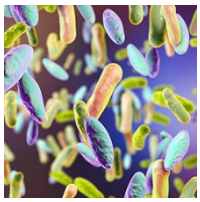

Best Practice Update on *Clostridium difficile* Infection: Focus on Prevention, Treatment and Recurrence

Proceedings of a Live Webinar

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- Kevin Garey
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- Krishna Rao
  - Merck, Inc.: Research support (Co-investigator)

On average how many patients with *Clostridium difficile* infection (CDI) do you provide care to each month?

a. None-I am not directly involved in patient care
b. 1-10 patients/month
c. 11-20 patients/month
d. 21-30 patients/month
e. More than 30 patients/month

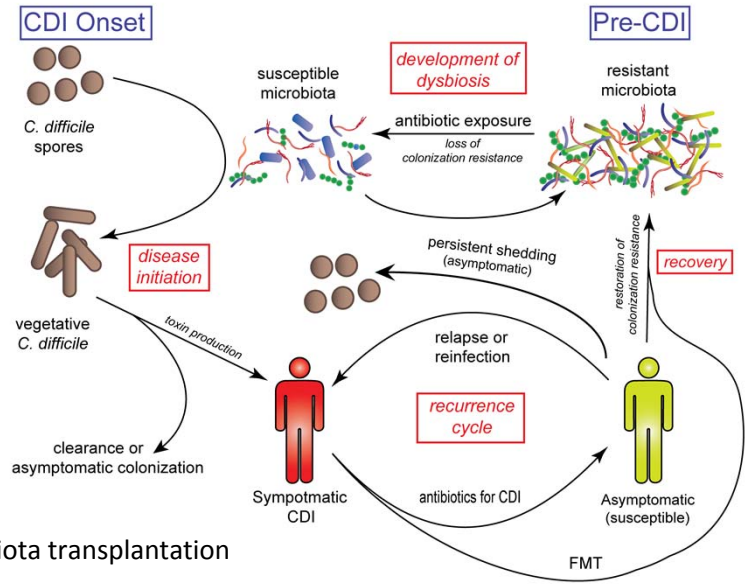
Learning Objectives

- Review updates of *Clostridium difficile* infection (CDI) guideline recommendations
- Apply antibiotic stewardship strategies for the primary prevention of CDI
- Discuss treatment of CDI with a focus on sustained clinical response

Clostridium difficile infection (CDI)

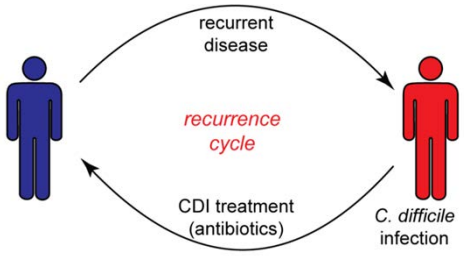
- Caused by gram-positive, spore-forming bacillus
- Acute, infectious colitis with features ranging from asymptomatic colonization to diarrhea to fulminant colitis and death
- Diagnosis = compatible syndrome + organism in stool
- 450,000 cases/year
- 35,000 deaths/year
- $1.5 billion/year

Pathogenesis of CDI



FMT=Fecal microbiota transplantation

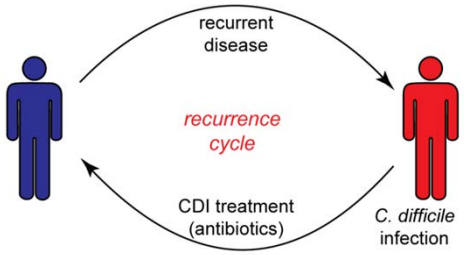
Recurrent Disease



- Definition: initial resolution of symptoms followed by clinical re-emergence with positive testing >2 weeks but <8 weeks from the index episode
- Happens in up to 25%!

Gough E et al. *Clin Infect Dis*. 2011; 53:994-1002.

Recurrent Disease



- 2nd Recurrence: 30-45% of 1st
- 3rd Recurrence: 45-60% of 2nd
- ≤5% of all pa. ents → chronic, recurrent pattern
- No universal treatment algorithm

Gough E et al. *Clin Infect Dis*. 2011; 53:994-1002.

Who should be tested: Symptomatic patients

- Diarrhea
  - ≥3 loose bowel movements (BMs)/24 hours
  - No alternate explanation
- Ileus + leukocytosis
- Colitis on imaging
- Acute abdomen with bowel wall thickening
- Toxic megacolon
- Pseudomembranes on endoscopy

Who should not be tested?

- Asymptomatic Patients
- Patients with Colonization
  - 60-70% of infants
  - 3% of healthy adults
  - 20-50% of adults receiving LTAC
  - Treatment not recommended
    - Doesn't decrease risk of CDI
    - Doesn't affect epidemiology or spread

LTAC=Long term acute care

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

Who should not be tested?

- While on therapy
- Immediately following therapy (prolonged shedding)
  - Up to 50% of patients 6 weeks after completion of therapy
  - 10-20% become long term carriers
  - Repeat testing for “cure” and retreatment not recommended during this period unless accompanied by symptoms

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

Who should not be tested?

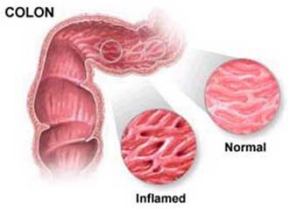
- Post-infectious IBS

- Long-term asymptomatic colonization following CDI
  - Occurs following treatment and recovery, transient irritable bowel syndrome (IBS) symptoms in 35%
  - Rarely persists as post-infectious IBS
  - Is difficult to distinguish from recurrent CDI

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

Controversy: Inflammatory Bowel Disease

- Asymptomatic carriage common (20-50%)
- CDI can mimic a flare
- CDI can trigger a flare
- Do you treat CDI, flare, or both?
  - Gastroenterologists divided evenly
  - Ben-Horin S et al. *Clin Gastroenterol Hepatol*. 2009; 7:981-7: combination therapy with worse outcomes



Berg et al. *Inflamm Bowel Dis*. 2012; 19:94-204. Yanai H et al. *Inflamm Bowel Dis*. 2011; 17:1540-6.

Differential Diagnosis

- **Antibiotic associated diarrhea**
- *Klebsiella oxytoca*
- **Post-infectious IBS**
- **IBD**
- Celiac disease
- **Ischemic colitis**
- Collagenous colitis
- Cytomegalovirus (CMV) colitis
- Routine enteric pathogens
- Parasitic pathogens
  - right risk factors or exposures (Giardia / Cryptosporidium)
- Carcinoid syndrome/other hypermotility states

How to test: Not all stools

Some labs only test diarrheal stool

Table 2. The Brecher Guidelines

Observation	Response
Look at the stool specimen	If it ain't loose, it's of no use
Put a thin lab grade stick in the specimen	If the stick stands, the test is banned
	If the stick falls, test them all

Brecher SM et al. *Clin Infect Dis*. 2013; 57:1175-81.

How to test: Different assays

- Can find organism, toxin, genes, or a combination
- Organism:
  - GDH EIA + toxin EIA
  - Toxin B Gene PCR
  - GDH EIA alone not sufficient (nontoxigenic strains)
- Toxin: toxin EIA (rarely used alone now and **not recommended**)

GDH=Glutamate dehydrogenase; EIA=Enzyme immunoassay; PCR=Polymerase chain reaction

Brecher SM et al. *Clin Infect Dis*. 2013; 57:1175-81.

NAAT/PCR

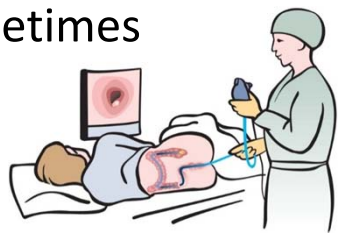
- Can be used to detect toxigenic *C. difficile*
- Performance characteristics good
- Sensitivity/specificity high (>90%)
- Does not detect toxin
  - Colonization vs. true disease?
  - Better prognosis?
  - Too sensitive? Real disease specificity?
- **Should be rejecting formed stools if this is your only test**

NAAT=Nucleic acid amplification test

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

Indications for Endoscopy with Biopsy

- Evaluating for other diseases on differential
- High clinical suspicion for *C. difficile* with negative laboratory assays
- Ileus or minimal diarrhea
- Visualization of pseudomembranes sometimes insufficient
  - Get histology!



Diagnosis Summary

- Lab testing alone will not make the diagnosis
- Must integrate results with clinical picture
- Test only symptomatic patients
- Don't "test for cure" and be aware of post-infectious IBS
- Repeat testing usually not indicated
- Endoscopy may be helpful when uncertainty exists or with ileus

1. Treatment for CDI: First Steps

- Don't treat asymptomatic patients!
  - Uncertain if colonization treatment has any effect
  - Treatment may increase colonization/spread!
  - Prophylaxis not well studied
- Stop other antibiotics
  - 15-20% clinical success in mild CDI (alone!)
- Stop proton pump inhibitors (PPIs) and antimotility agents
- Stop / alter use of binding agents (cholestyramine)
  - Can bind vancomycin/ metronidazole!

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

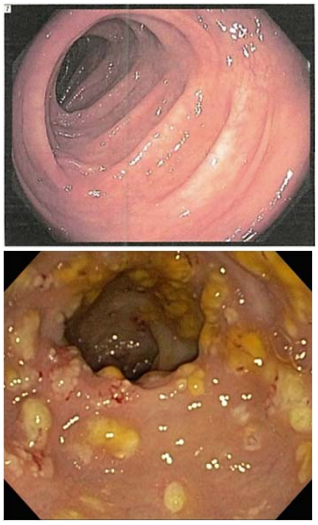
2. Classify Episode

- Note history of CDI
  - 1st or subsequent recurrences, alters therapy
  - Would consider vancomycin +/- taper or fidaxomicin
  - May need to plan / coordinate outpatient care for long courses

Bagdasarian N et al. *JAMA*. 2015; 313:398-408.

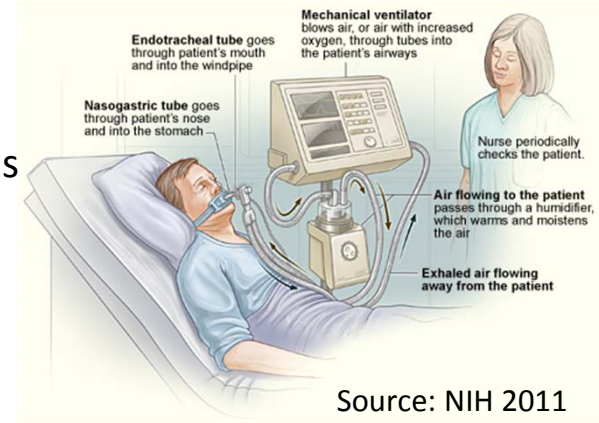
3. Classify CDI Severity

- Severe CDI Clinical Features
  - IDSA criteria
    - WBC >15,000 cells/mL
    - Acute kidney injury (AKI) (SCr >1.5 x premorbid level)
  - Other criteria
    - Age >65 years
    - Albumin <2.5 g/dL
    - Fever
    - Colonic thickening / Severe abdominal pain
    - Pseudomembranous colitis



3. Classify CDI Severity

- Complicated CDI
  - IDSA criteria
    - Hypotension / shock / sepsis
    - Ileus / megacolon
  - Other features
    - Peritonitis
    - Bowel perforation



Source: NIH 2011

4. Select Treatment Based on Recurrence and Severity

Clinical Definition	Supportive Clinical Data	Recommended Treatment	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	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	Strong/Moderate

✦=new in 2018

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

No recommendation for the following

- Probiotics for prophylaxis or treatment
- Antibiotic prophylaxis
- Rifaximin
- Tigecycline
- Nitazoxanide
- Bezlotoxumab (although it was approved by FDA at the time the IDSA/SHEA guidelines were finalized)

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

Surgery Consult Indications?

- Complicated or suspected complicated CDI
- Clinical deterioration
  - Worsening abdominal distention/pain and/or peritonitis
  - Bowel obstruction
  - Intubation
  - Vasopressor requirement
  - Mental status changes
  - New or worsening acute kidney injury
  - Worsening lactate > 5mmol/L
  - Persistent or worsening leukocytosis (WBC ≥35,000 cells/mm^3)
  - Hirschsprung's disease
- Failure to improve with standard therapy within 5 days as determined by resolving symptoms and physical exam, resolving WBC/band count

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

Surgery Consult Outcome

- Loop ileostomy + anterograde vancomycin enemas
  - New colectomy-sparing procedure
  - Non-inferior to colectomy
- Full/partial colectomy

Neal MD et al. *Ann Surg*. 2011; 254:423-7.

The Best Defense is a Good Offense

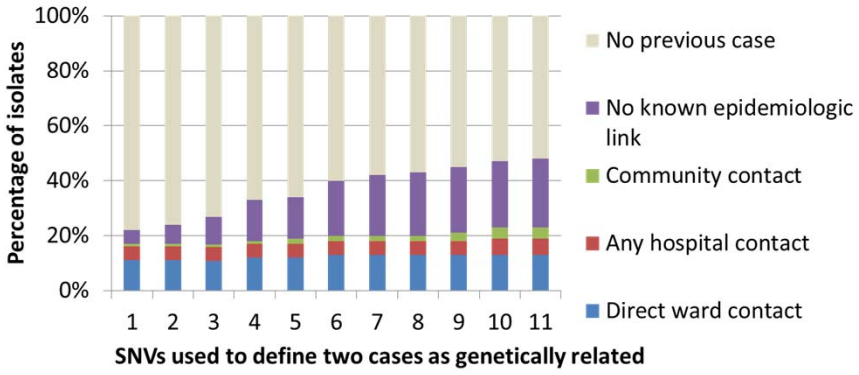
How to prevent CDI in the first place?

C. diff and Antibiotics

Is exposure to *C. diff* a rare (chance) event with a particular 'hypervirulent' strain?

How much antibiotic exposure do you need to be at risk (and which antibiotics)?

How do patients get infected in the first place? Where are *C. diff* strains coming from?



- Leeds, England: Whole genome sequencing of 1223 cases of CDI. This allows for a highly discriminatory way to see where *C. diff* strains are coming from.

Eyre DW. *N Engl J Med*. 2013; 369:1195-205.

Is *C. diff* ubiquitous in our environment?

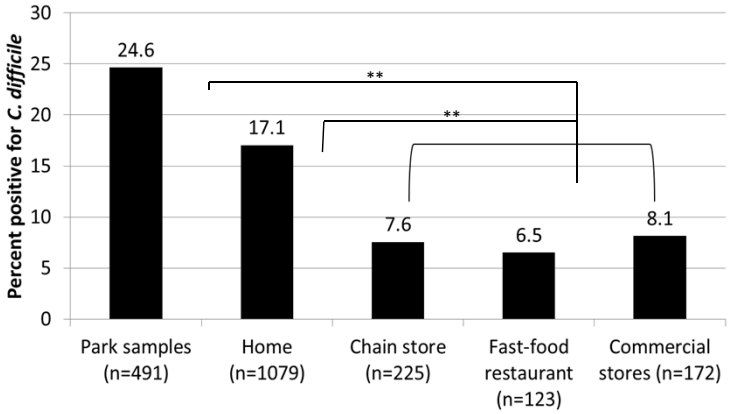
- We hypothesized the community environment may contain a large burden of *C. diff* contamination
- We recently completed a large field study to assess community environmental contamination of toxigenic *C. diff*

Results, number of samples

Isolate source	Number
Environmental	
Home	1173
Chain stores	230
Fast-food restaurants	125
Parks	540
Clinical isolates	613

Alam MJ et al. *Open Forum Infect Dis* 2017; 4(1): ofx018.

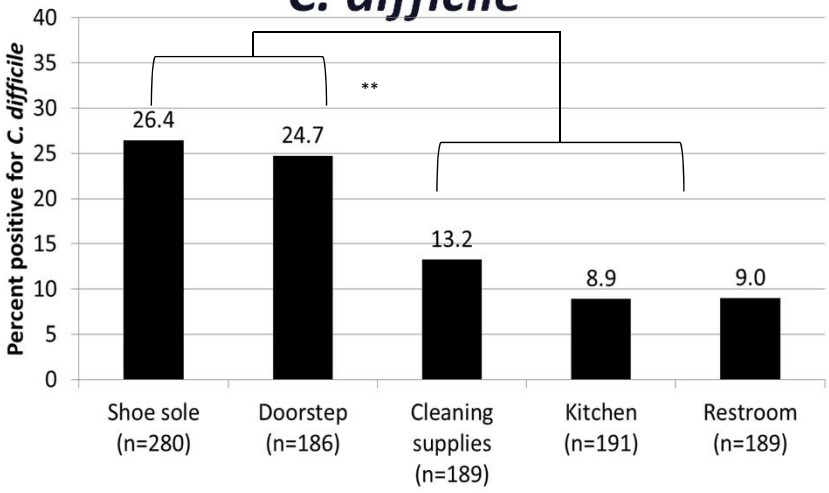
Community environmental contamination of toxigenic *C. difficile*



**p<0.001 compared to either chain stores, fast-food restaurants, or other commercial stores

Alam MJ et al. *Open Forum Infect Dis*. 2017; 4(1):ofx018.

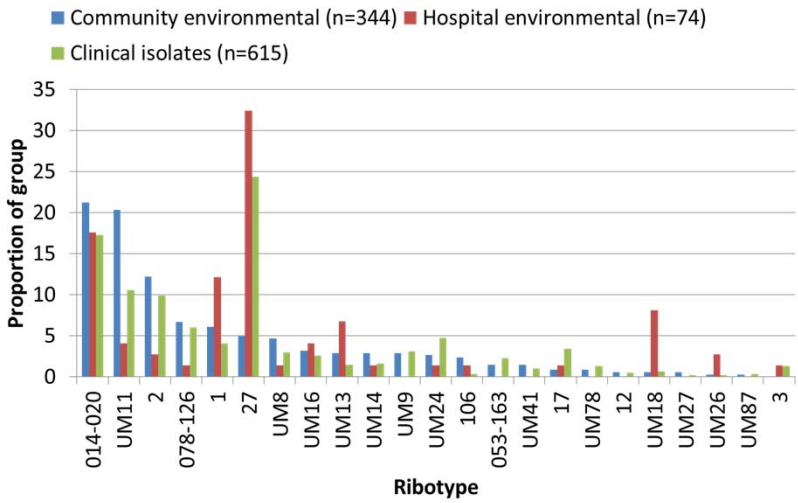
Home environmental contamination of toxigenic *C. difficile*



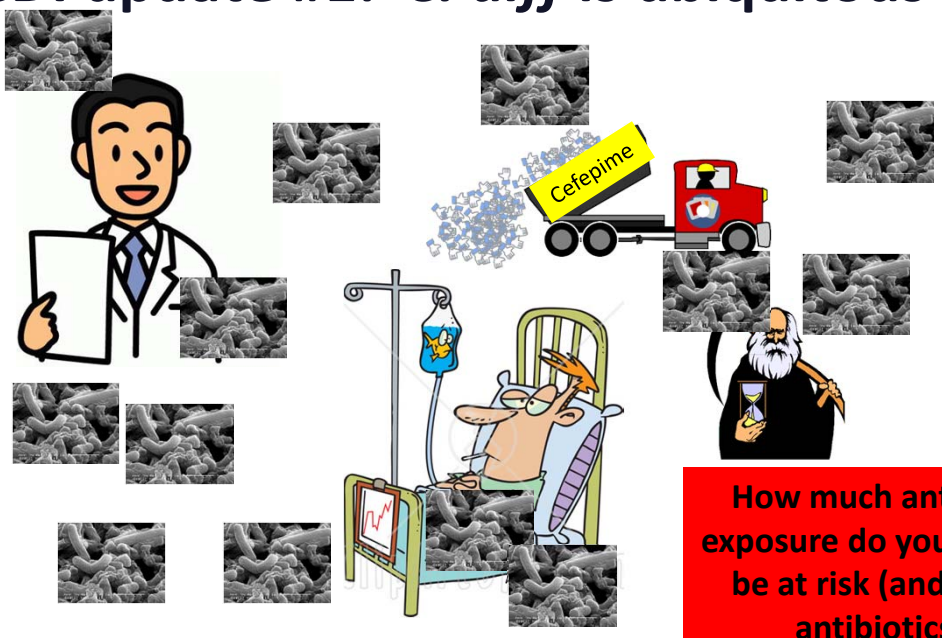
**p<0.001 comparing shoe soles and doorsteps to cleaning supplies, kitchen and restroom samples

Alam MJ et al. *Open Forum Infect Dis.* 2017; 4(1):ofx018.

Ribotype distribution of clinical vs. environmental *C difficile* isolates

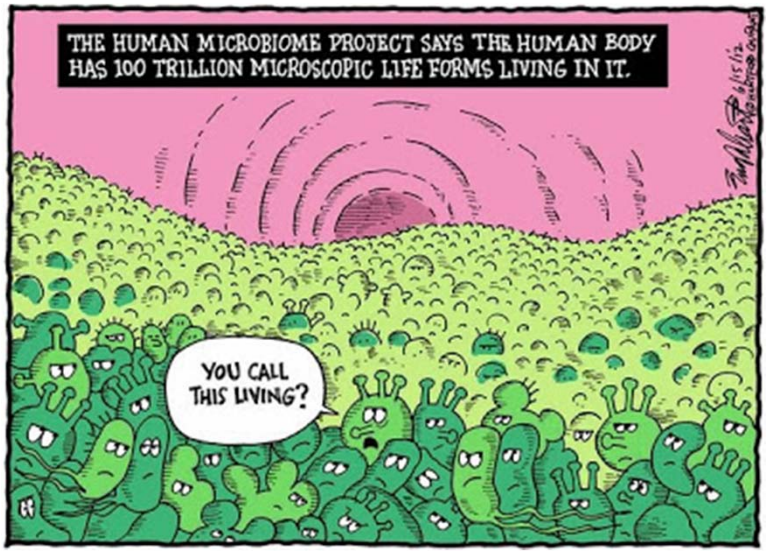


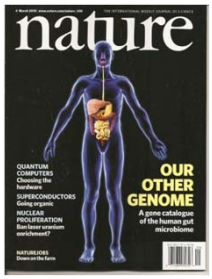
CDI update #1: *C. diff* is ubiquitous



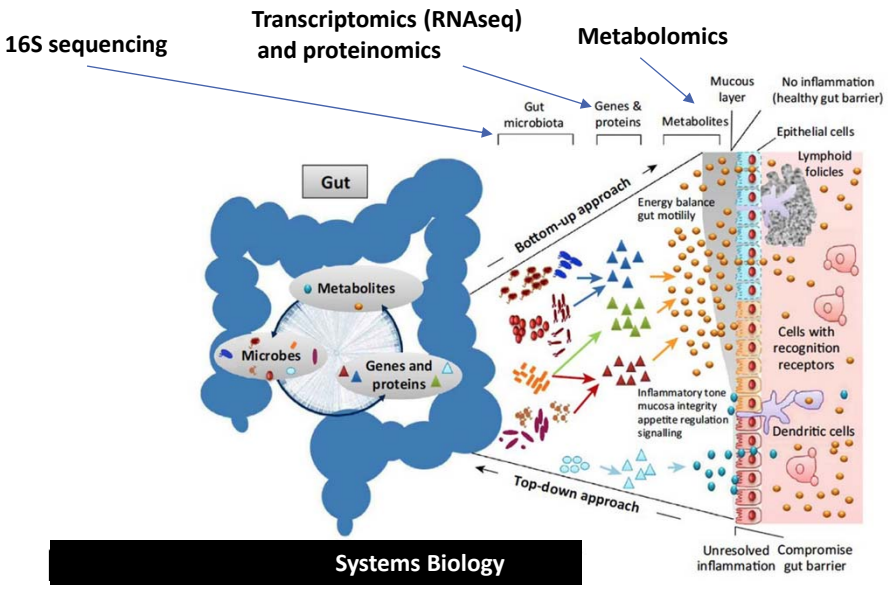
How much antibiotic exposure do you need to be at risk (and which antibiotics)?

Next: Welcome to the wonderful world of the microbiome!





Welcome to a whole new area of 'omics' science!



Gut microbiota: 16S RNA sequencing

Formicates

- Mostly good (*C. diff* is a formicate)
- Mostly spore formers (think: probiotic)
- Usually largest component of microbiota

Bacteroidetes

- Mostly good (Bacteroides predominates)
- Non-spore forming
- Usually tied for largest component

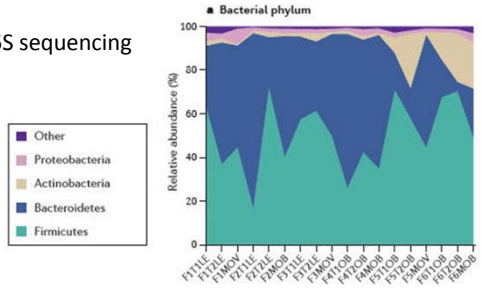
Actinobacteria

- Mostly good
- Not very common, sort of the ugly stepsister of the healthy microbiota

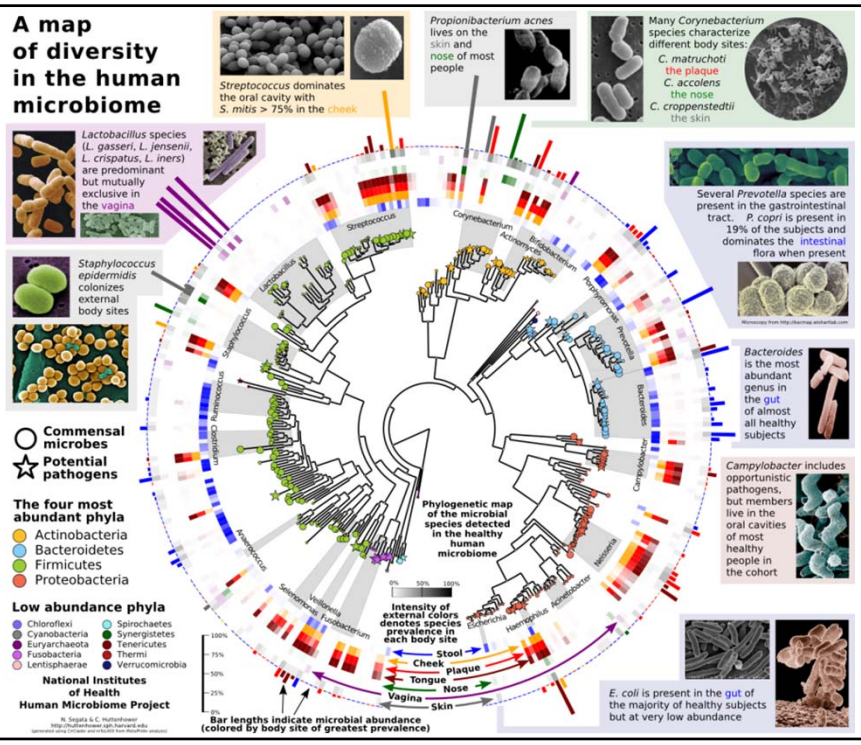
Proteobacteria

- Good in small quantities (this is *E. coli*, *Klebsiella*, etc.)
- This is where the 'overgrowth' occurs after antibiotic therapy

16S sequencing

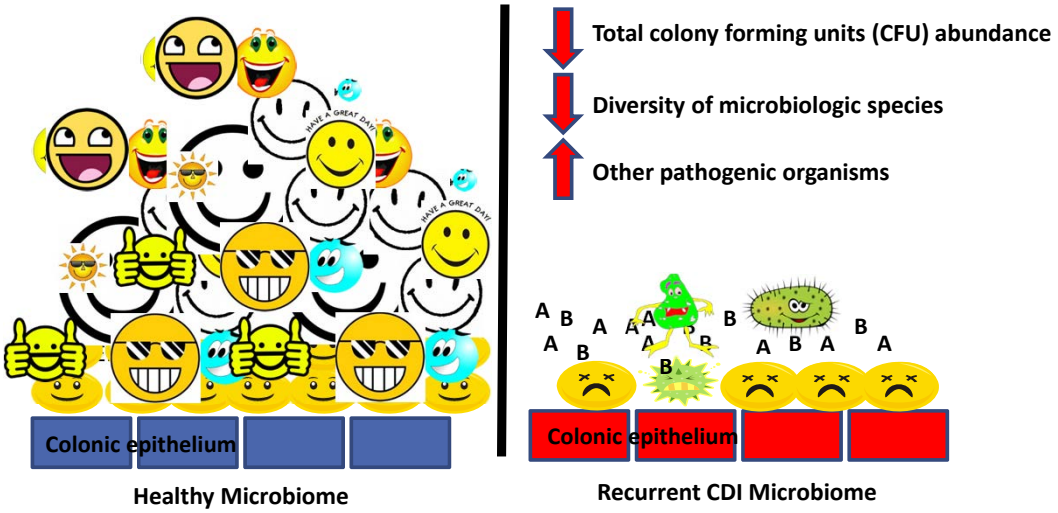


Cho et al. *Nat Rev Genet* 2012;13:260-70.



Microbiome analysis is all about abundance, diversity, and types of organisms present

Microbiome of non-CDI patients vs. CDI patients

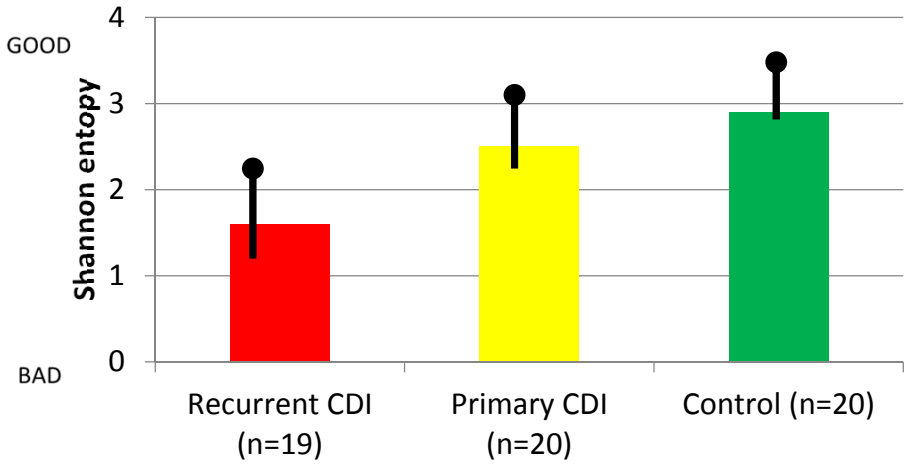


Healthy Microbiome

Recurrent CDI Microbiome

The microbiome of recurrent CDI patients is much less diverse

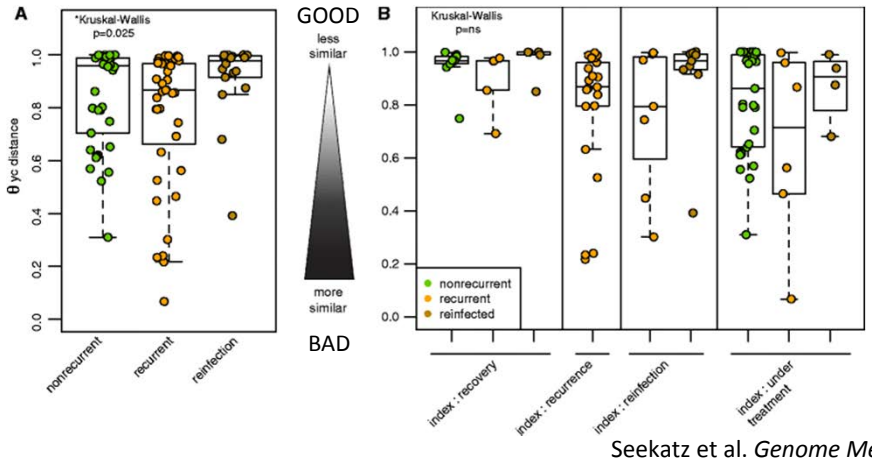
Boston, USA: Decreased microbiome diversity observed in patients with recurrent CDI



Allegretti et al. *Aliment Pharmacol Ther* 2016; 43(11):1142-53

The microbiome "organ" continues to be damaged with recurrent CDI

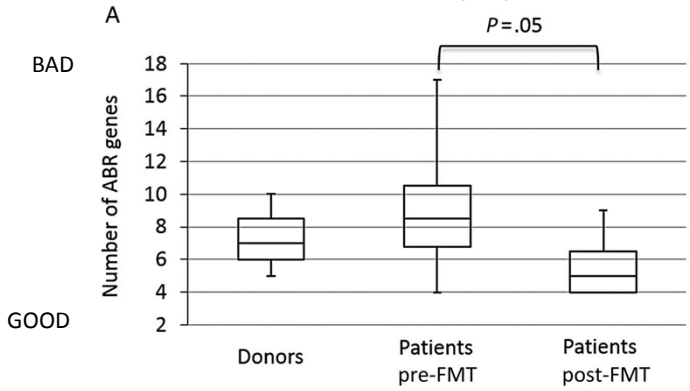
Michigan: 93 patients with CDI. Fecal microbiome diversity during initial infection (A) and during follow up period



Seekatz et al. *Genome Med* 2016;8(1):47
https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0298-8

What else do we have in our damaged microbiome?

Canada: Number of antibiotic resistant genes (ABR) present in stool samples from patients with recurrent CDI before and after FMT (n=8)

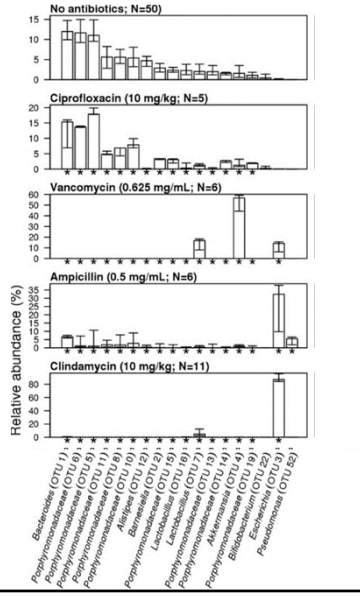


Jouhten et al. *Clin Infect Dis*. 2016; 63(5):710-11.

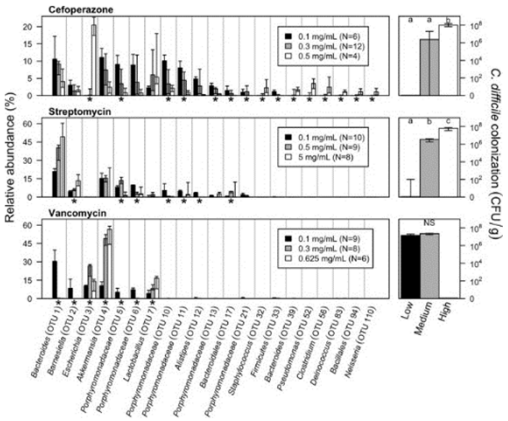
Now that we have an understanding of how microbiome studies work, we can apply this technology to better understand how antibiotics kill our microbiota and what we can do about it!

C. diff colonization in mice exposed to a variety of antibiotics for 5 days

5 days of antibiotics are more than enough to completely change the microbiota

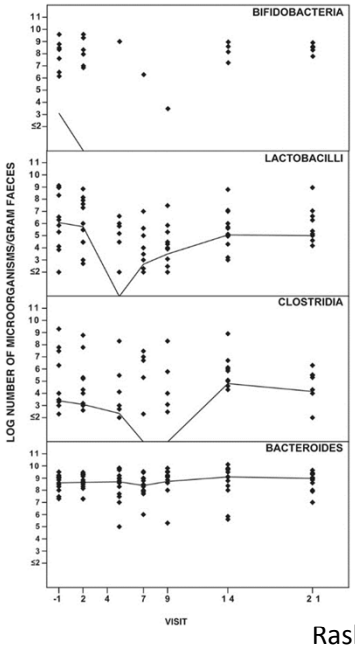


….and this disruption is more than enough to support *C. diff* colonization



Schubert et al. *Mbio*. 2015;6:e00974

The effect on the microbiome starts almost immediately



- 14 healthy volunteers given ceftaroline-avibactam X 7 days
- Changes in microbiota assessed over 21 days

Rashid et al. *Antimicrob Agents Chemother*. 2015;59:4504-9.

We are now able to predict the antibiotics most likely to cause CDI!!

- Any antibiotic that kills Firmicutes and/or Bacteroides will almost immediately increase CDI risk
- Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI

Antibiotics that increase CDI risk

Drug	Kills Firmicutes	Kills Bacteroidetes	Commonly Used
Ampicillin-sulbactam	Yes	Yes	Medium
Cefepime	Yes	No	Yes
Ceftriaxone	Yes	No	Yes
Carbapenems	Yes	Yes	Yes and increasing
Piperacillin-tazobactam	Yes	Yes	Yes
Clindamycin	Yes	Yes	No
Fluoroquinolones	Yes	Yes	Not as much

Which antibiotics are risk factors at our hospital?

30-day risk of CDI among 97,130 hospitalized patients 1,481 of whom developed CDI

Individual Antibiotic	Odd Ratio*	*P*-Value	Antibiotic Use
Ampicillin/Sulbactam	1.640	0.012	1.7%
Cefepime	1.673	< 0.001	16.1%
Ceftriaxone	1.464	< 0.001	21.8%
Ertapenem	1.864	< 0.001	3.6%
Imipenem	2.077	< 0.001	3.2%
Meropenem	1.335	0.020	2.8%
Piperacillin/Tazobactam	1.655	< 0.001	16.6%
Age	1.009	< 0.001	N/A
Proton Pump Inhibitor (Y/N)	1.375	< 0.001	N/A
Charlson Comorbidity Index	1.208	< 0.001	N/A

*Antibiotic received; yes or no.

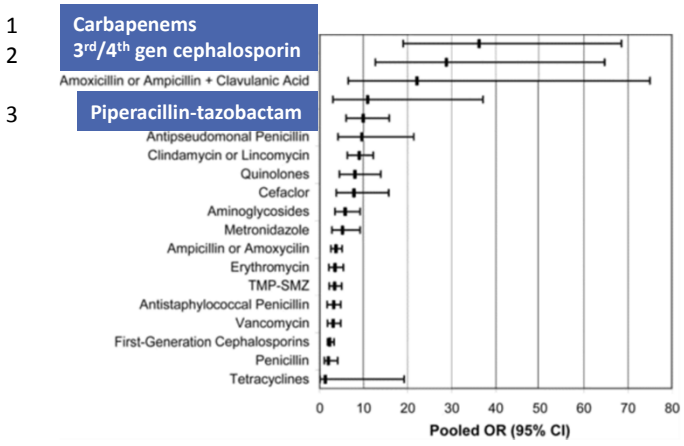
Davis M. *Clin Microbiol Infect*. 2018. Feb 16. In press.

Risk of CDI increased from 0.14% to 6.21% in comorbid patients who received high risk antibiotics and a proton pump inhibitor

Received High Risk Antibiotic?	No						Yes					
Charlson Comorbidity Index	0		1		≥2		0		1		≥2	
Received PPI?	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
CDI Incidence (%)	0.14	0.58	0.82	0.70	2.31	1.84	0.73	1.33	1.30	2.59	4.04	6.21

Independent of receipt of high risk antibiotic, more severe Charlson comorbidity index increases CDI risk

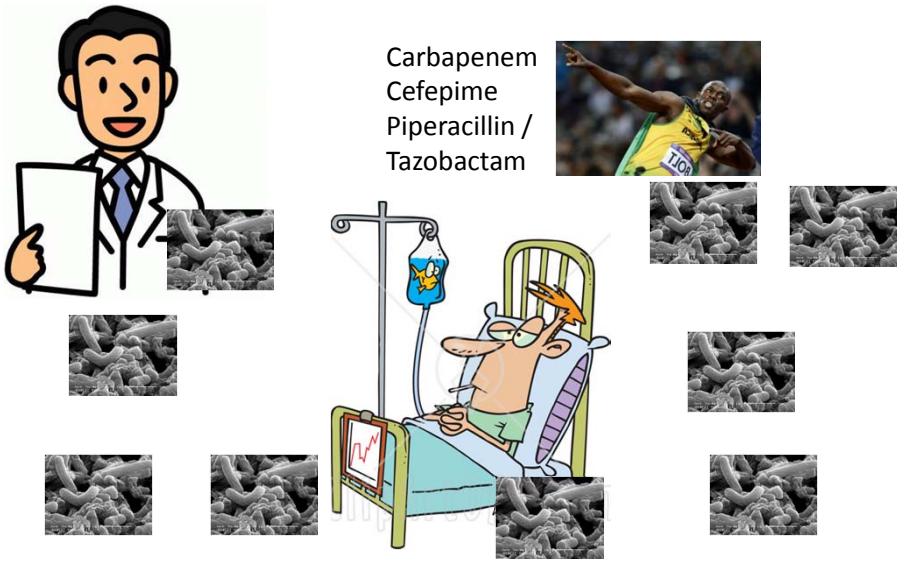
We can now update an old slide with newer antibiotics



If I was a betting man, I would guess that carbapenems will be the 'cause' of the next *C. diff* epidemic.

Clin Infect Dis. 2008;46(Supplement_1):S19-S31. doi:10.1086/521859

CDI update #1 and #2:
C. diff is ubiquitous and antibiotic risk happens quickly



Stewardship approaches to protect the microbiome

Stewardship intervention	Will it work to decrease CDI rates	Caveat
Antibiotic time-out	Yes	Get an initial microbiome hit that persists but perhaps faster restoration
Rapid diagnostics	Yes	Especially if get rid of early, broad-spectrum antibiotic use
IV to PO conversion	Maybe	Only if switch to oral that doesn't damage microbiome (aka, no cipro or amox-clav, please)
Formulary restriction	Yes	Most evidence supports this approach
Anything that slows down carbapenem use	Yes	No caveats here, this is always a good idea when you can do it!!

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

Stewardship interventions and CDI rates

Year	Country	Stewardship method	Pre-intervention	Post-intervention	Reduction in CDI rates
1994	USA	Restrictive use	15.8	1.9	88%
1997	UK	Restrictive use	5.3	2.3	57%
1998	USA	Restrictive use	11.5	3.3	71%
2003	UK	Restrictive use	14.6	3.4	77%
2003	USA	Prospective audit and feedback	2.2	0.3	86%
2004	UK	Restrictive use	46	22	52%
2004	USA	Restrictive use	1.32	0.51	61%
2007	UK	Prospective audit and feedback	NR	NR	65%
2007	Canada	Restrictive use	2.03	0.82	60%
2011	UK	Restrictive use	2.22	0.45	80%
2012	Canada	Prospective audit and feedback	1.12	0.71	37%
2013	UK	Restrictive use	2.40	1.2	50%

Clinical studies examining CDI bundles

Study	CDI setting	Population	Control bundle	Effect size (Before/after)
Bishop, 2013	Endemic	Surgical inpatients (17,145)	Resident rounding, hand hygiene, stop PPI, ASP	2.8/1000 pd 1.8/1000 pd
Koll, 2013	Endemic	Adult inpatients (14,591)	Contact precautions, hand hygiene, isolation, environmental cleaning	12/10,000 hosp 8/10,000 hosp
Abbett, 2009	Endemic	Adult inpatients (881)	Contact precautions, hand hygiene, EVS, vancomycin for Rx	1.1/1000 pd 0.66/1000 pd
Salgado, 2009	Epidemic	Adult inpatients	Contact precautions, EVS, hand hygiene	1.8/1000 pd 1.2/1000 pd
Weiss, 2009	Epidemic	Adult inpatients	EVS, contact isolation, ASP	37.3/1000 pd 14.5/1000 pd
Muto 2007	Epidemic	Adult inpatients	EVS hand hygiene, contact isolation, ASP	7.2/1000 pd 3.0/1000 pd

PPI=proton pump inhibitor; EVS=Environmental services

Yakob L et al. *Emerg Microbes Infect*. 2014; 3:e43.

Despite our best stewardship efforts, patients are still going to get CDI

….and many of them will get recurrent CDI

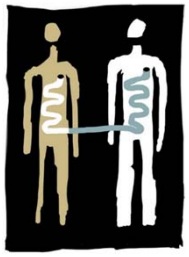
Fecal Microbiota Transplantation—The Solution?

- 1983 FMT enema (Schwann A et al., 65 y/o woman with CDI; better in 24 hr)
- 1991 NG tube (Aas, Gessert, Bakken)
- 2000 colonoscopy (Persky, Brandt)
- 2010 self-administered enemas (Silverman, Davis, Pillai)
- Slow acceptance due to concerns over safety and acceptability (no longer true?)

Schwan A et al. *Lancet*. 1983; 2:845. Aas J et al. *Clin Infect Dis*. 2003;36:580-5. Persky SE et al. *Am J Gastroenterol*. 2000; 95:3283-5. Silverman MS et al. *Clin Gastroenterol Hepatol*. 2010; 8:471-3.

FMT: Fecal Microbiota Transplantation

- A consideration for recurrent CDI refractory to medical therapy
  - Only FDA approved indication



- Not proven in severe CDI or primary CDI
- Mechanism of action poorly understood
- Appears to be safe and effective

First Word: FMT is Effective

- 92% of patients had resolution, 89% after 1 treatment and 5% after retreatment
- 4% had a relapse; 87.5% had resolution with retreatment
- No serious adverse events

REVIEW ARTICLE

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Ethan Gough,[1] Henna Shaikh,[2] and Amee R. Manges[1,3]

Departments of [1]Epidemiology Biostatistics and Occupational Health, and [2]Biology, McGill University, and [3]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Gough E et al. *Clin Infect Dis*. 2011; 53:994-1002.

FMT Goes Randomized Controlled Trial (RCT)

- **The study was stopped early**
- Off-protocol FMT offered to patients in other treatment arms (n=18):
  - 83% cure rate

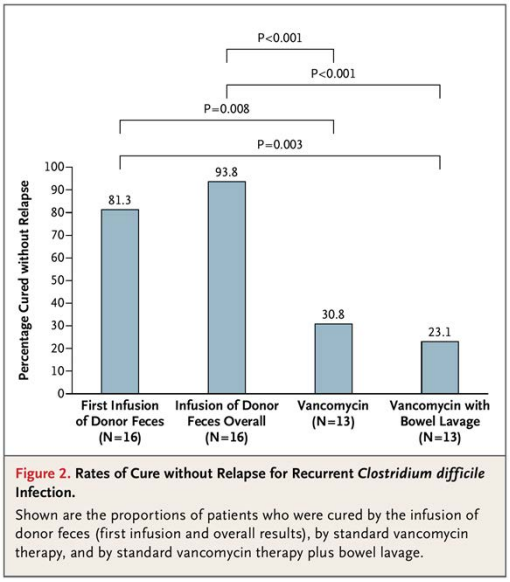


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

van Nood E et al. *N Engl J Med*. 2013; 368:407-15.

Another FMT RCT stops early

- Open label RCT
- Stopped after 39 patients
- 90% efficacy in FMT arm vs. 26% in vancomycin arm

Cammarota G et al. *Aliment Pharmacol Ther*. 2015; 41:835-43.

Frozen vs. Fresh?

- 219 patients enrolled in RCT
- Cure 75% frozen, 70.3% fresh (mITT)
- Noninferiority reached
- Context and issues in editorial:


EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Expanded Evidence for Frozen Fecal Microbiota Transplantation for *Clostridium difficile* Infection
A Fresh Take

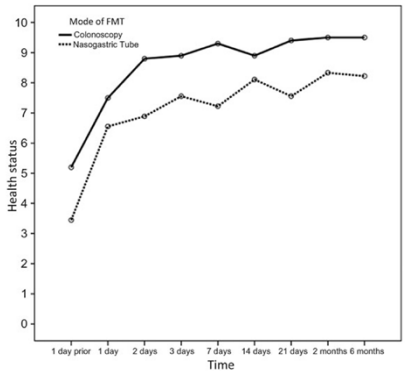
Preeti N. Malani, MD, MSJ; Krishna Rao, MD, MS

mITT=Modified intention to treat

Lee CH et al. *JAMA*. 2016; 315:142-9. Malani PN et al. *JAMA*. 2016; 315:137-8.

FMT route?

- Small RCT comparing nasogastric to lower route showed no difference (n=20)
- Overall cure 90%



Youngster I et al. *Clin Infect Dis*. 2014; 58:1515-22.

Hold on a second: placebo and/or non-bacterial FMT works?

- 90% cure with patients' own stool in recent RCT
- Filtered stool confirmed on culture and polymerase chain reaction (PCR) to be bacteria-free: cured 5 patients

Kelly CR et al. *Ann Intern Med*. 2016; 165:609-16.
Ott SJ et al. *Gastroenterology*. 2017; 152:799-811.e7.

Does FMT really work that well?

- Prior studies used non-standard comparators (2 weeks of vancomycin, chronic recurrence)
- No better than vancomycin taper in recent RCT on acute CDI patients, although enema only
- The authors on difference with prior RCTs not using a placebo control arm (emphasis mine):

  "Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free ***had their antibiotics been simply discontinued***."

  Hota SS et al. *Clin Infect Dis*. 2017; 64:265-71.

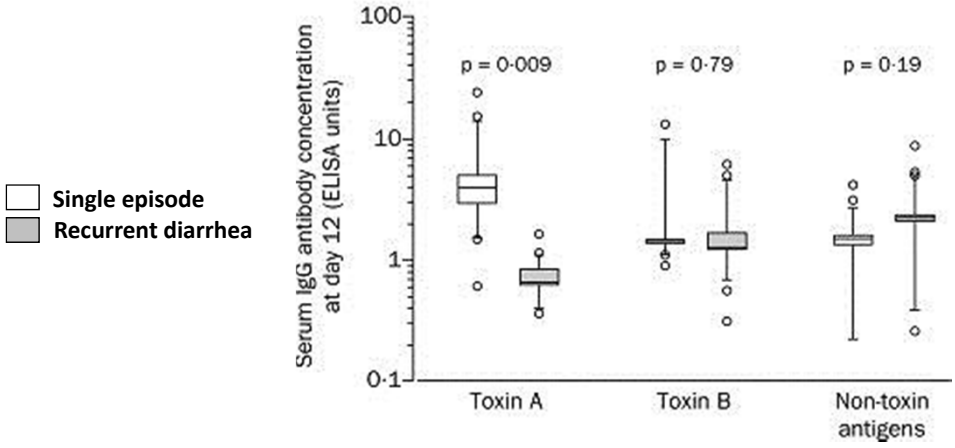
FMT: Open Questions

- Who benefits the most? Unknown
- Long term safety? Unknown
  - Microbiota associated with diabetes mellitus, obesity, cancer, atopic/autoimmune disorders
- Safe in immunocompromised? Possibly
  - Concern in patients with IBD raised
- Effective/safe for primary/severe CDI?
  - Yet to be established
- Optimal route, preparation, and stool characteristics unknown
- Other indications?
  - Beyond scope of this talk

Despite the fact that FMT is awesome, it is not available for everyone

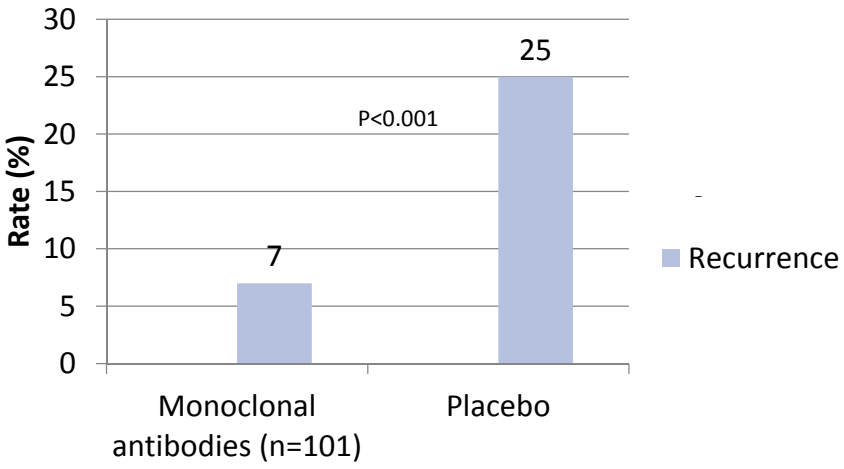
…..any other strategies we can use?

Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens



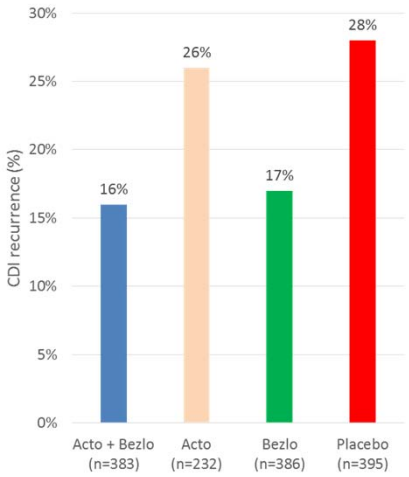
Kyne et al. *Lancet* 2001;357:189-93

Monoclonal antibodies: phase II study

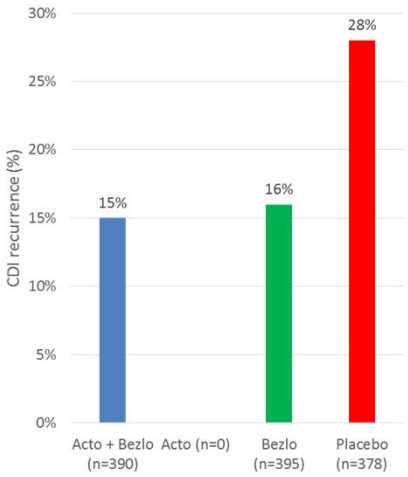


Lowy I et al. *N Engl J Med*. 2010; 362:197-205

Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo): Overall



Modify I

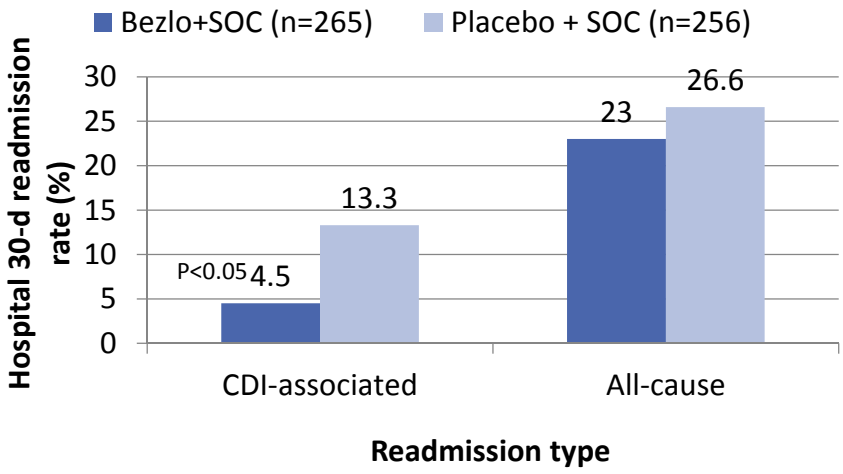


Modify II

71

Wilcox et al. *ICAAC* 2015. Gerding et al. *ICAAC* 2015. Wilcox et al. *N Engl J Med* 2017;376(4):305-17.

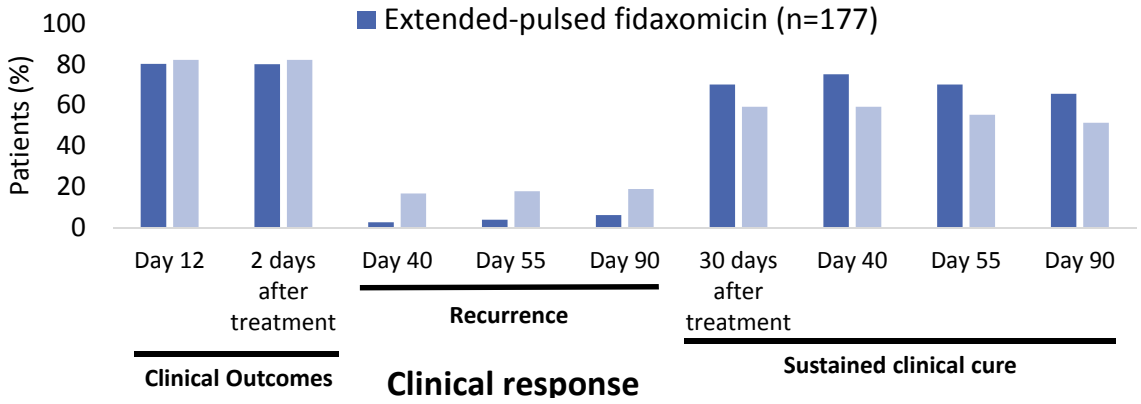
BEZLO was also shown to reduce hospital readmissions (European population)



SOC=Standard of care

Extended-Pulsed Fidaxomicin vs. Standard Dose Vancomycin* in Patients >60 years of age

EXTEND: randomized, controlled, open-label, phase 3b/4 trial in patients ≥60-year-old with initial or recurrent CDI confirmed by presence of toxin A or B in stool sample



*Dosage: Fidaxomicin: 200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25; Vancomycin: 125 mg oral capsules, four times daily on days 1–10. Guery B, et al. *Lancet Infect Dis*. 2017;18(3):296-307.

Conclusions

- New IDSA/SHEA guidelines de-emphasize use of metronidazole and increased use of vancomycin and fidaxomicin
- Antimicrobial stewardship strategies have been shown to be effective to decrease CDI rates, use science to your advantage
- FMT, novel uses of indicated agents (fidaxomicin), and new treatment modalities (bezlotoxumab) may help decrease the burden of recurrent CDI

Which of these practice changes will you consider making?

- Discuss with colleagues the disease burden of CDI
- Educate staff on the emerging and current treatment options for managing patients with CDI
- Incorporate most current evidence-based guidelines into practice when treating patients with CDI
- Apply emerging evidence and treatment recommendations for managing patients with CDI
- Collaborate with other healthcare professionals to achieve optimal outcomes for preventing and treating patients with CDI