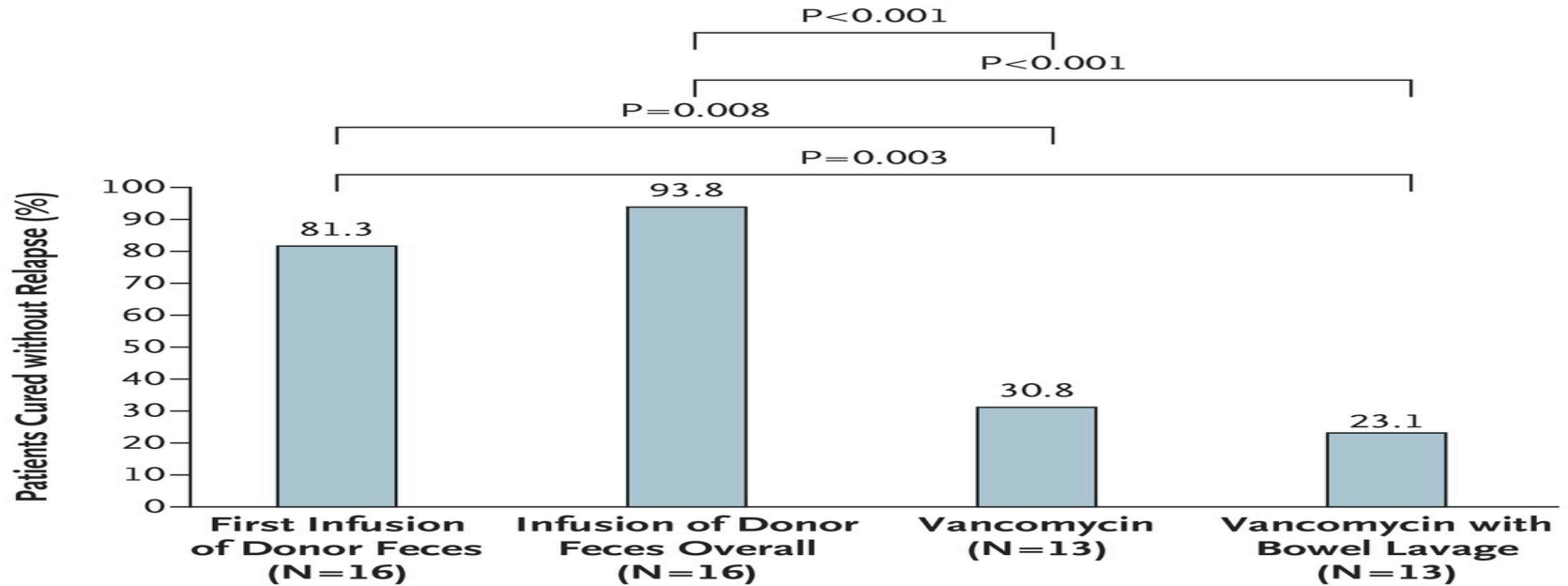
FMT in chronic or refractory *C. difficile* colitis

- Abx treated mice infected with *C. difficile* develop chronic dysbiosis; opportunistic pathogens similar to humans.
- Over 376 human cases by 2011, 91% cure rate by FMT
- *C. diff* recurrence very low; microbiota transplant persists
- No serious adverse events, FDA approved
- Randomized controlled trial halted as FMT was 3 times more effective than abx in curing recurrent *C. diff* (N Engl J Med January, 2013, Vol 368, No.5, 407-415)

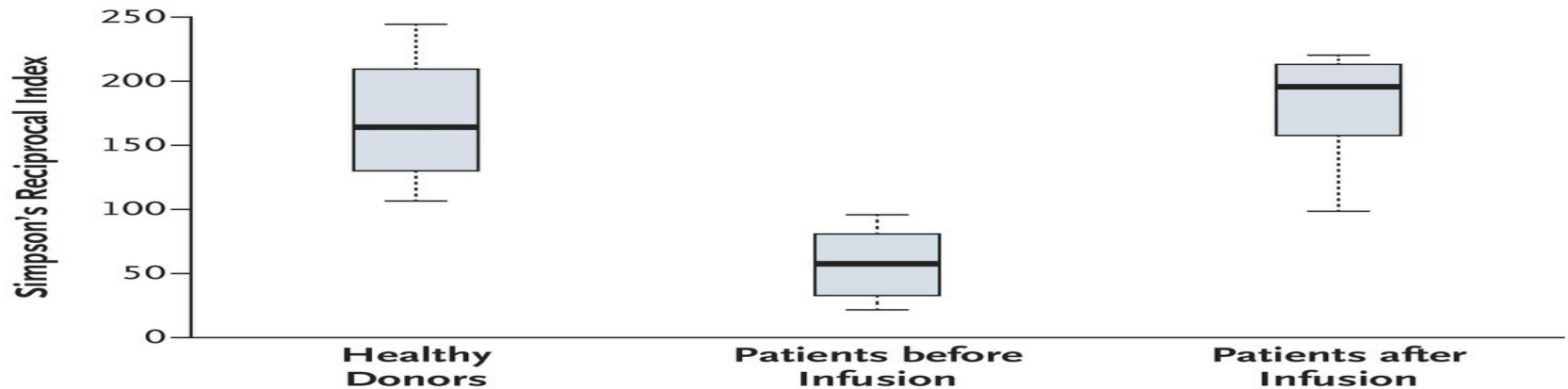


Rates of Cure and Changes to the Microbiota after Fecal Microbial Transplantation for Recurrent *Clostridium difficile* Infection.

A Rates of Cure



B Microbial Diversity



Our Phones were Ringing!

Got poo?

Masz kal?



FMT-Technique

- Fresh specimen <8 hours ideal, refrigerate or freeze in small plastic container. Anaerobes are devitalized in oxygen.
- Mix with non-bacteriostatic saline, about 50 grams feces with 250-300cc diluent
- Blenderize, shake or stir, then filter through gauze to remove large particles that might clog the endoscope channel
- Recipient takes large volume gavage, stops abx 1-3 days prior. Give loperamide prior to or just after procedure to help with retention
- Deliver with syringe via accessory channel in cecum or ileum. Keep the patient supine as long as possible. NG delivery not as successful.

FMT- Logistics

- Donor screening \$300; may not be covered by insurance
- The doctor or the patient must know the donor
- Must have informed consent document stating that outcomes are uncertain, and transmission of infection is a concern
- Only available at major Universities
- Patients are performing transplants on each other

FMT Donors, Related or Not?

- **Screen stool for ova and parasites, giardia, *C. diff*, serum for HIV, Hep A,B, C, syphilis**
- **Exclude if history of gastric or colon cancer, H pylori, high risk behaviors, body piercing or tattoos in prior 3 months**
- **Exclude if abx use or hospital worker within 3 months, inflammatory bowel disease, neurological disease**



Clinical Case One

- 60 year old male with Chronic Hepatitis C and alcohol abuse, recently diagnosed with renal cell carcinoma, electively admitted for nephrectomy. Post-op complicated with hypoxia, acute kidney injury, MRSA; treated with linazolid and levofloxacin.
- Hospital day 6: profuse diarrhea, stool *C. diff* positive, WBC 48K, BP 82/51, pulse 121, temp 100. Abdomen markedly distended with hypoactive bowel sounds. CT abdomen with dilated, air and fluid filled thick walled bowel loops, “toxic megacolon”
- Colorectal surgery was consulted for emergency colectomy

Case One- Outcome

- Emergency colectomy, with ileostomy
- Post op continued IV Metronidazole, po Vancomycin
- Remained septic
- Expired day 23



Clinical Case Two

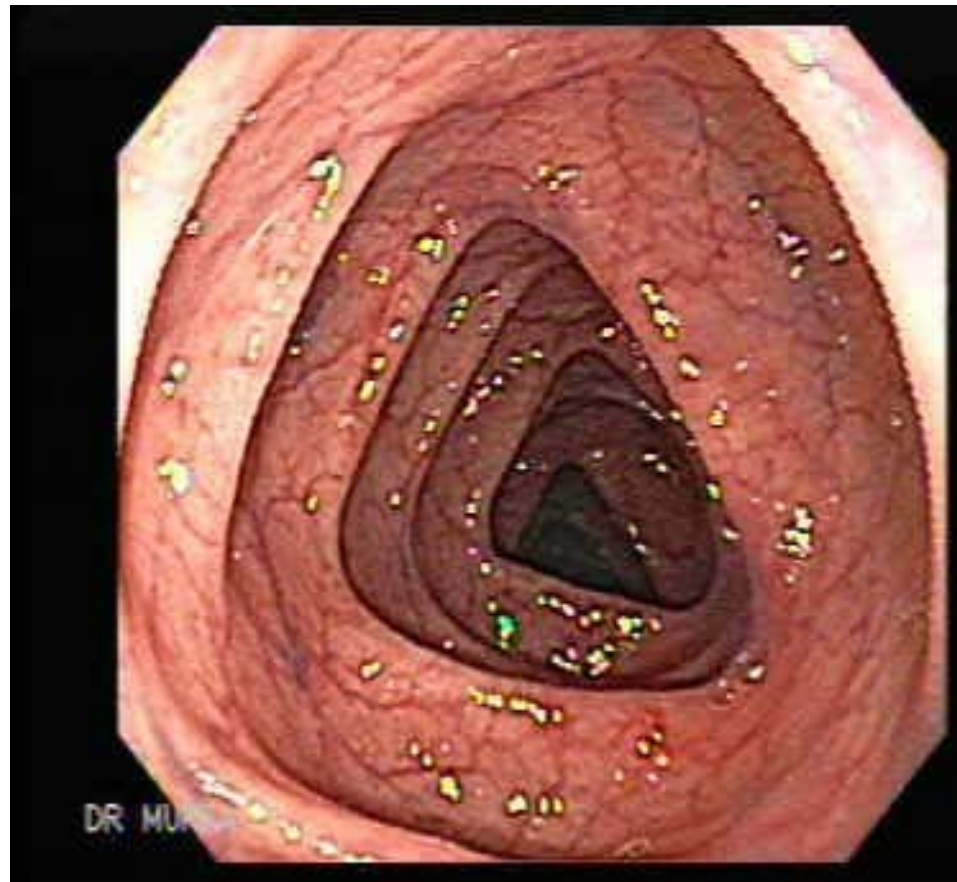
- 75 year old female with NASH cirrhosis, ascites, recurrent *C. difficile* with multiple hospitalizations on antibiotics over 4 months, now admitted with >10 watery stools, profound weakness, tender abdomen with guarding but no rebound. T 102.5, BP 90/50, HR 110
- WBC 22K, creatinine 3.25, abdominal plain films with featureless loops of fluid filled bowel, no free air
- Treatment: Oral Vancomycin 500mg QID, IV Metronidazole 500mg TID, Florastor (probiotic) Cholestyramine 4grams QID

Case Two – Hospital Course

- Despite treatment diarrhea and fevers persisted. Abdominal CT scan showed thickened distal colon bowel wall. A flexible sigmoidoscopy revealed pseudomembranes
- Trial of fidaxomicin 200mg BID, continued probiotics and cholestyramine
- Colorectal surgery opined that surgical risk outweighed benefits (no peritoneal signs or toxic megacolon)
- What's the next best treatment option?

Case Two – Outcome

- 75y female with recurrent *C. diff*, medical comorbidities precluding surgery
- FMT donor: husband
- Recovered to health baseline in 7 days
- C- scope normal at 2 weeks



FMT: One Big Crap Shoot?

- Potential liability/disease transmission
- Donor pool?
- Is it safe in critically ill patients with mucosal ulcerations? Sepsis? Toxic megacolon? Immunosuppression?



The Future of FMT Stool Bank vs. Synthetic?



Preferred by 59% of consumers over strawberry

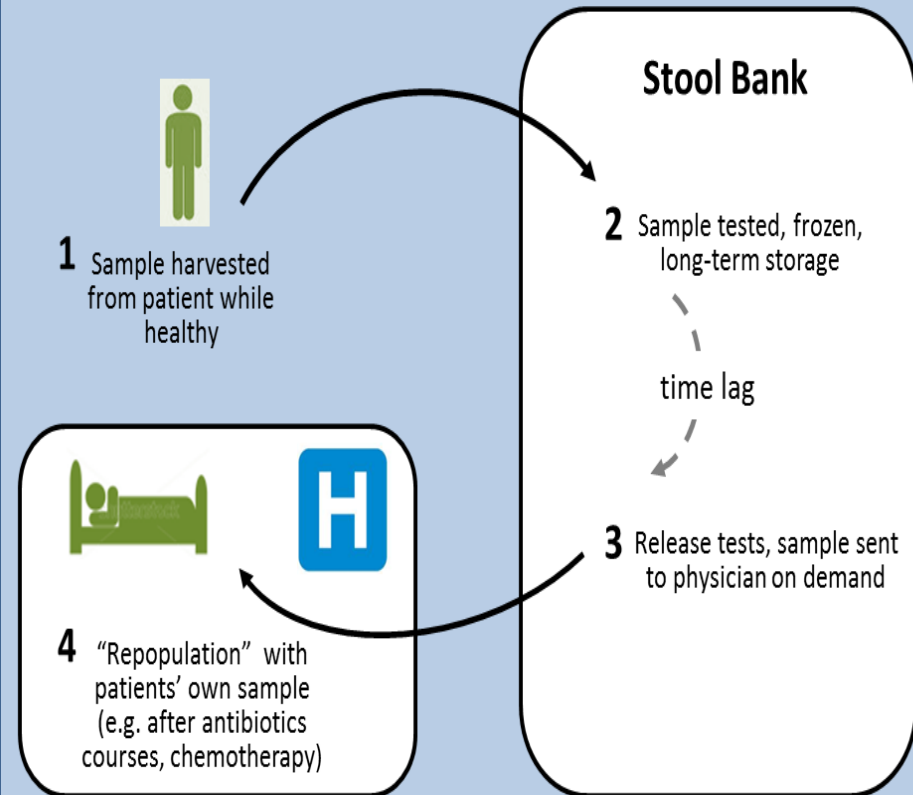


Figure 1c: Preemptive banking

Targeted “Bacterotherapy” (preferred term for FMT)

- Administration of nontoxigenic *C. difficile* (M3) strain for prevention of recurrent infection (randomized, double blind placebo controlled)
- 173 patients, 44 study centers in US and Canada
- Patients with initial or first recurrence of *C. difficile*
- Oral spores given (several doses and duration vs. placebo)
- Recurrent infection was markedly reduced if the subject was successfully colonized with the non-virulent strain (30% vs. 11%)

Immunotherapy for *C. difficile*

- Currently underway randomized placebo controlled vaccine studies: 3 doses toxoid vaccine vs. placebo, with 3 year follow up
 - ?primary vs. secondary prevention
 - ?lessen severity of clinical disease
- Enteragam TM Serum derived bovine immunoglobulin (IgG)- “medical food” FDA approved as orphan drug showing improvement in barrier function of the gut, maintenance of gut homeostasis.
 - Used for diarrhea and malabsorption
 - ?unclear role in *C. difficile* (clinical trials pending)

Probiotics and Gut Health

- Improve transit time, relieve constipation
- Improve absorption of nutrients
- Alter microbial environment by increasing “good” commensal organisms
- No convincing role for prevention of *C. difficile*



Be Kind to your Microbiota!



Summary: Treatment for *C- Difficile* Infection

- Stop offending antibiotic and avoid antibiotics if possible
- Treat for 10-14 days: Metronidazole 500mg BID or Vancomycin 250mg QID; higher doses and duration up to a month for recurrences, or switch to fidaxomicin 200mg BID for 10 days
- Probiotics *saccharomyces boulardii*, *lactobacillus acidophilus* (or Greek yogurt) augment microbiota and reduce duration of diarrhea
- Cholestyramine used to bind enterotoxin A and B (4grams BID)
- IV immunoglobulin for immunocompromized hosts, consider oral IgG as adjunct or after initial antibiotic treatment
- Surgery for total or partial colectomy in severe/life threatening cases
- FMT for recurrent infection (emerging as BEST CHOICE)



Microbiota

- Hippocrates said “All disease begins in the gut”
- Today he might say “Health is determined by the microbiota in our gut” (L. Brandt)
- Depending on your status, you may or may not want to order the yellow soup