C. Difficile Infection: Epidemiology, Risk Factors, Diagnosis, Standard Treatment and New Remedies

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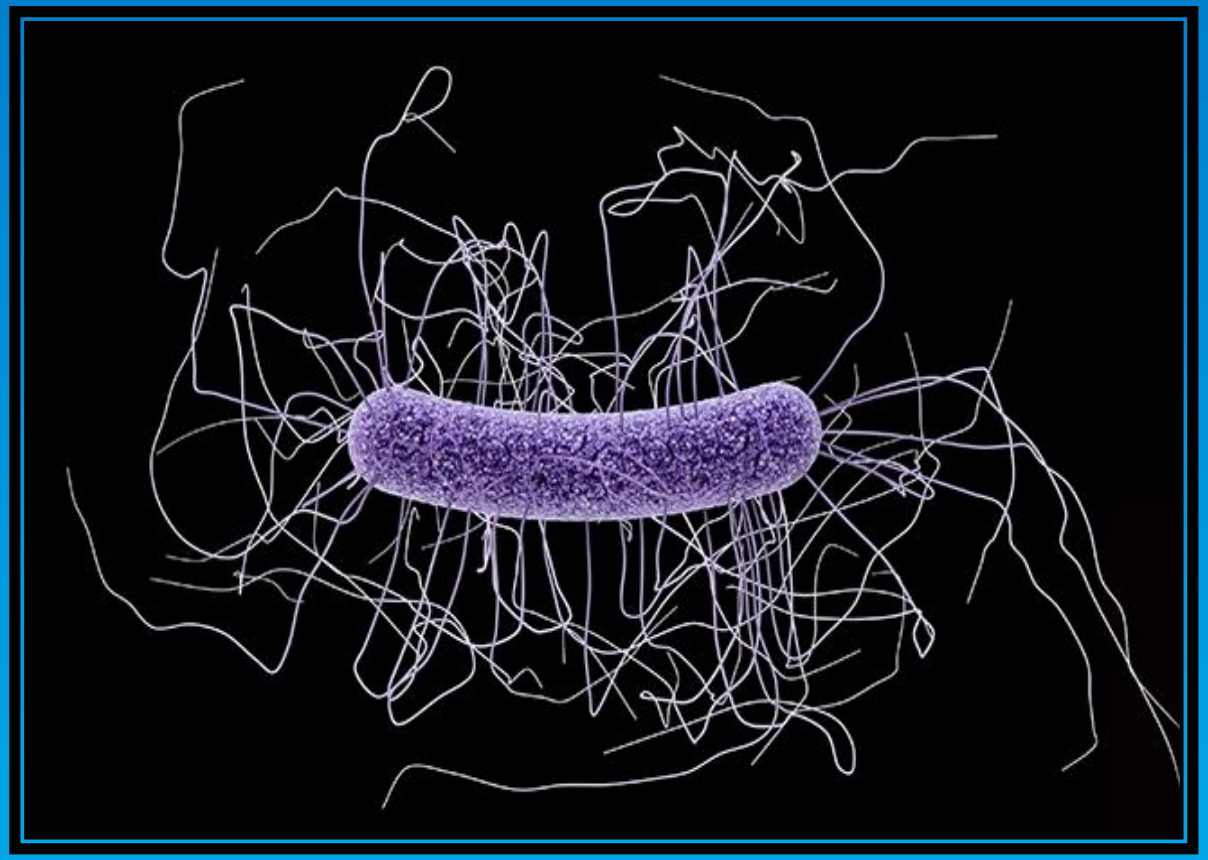
Pathophysiology

What is *Clostridium difficile*?



- Gram positive
- Spore forming
- Anaerobic
- Rod

https://www.minnpost.com/sites/default/files/imagecache/article_detail/images/articles/CDiffBacterium640.png

Microbiology

Vegetative Form

Survives on moist surfaces for up to 6 hours[1]

Susceptible to:[2]

- Gastric acid
- Antibacterial soaps
- Alcohol-based hand sanitizers

Spore Form[2,3]

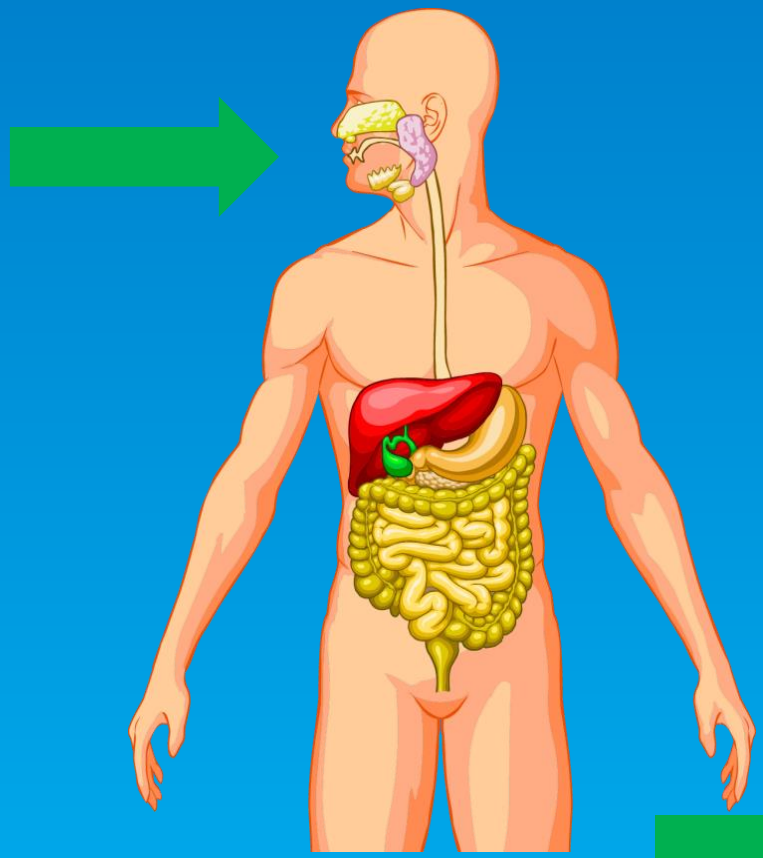
Survives on surfaces for months

Resistant to:

- Gastric acid
- Antibacterial soaps
- Alcohol-based hand sanitizers
- Rapidly changes to vegetative form

1. Jump RL et al. *Antimicrob Agents Chemother.* 2007;51(8):2883–2887.
2. Fordtran JS. *Proc (Bayl Univ Med Cent).* 2006;19(1):3–12.
3. Cohen SH et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431–455.

Pathogenesis and Transmission

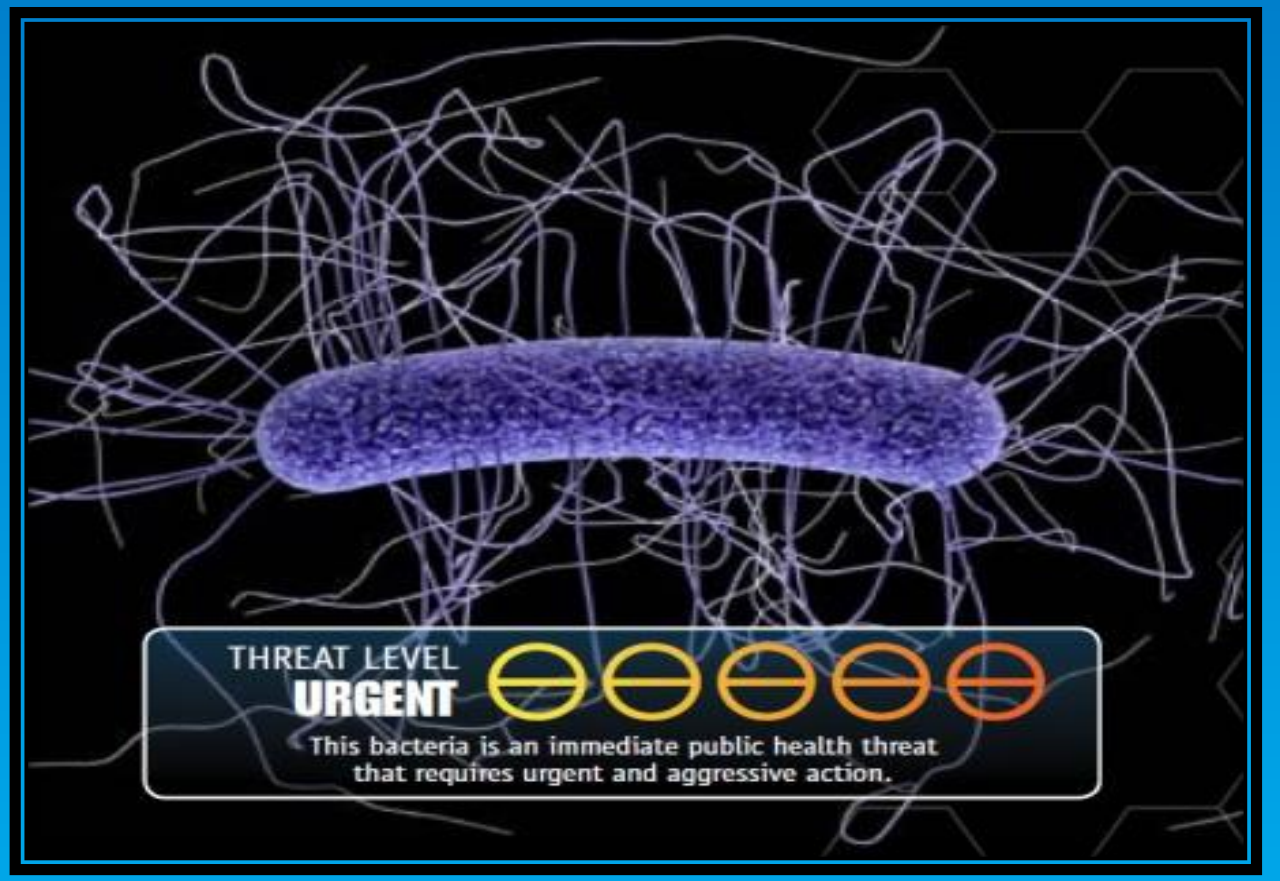


Symptoms

- Diarrhea
- Constipation
- Ileus
- Megacolon

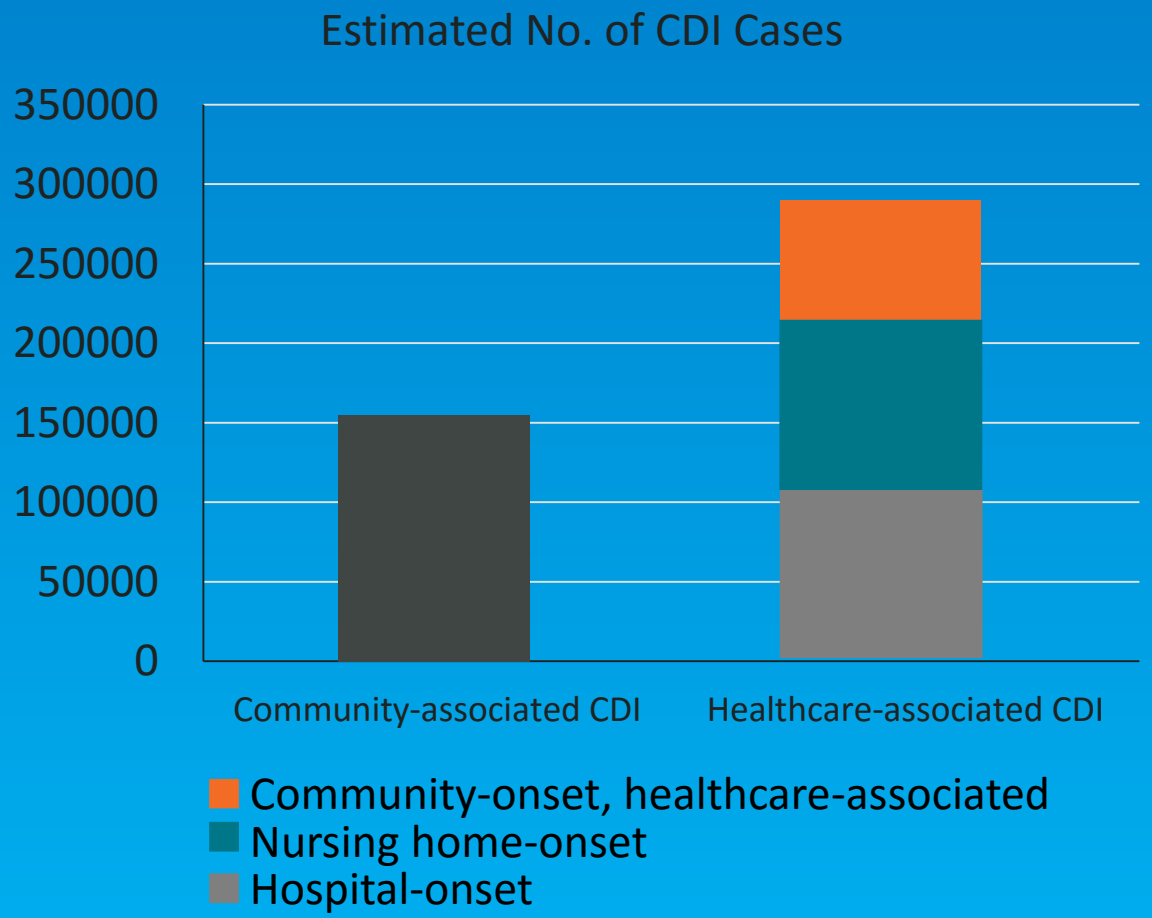
Epidemiology

The *C. difficile* Epidemic



http://www.cdc.gov/drugresistance/threat-report-2013/

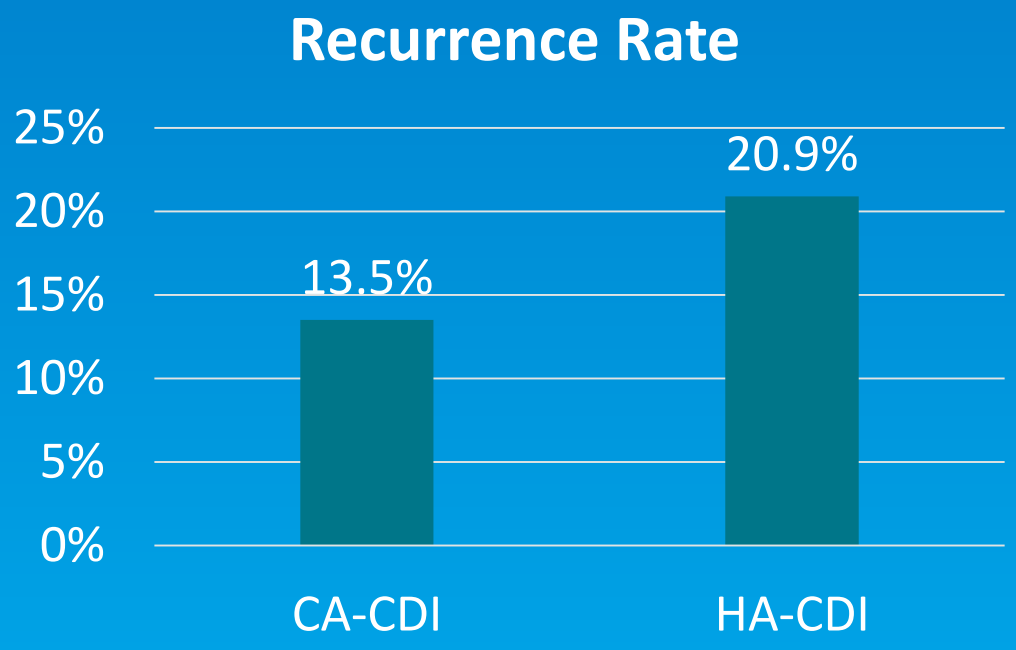
Estimated U.S. Burden of *C. difficile* Infection, According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011



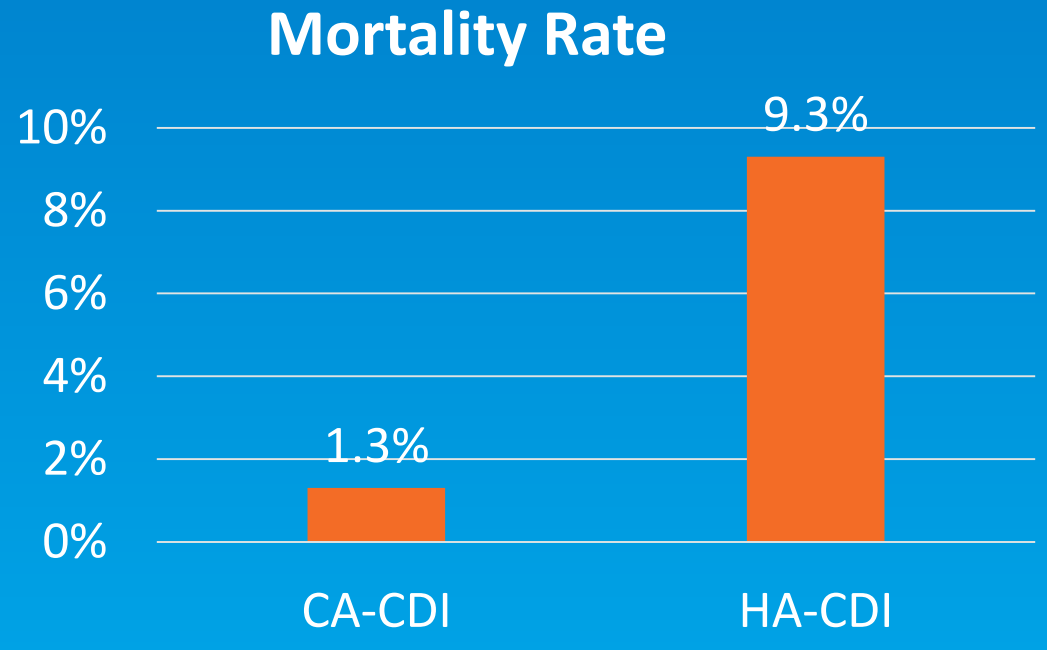
- Of community-associated CDI, 82% were estimated to be associated with outpatient healthcare exposure
- ~2/3 were healthcare-associated infection but ~1/4 were hospitalized when symptoms began

Leesa FC et al. *N Engl J Med*. 2015;372(9):825-34.

Adjusted U.S. National Estimates of Recurrences and Deaths Associated with CDI



14 through 56 days following initial CDI



Within 30-days of the initial positive *C. difficile* testing results

Lessa FC et al. *N Engl J Med*. 2015;372(9):825-34.

Risk Factors

Overall Risk Factors for *C. difficile* Infection

Demographics[1,2,3]

- Age older than 65
- Female gender
- Immunocompromised
  - Diabetes
  - HIV
  - Chronic Kidney Disease
- Prior episode of CDI

Alteration of the Microbiome

- Exposure to antimicrobial agents
- Chemotherapy
- Gastrointestinal surgery
- Nasogastric Tube
- Acid suppression medications

Healthcare Factors

- Extended stay at a hospital and/or residence in a long-term care facility
- Contact with contaminated environment and/or health worker hand colonization
- Direct contact with a patient with CDI

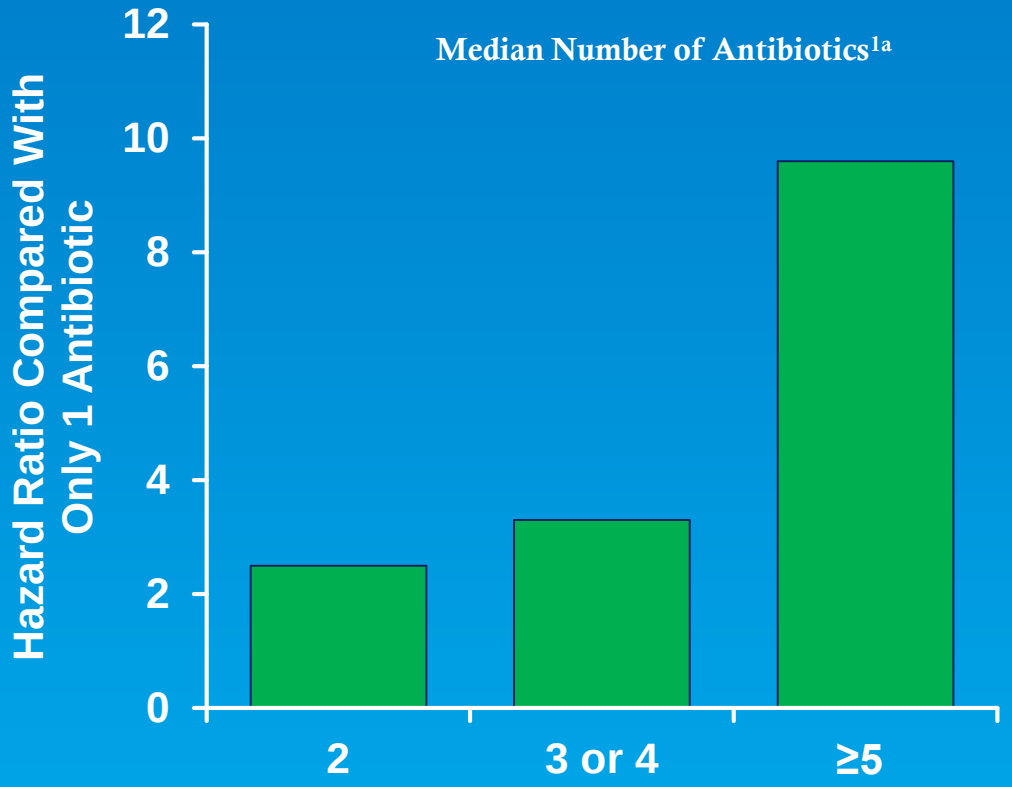
1. Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455;
2. Fekety R, et al. Clin Infect Dis. 1997; 24(3): 324-333
3. Shakov R, et al. *Am J Infect Control*. 2011;39(3):194-198.

Antibiotics That Increase Risk of CDI

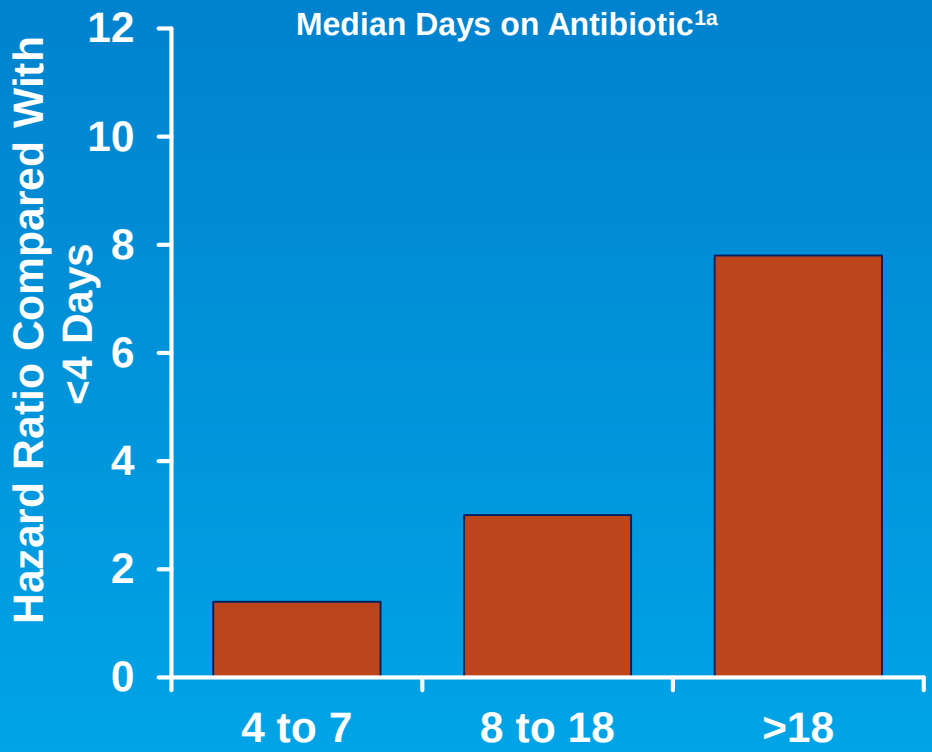
Frequently	Occasionally	Rarely
Fluoroquinolones	Macrolides	Aminoglycosides
Clindamycin	Trimethoprim	Tetracyclines
Penicillins (broad spectrum)	Sulfonamides	Chloramphenicol
Cephalosporins (broad spectrum)		Metronidazole
		Vancomycin

1. Stevens V et al. *Clin Infect Dis*. 2011;53(1):42–48.
2. Bignardi GE. *J Hosp Infect*. 1998;40:1–5.
3. Kelly CP et al. *N Engl J Med*. 1994;330(4):257–262.

Antibiotic Exposure and Risk of Recurrent CDI



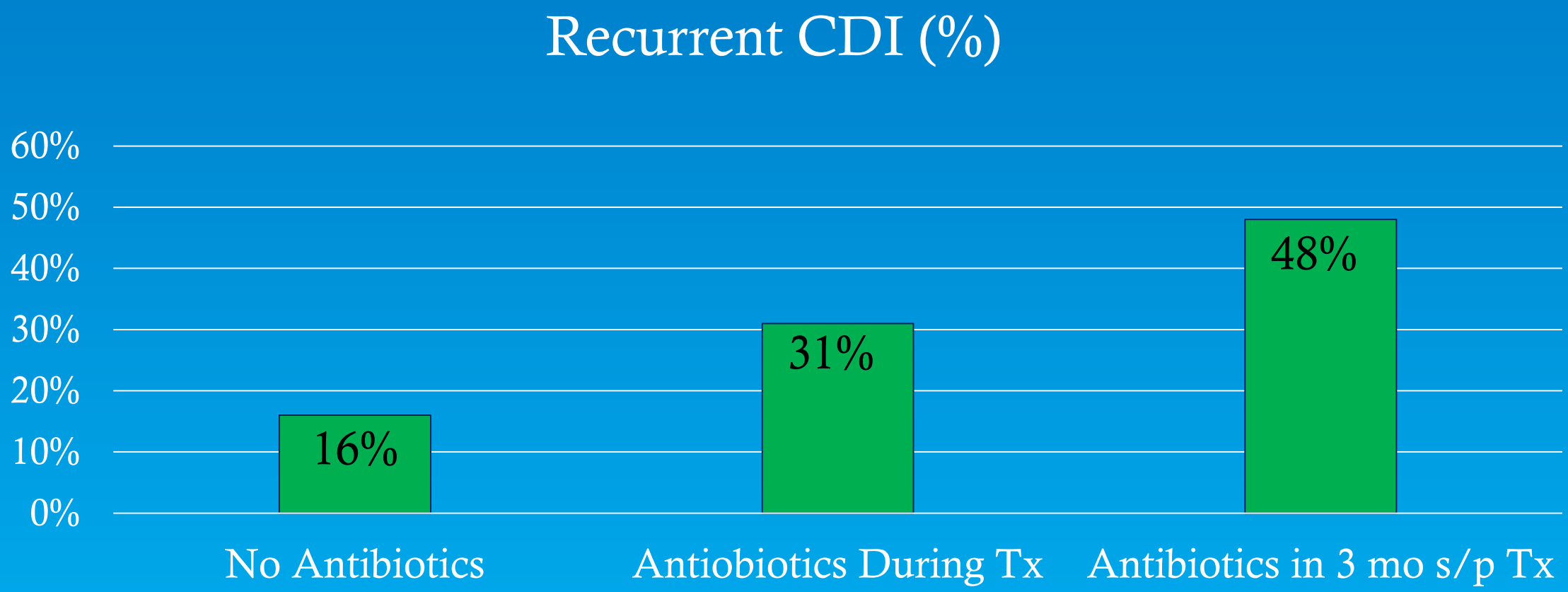
Number of antibiotics received



Antibiotic days

Stevens V, et al. *Clin Infect Dis*. 2011;53(1):42-48; 2. Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

Concomitant or Subsequent Antibiotics and Recurrence CDI

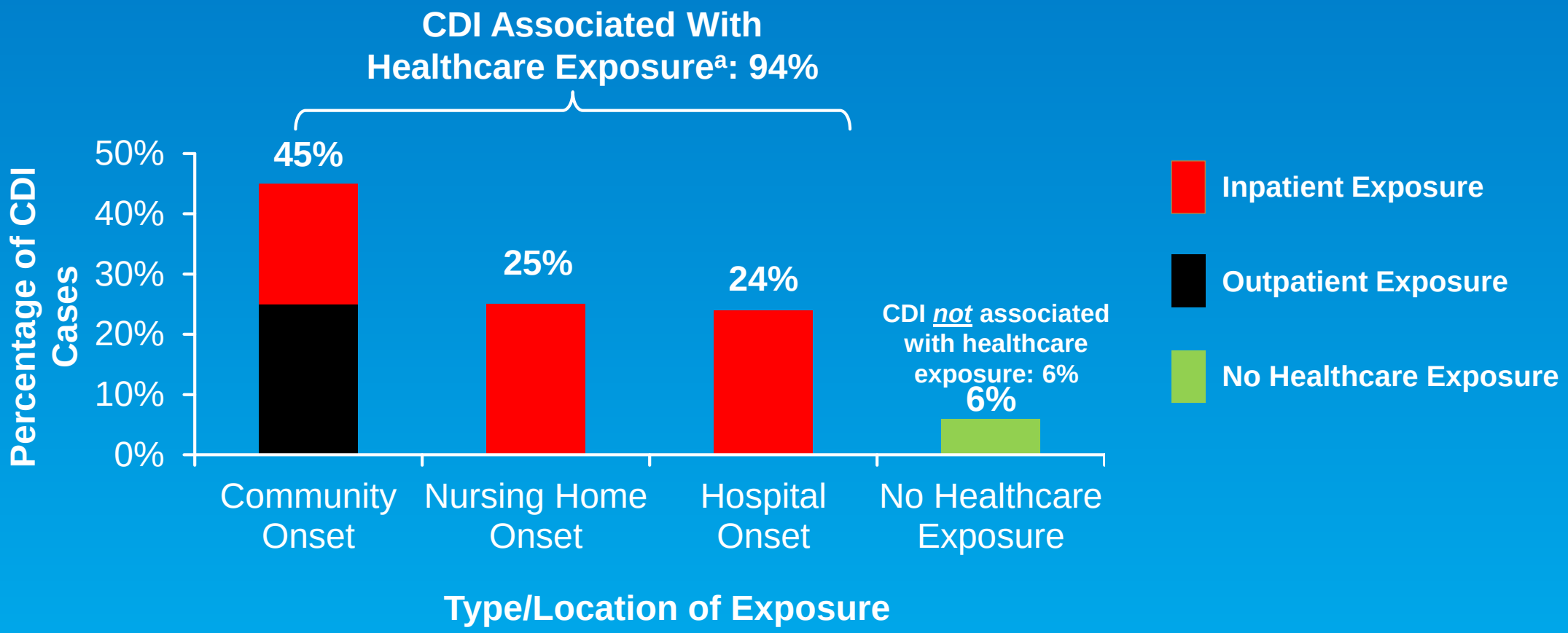


Drekonja et al.. Am J Med. 2011

Risk Factors for *C. difficile* Infection

- Age
- Immune Compromise
- Solid Organ Transplantation
- Chronic Kidney Disease

CDI Risk Factor: Healthcare Exposure

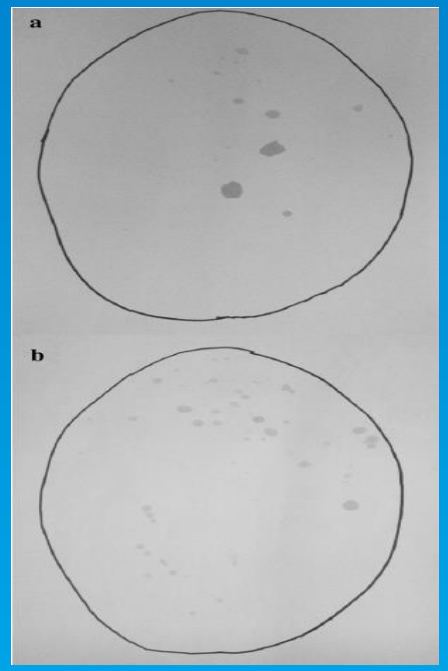


Centers for Disease Control and Prevention (CDC). *Morb Mortal Wkly Rep*. 2012;61(9):157-162.

Flushing Toilet and Spread of CDI

Comparison of recovery of *Clostridium difficile* from the air with the toilet seat open and closed ($N = 2$)

Sample time	Mean cfu *C. difficile* detected in air samples 0–90 min after each flush					
	Control tests (water only added)	Toilet lid closed		Toilet lid open		
		10 cm above	Seat height	25 cm above	10 cm above	Seat height
0–30 min	0	4	3	7	6	35
30–60 min	0	1	7	4	0	3
60–90 min	0	0	0	1	0	0



Best EL et al. *J Hosp Infect*. 2012;80(1):1-5.

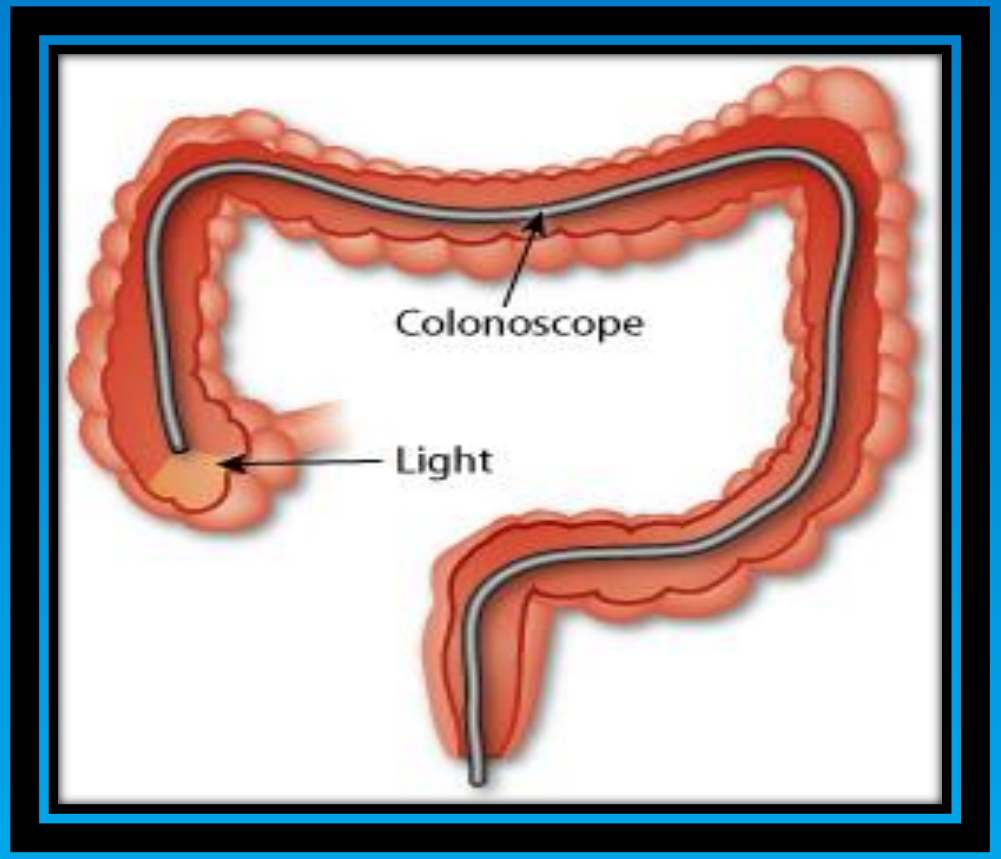
Diagnosis and Triage

C. difficile Diagnostic Laboratory Tests

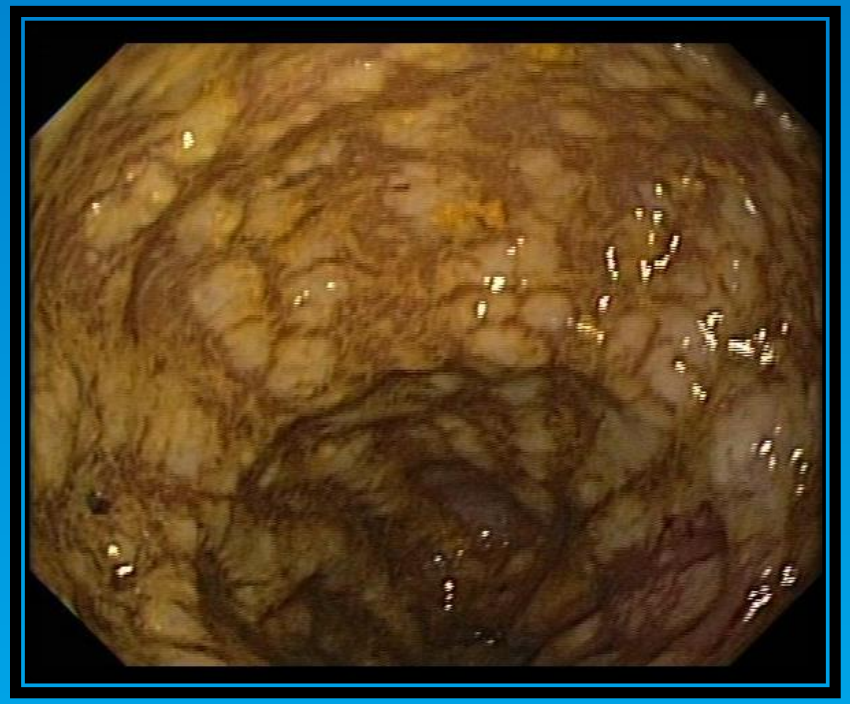
Assay	Sensitivity	Specificity	Speed	Convenience	Description
Toxigenic culture	++++	++++	+	+	• *C. difficile* cultured in an anaerobic environment[2] • Detects the ability of the bacteria to produce toxin and not toxin itself • Check only patients with active diarrhea
Toxin EIA	+	+++	++++	++++	• Detects *C. difficile* toxin A and toxin B[1,2] • Limited sensitivity and specificty
Cytotoxin neutralization (CCCN)	++++	++	++	++	• Uses tissue cultures to detect cytotoxic phenotype[1] • Detects toxigenic and non-toxigenic *C. difficile*
GDH-based algorithm	++++	++	++/++++	+++	• Detects GDH, *C. difficile* common antigen[1] • Can be used for initial screening, with cytotoxicity assay to confirm[1,2]
Molecular assay	++++	++++	+++	+++	• Includes PCR and LAMP[1]

Wilcox MH, et al. *J Clin Microbiol*. 2010;48(12):4347-4353; 2. Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

Colonoscopy



Colonoscopy



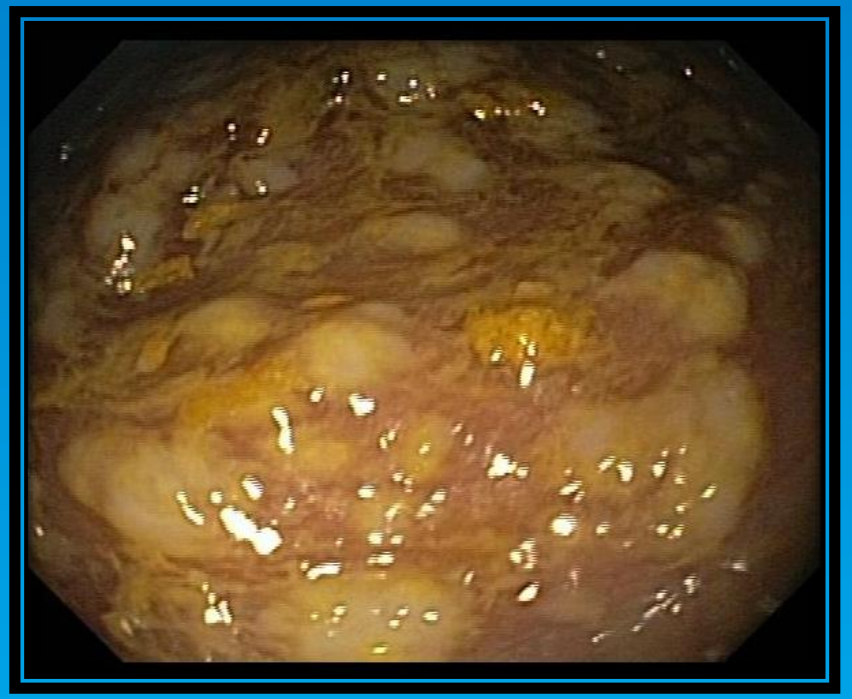


Image: Feuerstadt P

Severity of Disease

New Yorker

Definitions of Severity of CDI SHEA/IDSA Guidelines

Initial episode severity	Definition
Mild or moderate	• Leukocytosis, WBC count ≤ 15,000 cells/μL **– and –** • Serum creatinine < 1.5 times premorbid level
Severe	• Leukocytosis, WBC count > 15,000 cells/μL **– or –** • Serum creatinine ≥ 1.5 times premorbid level
Severe, complicated	• Hypotension or shock, ileus, megacolon

Cohen SH et al. *Infect Control Hosp Epidemiol*. 2010.

American Journal of Gastroenterology Clinical Guidelines

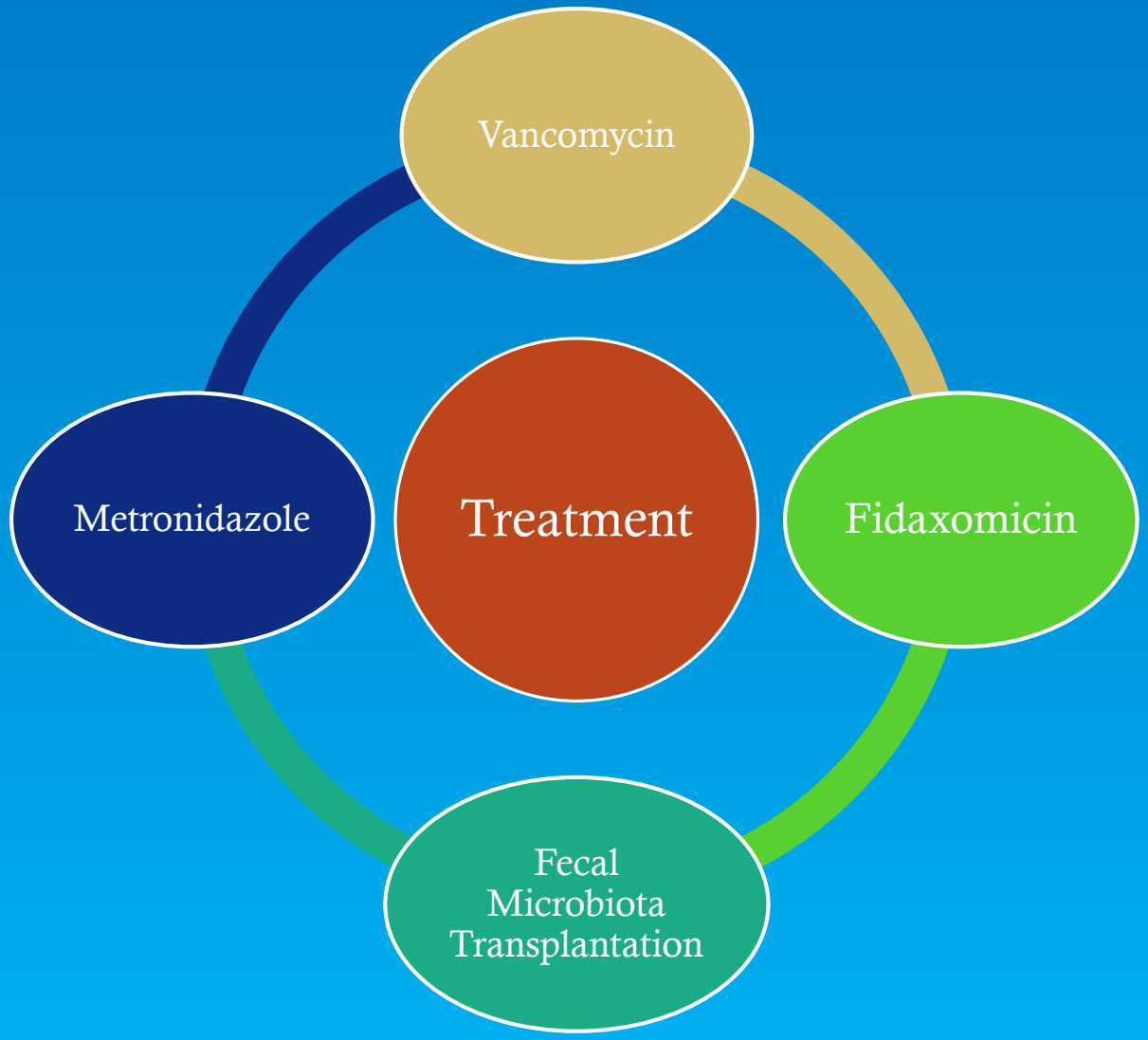
Initial episode severity	Definition
Mild or moderate	• Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria
Severe	• Serum albumin < 3 g/dl plus one of the following: WBC > 15,000 cells/mm^3 Abdominal tenderness
Severe, complicated	Any of the following attributable to CDI: • Admission to ICU • Hypotension with or without use of required vasopressors • Fever > 38.5 ºC • Ileus or significant distension • Mental status changes • WBC > 35,000 cells/mm^3 or < 2,000 mm^3 • Serum lactate levels > 2.2 mmol/l • End organ failure (mechanical ventilation, renal failure)

Surawicz, et al. *Amer J Gastro*. 2013

Treatment

How do we treat *C. difficile* infection?

Treatment


Vancomycin
Metronidazole
Treatment
Fidaxomicin
Fecal
Microbiota
Transplantation

Metronidazole vs. Vancomycin

Clinical Cure

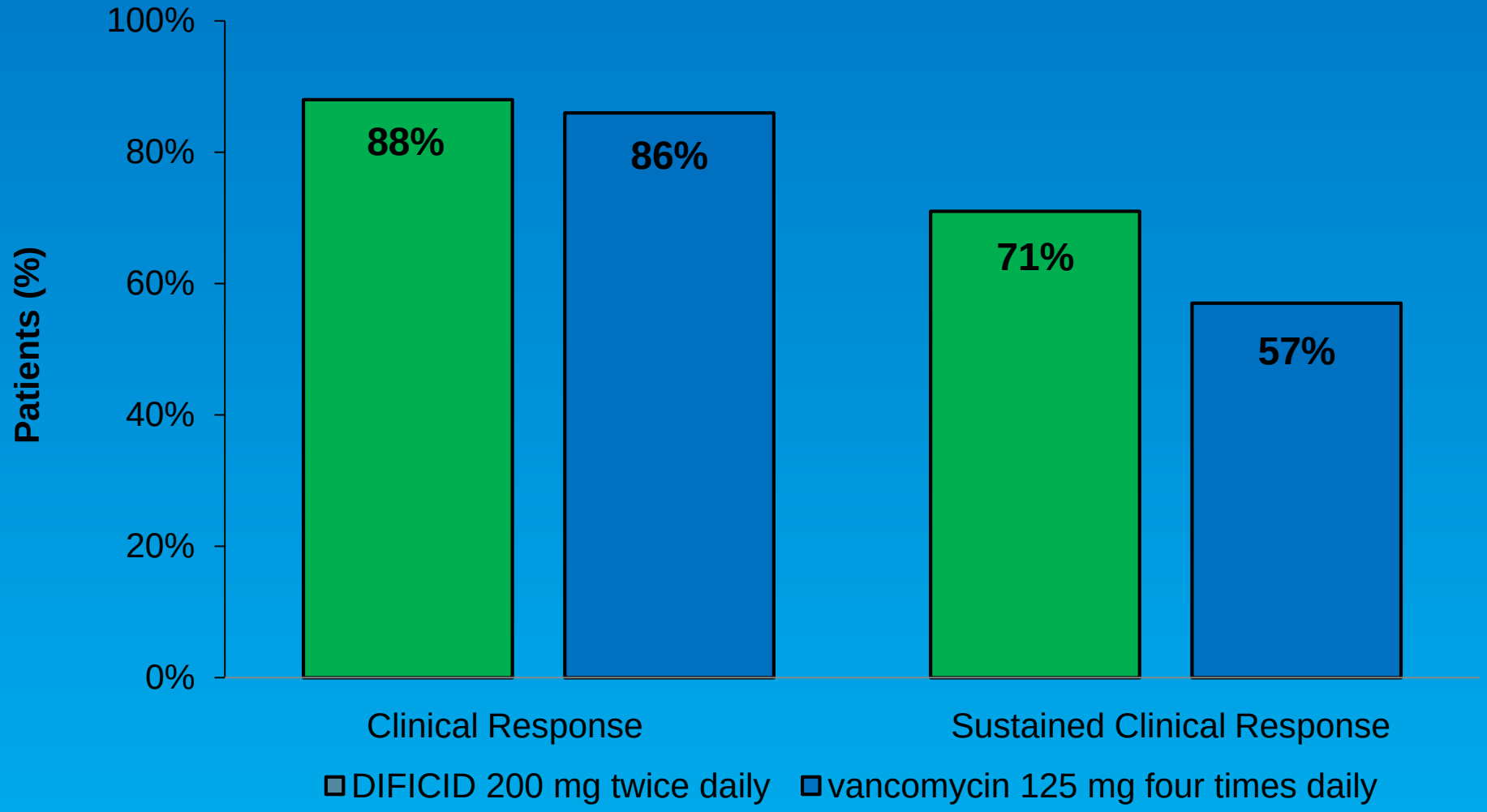
	Metronidazole	Vancomycin	p-value
Mild CDI	90%	98%	0.36
Severe CDI	76%	97%	0.02

Recurrent Symptoms

	Metronidazole	Vancomycin	p-value
Mild CDI	8%	5%	0.67
Severe CDI	21%	10%	0.30

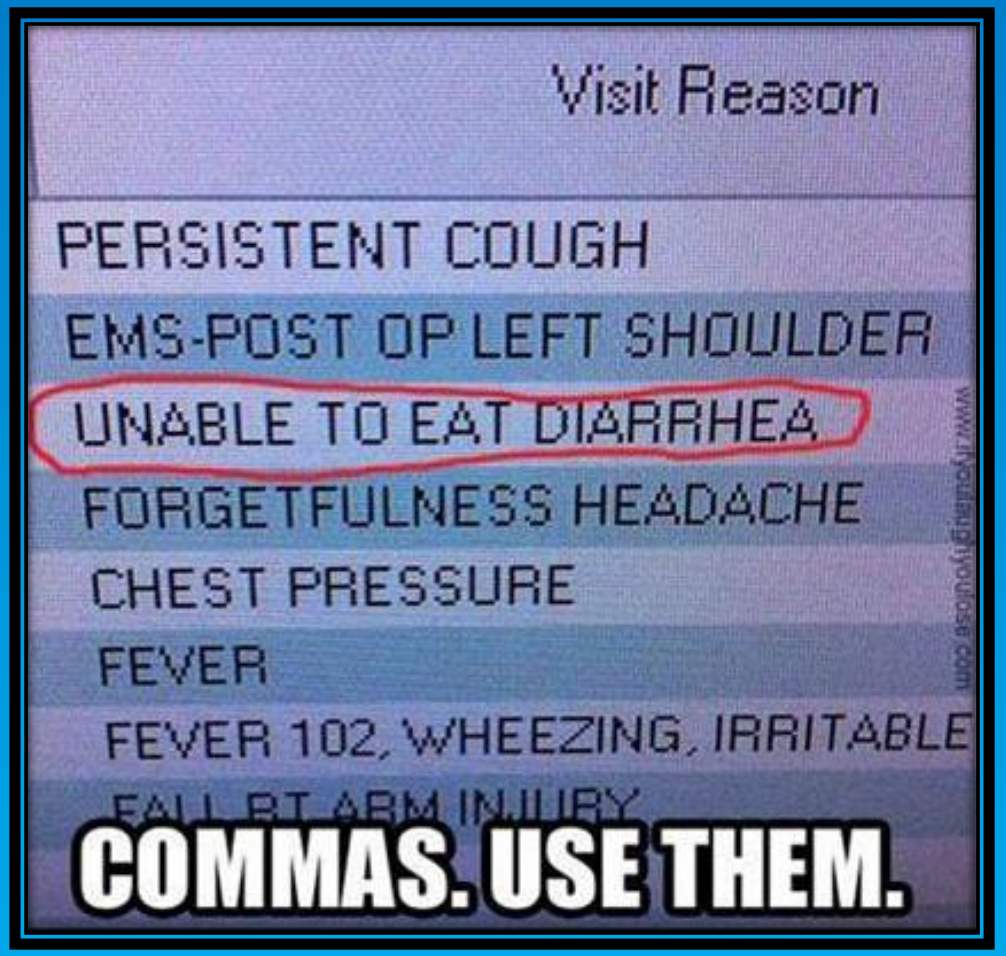
Zar, et al. Clin Infect Dis, 2007

Fidaxomicin vs. Vancomycin in 2 Large Phase 3 Trials

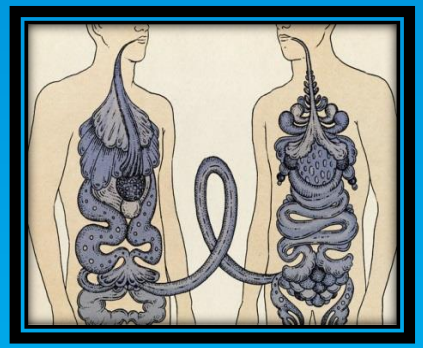


Louie et al. 2011. NEJM, Cornely et al. 2012 Lancet

Fecal Microbiota Transplantation



Headlines



Gastroenterologists worldwide make a breakthrough

Fecal transplants successful in treating intestinal ailment

An infusion of feces from a healthy person is much more effective than an antibiotic in treating C. difficile, a recurrent intestinal infection, researchers find.

A new study has found that an infusion of feces from a healthy person into an ailing patient's gut was significantly more effective than a traditional antibiotic treatment — raising hopes that the unconventional approach could one day help combat obesity, food allergies and a host of other maladies.

The study, published online Wednesday by the New England Journal of Medicine, a reference magazine for the medical community worldwide, demonstrated that the fecal transplant cleared up a recurrent bacterial infection far more reliably than the routinely prescribed medication. In fact, the transplant was so successful that the research trial was ended early so that patients in the control groups could be given the remedy as well.

As a treatment for recurrent Clostridium difficile infection — an ailment that affects nearly 1% of patients hospitalized in the U.S. and plays a role in an estimated 100,000 deaths a year — the transplant had a 94% cure rate, three times greater than for those who took only the antibiotic vancomycin.

"It's a strange concept to use stool, which has always been looked on as something dirty," said Dr. Lawrence Brandt, a gastroenterologist at the Albert Einstein College of Medicine in New York who has conducted transplants for 14 years but wasn't involved in the study. "We're entering a very exciting new chapter in medicine."[...]

Source

The New England Journal of Medicine

Duodenal Infusion of Donor Feces for Recurrent Clostridium *difficile*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

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.

REVIEW

Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-Analysis

Zain Kassam, MD, FRCPC[1], Christine H. Lee, MD, FRCPC, FIDSA[2,3,4], Yuhong Yuan, MD, PhD[1,5] and Richard H. Hunt, MB, FRCP, FRCPC, MACG, AGAF[1,5]

Research

Preliminary Communication

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection

Ilan Youngster, MD, MMSc; George H. Russell, MD, MSc; Christina Pindar, BA; Tomer Ziv-Baran, PhD; Jenny Sauk, MD; Elizabeth L. Hohmann, MD

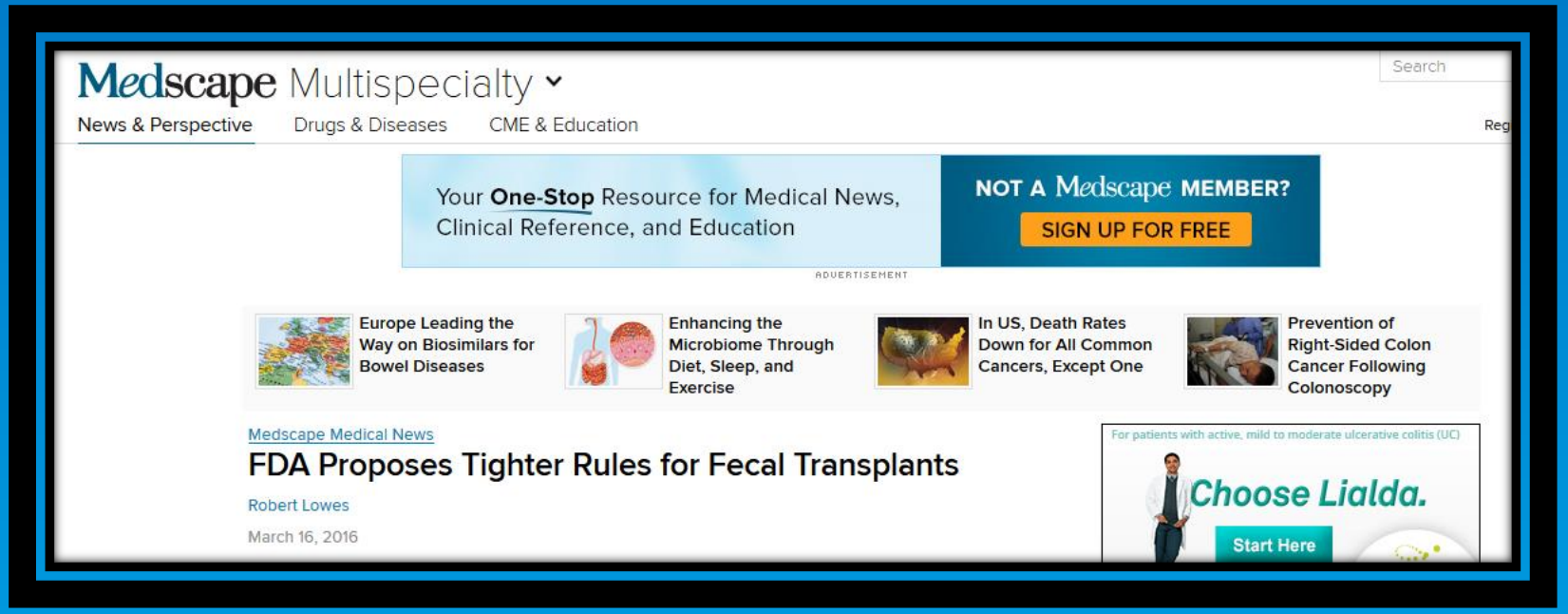
FDA and FMT, July 2013

Guidance for Industry

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies

This guidance is for immediate implementation.

FDA and FMT, March 2016

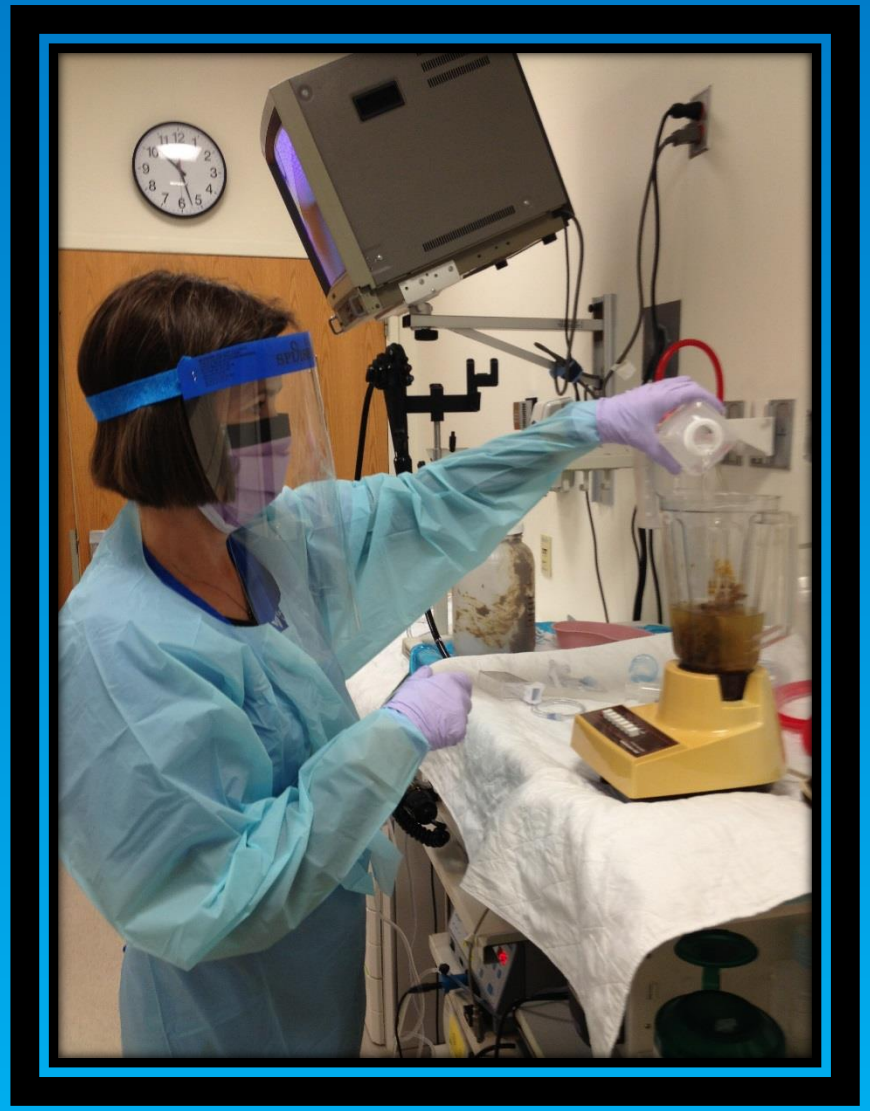


…FDA said that it would continue to exercise enforcement discretion for FMT regarding *C difficile*, but the agency added more conditions. Either the patient receiving the transplant or the treating clinician must know the donor. And the treating clinician must oversee the screening and testing of both the stool donor and the stool.

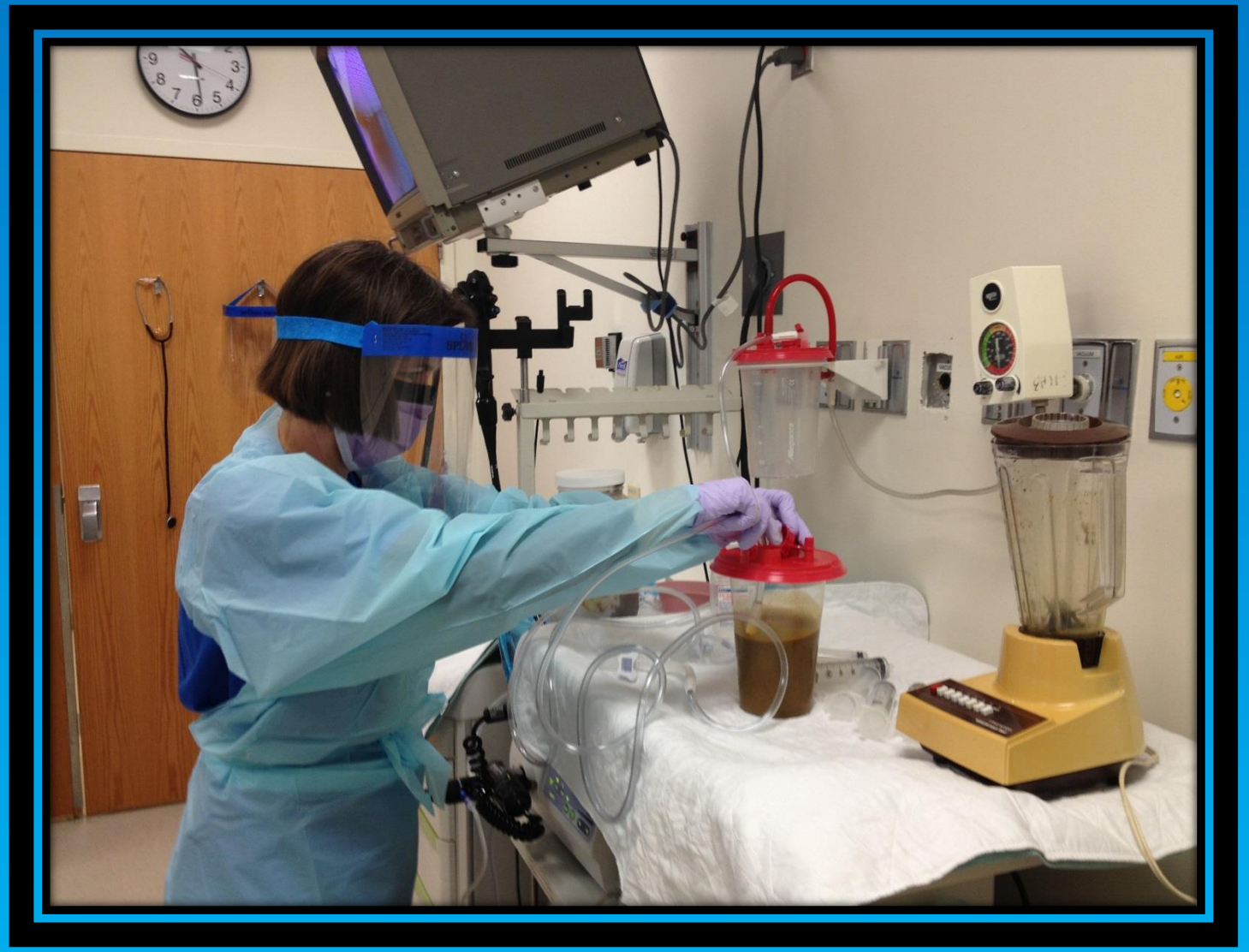
Identification of a Donor

Fecal Microbiota Transplantation

Fecal Microbiota Transplantation



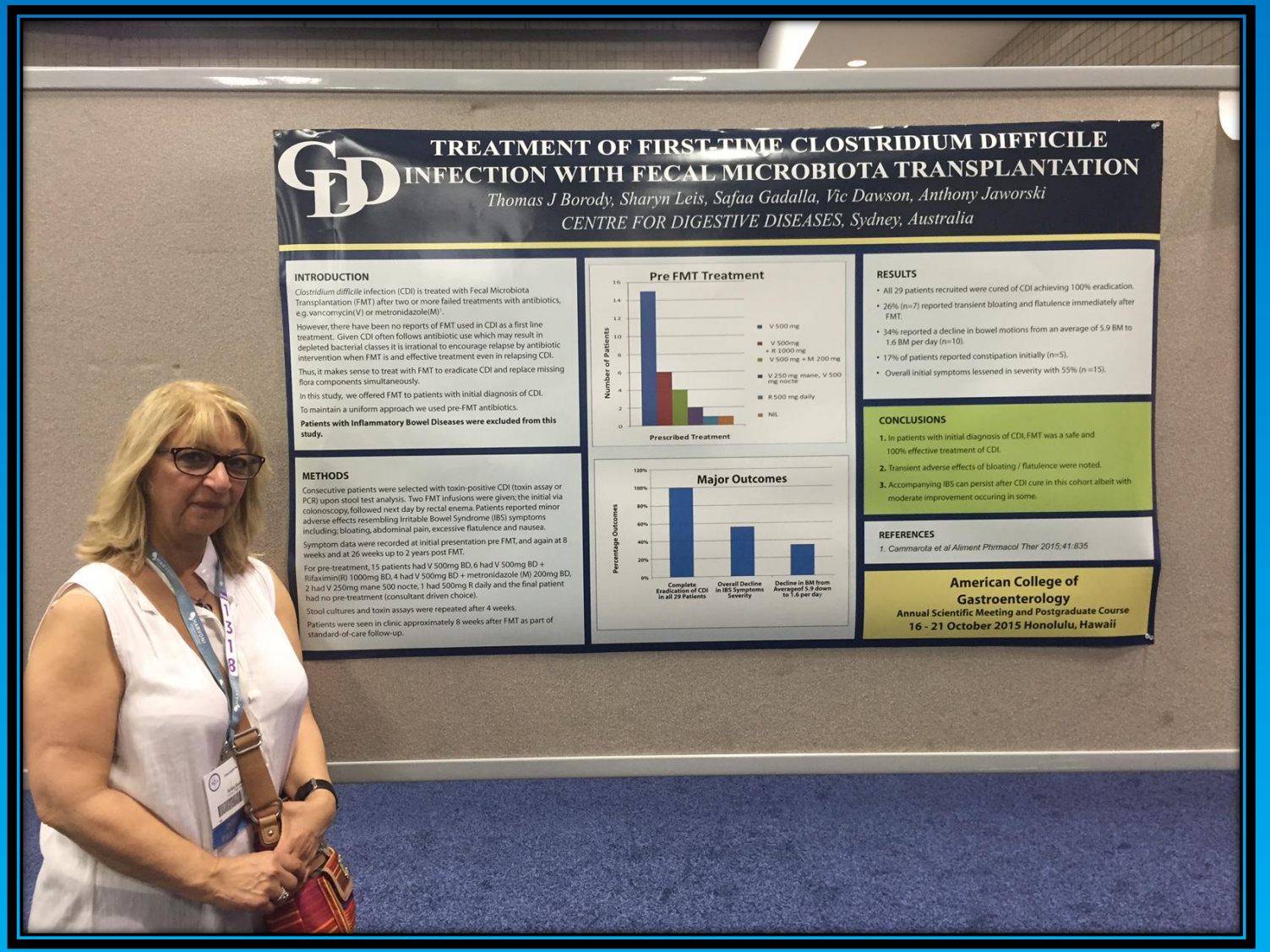
Fecal Microbiota Transplantation



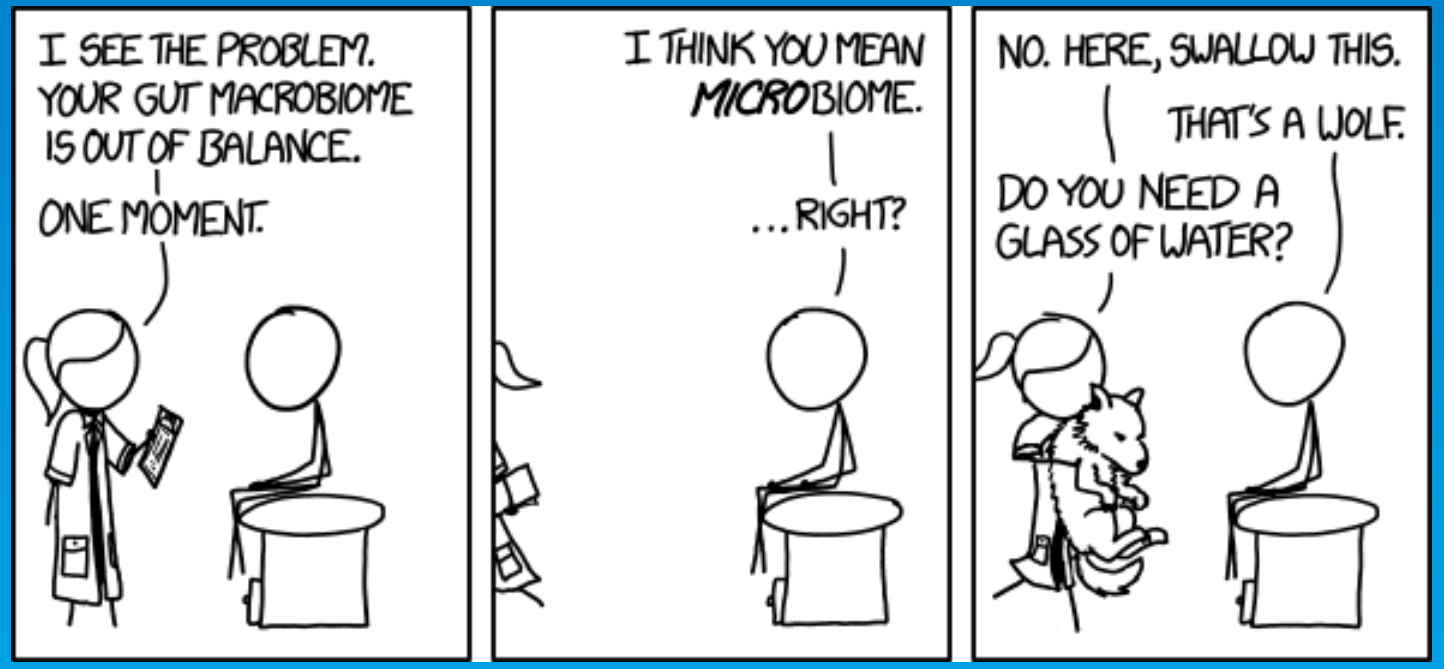
Fecal Microbiota Transplantation

Fecal Microbiota Transplantation

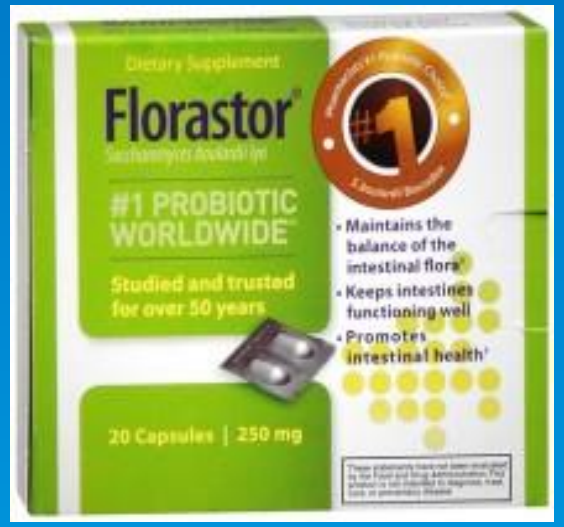
FMT as First Line Therapy?



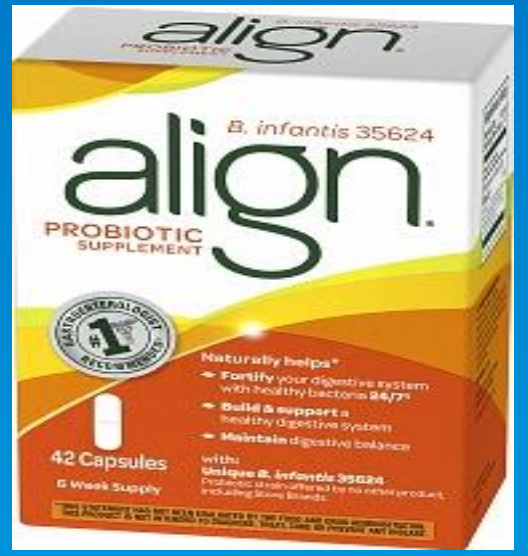
Fecal Microbiota Transplantation



Probiotics


Dietary Supplement
Florastor
#1 PROBIOTIC WORLDWIDE
Studied and trusted for over 50 years
• Maintains the balance of the intestinal flora*
• Keeps intestines functioning well
• Promotes intestinal health*
20 Capsules | 250 mg

Culturelle
PROBIOTIC
Natural Health & Wellness
Boosts your immune system
Improves digestive health
Restores the natural balance of good bacteria in your digestive tract
30
Culturelle

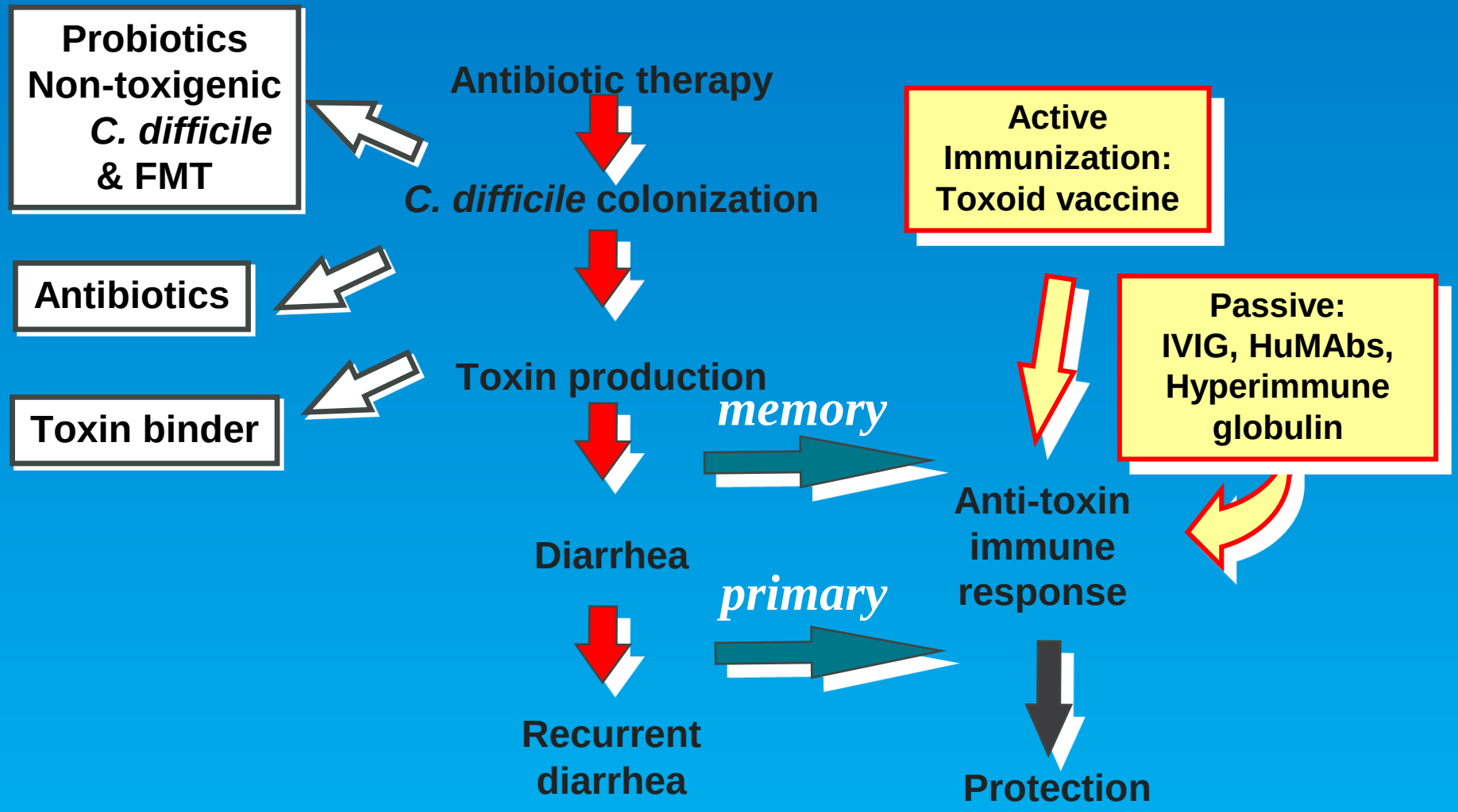

align
B. infantis 35624
align
PROBIOTIC SUPPLEMENT
#1
Naturally helps*
Fortify your digestive system with healthy bacteria 24/7*
Build & support a healthy digestive system
Maintain digestive balance
42 Capsules
6 Week Supply

Original Kefir
Kefir
Kefir
Kefir
Kefir
Kefir
Kefir
Kefir
Kefir
Kefir

Enteragam®

- Serum-derived Bovine Immunoglobulin/Protein Isolate:
  - Contain the immune experience of all these cows
  - ~60% Immunoglobulins
    - >50% IgG
    - 1% IgA
    - 5% IgM
  - Albumin
  - Other proteins (similar to those found in milk and colostrum)

New Treatment Approaches for *C. difficile* Infection



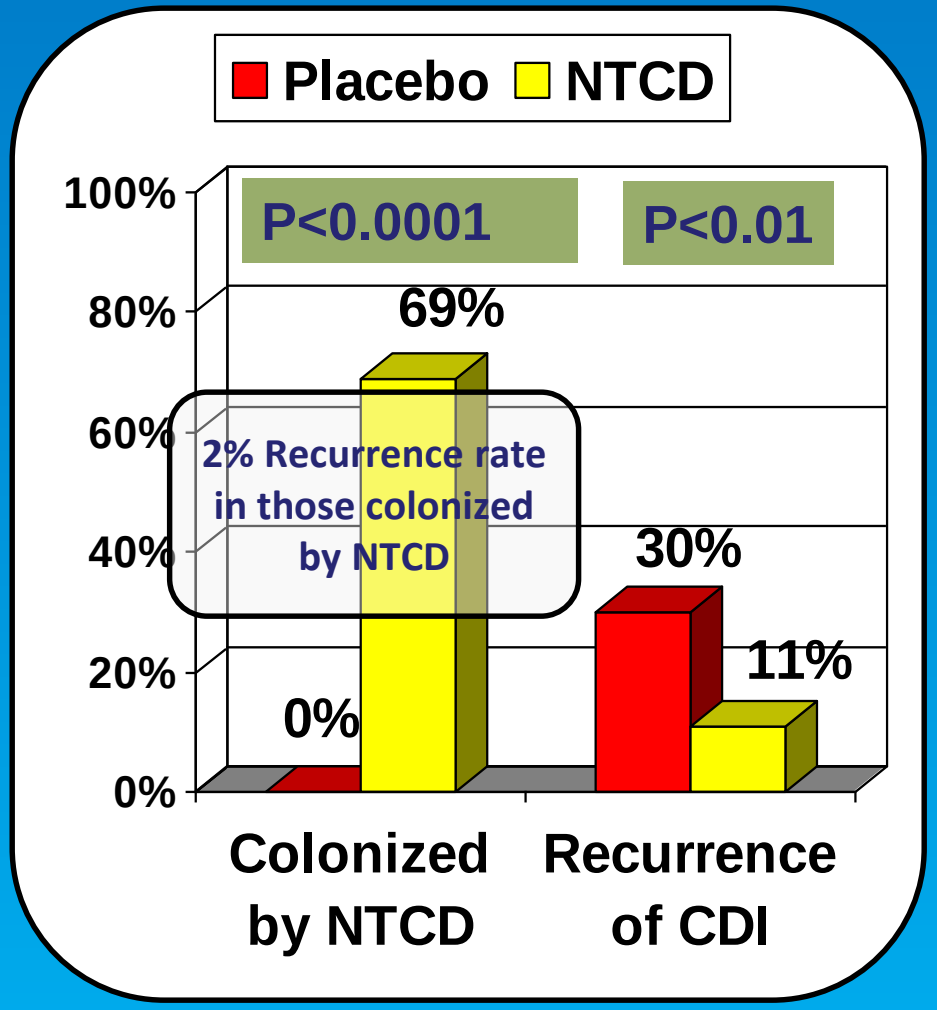
Non-toxigenic *C. difficile* spores; Nature's tailor-made probiotic?

- **NTCD** **(Non-toxigenic *C. difficile*)**
  - Spores of strain VP20621
- **Protects hamsters** against colonization by toxigenic *C. difficile* and against CDI

Phase II trial:

Pts with CDI on standard treatment (vanco or metro) randomized to:

- **Placebo (n=43)**
- ***or* NTCD (Total n=125)**
  - 10^4 x 7 days (n=41)
  - 10^7 x 7 days (n=43)
  - 10^7 x 14 days (n=41)

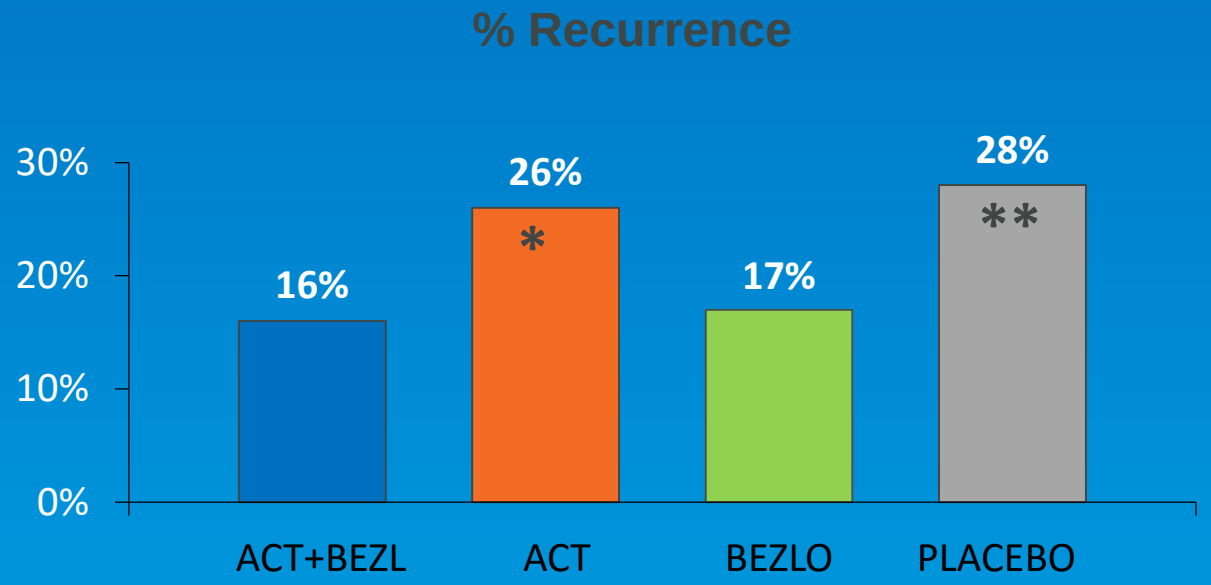


Gerding DN, et al. *JAMA*. 2015;313:1719-27.

Recurrent CDI Rates in Two Phase 3 Trials of Actoxumab/Bezlotoxumab

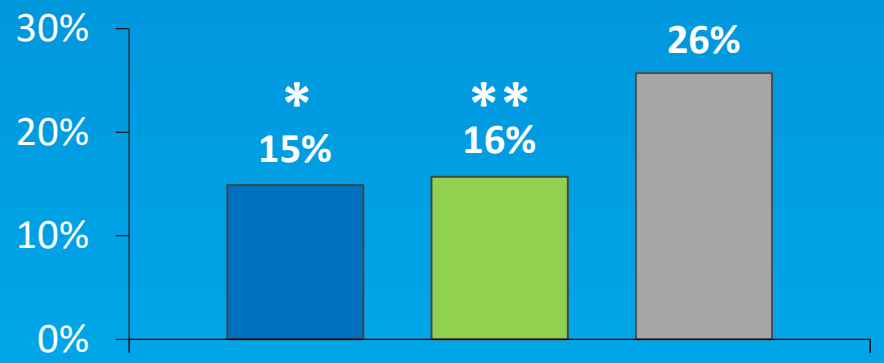
**MODIFY I

*ACT+BEZLO vs Pbo: P<0.0001
**BEZLO vs Pbo: P=0.0003



**MODIFY II

*ACT+BEZLO vs Pbo: P<0.0001
**BEZLO vs Pbo: P=0.0003

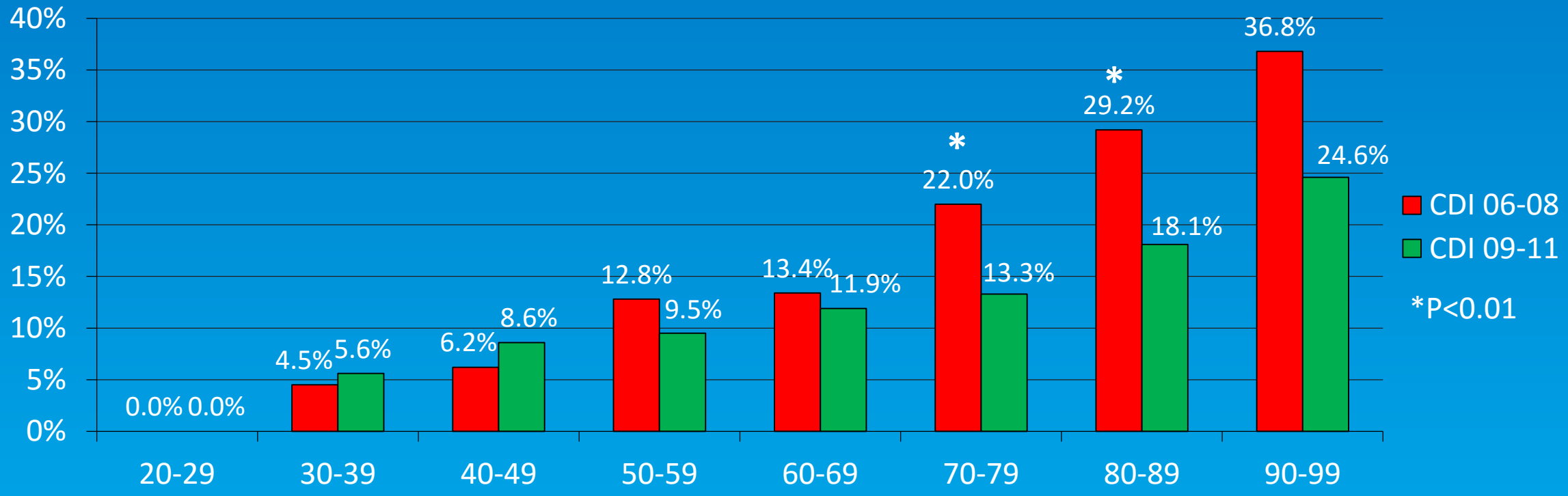


Wilcox M et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

The race begins…

So How Do I treat Patients?

C. difficile Infection 30-Day Mortality by Decade of Life



Feuerstadt P et al. *Am J Gastroenterol*. 2014;109(8):1265-76.

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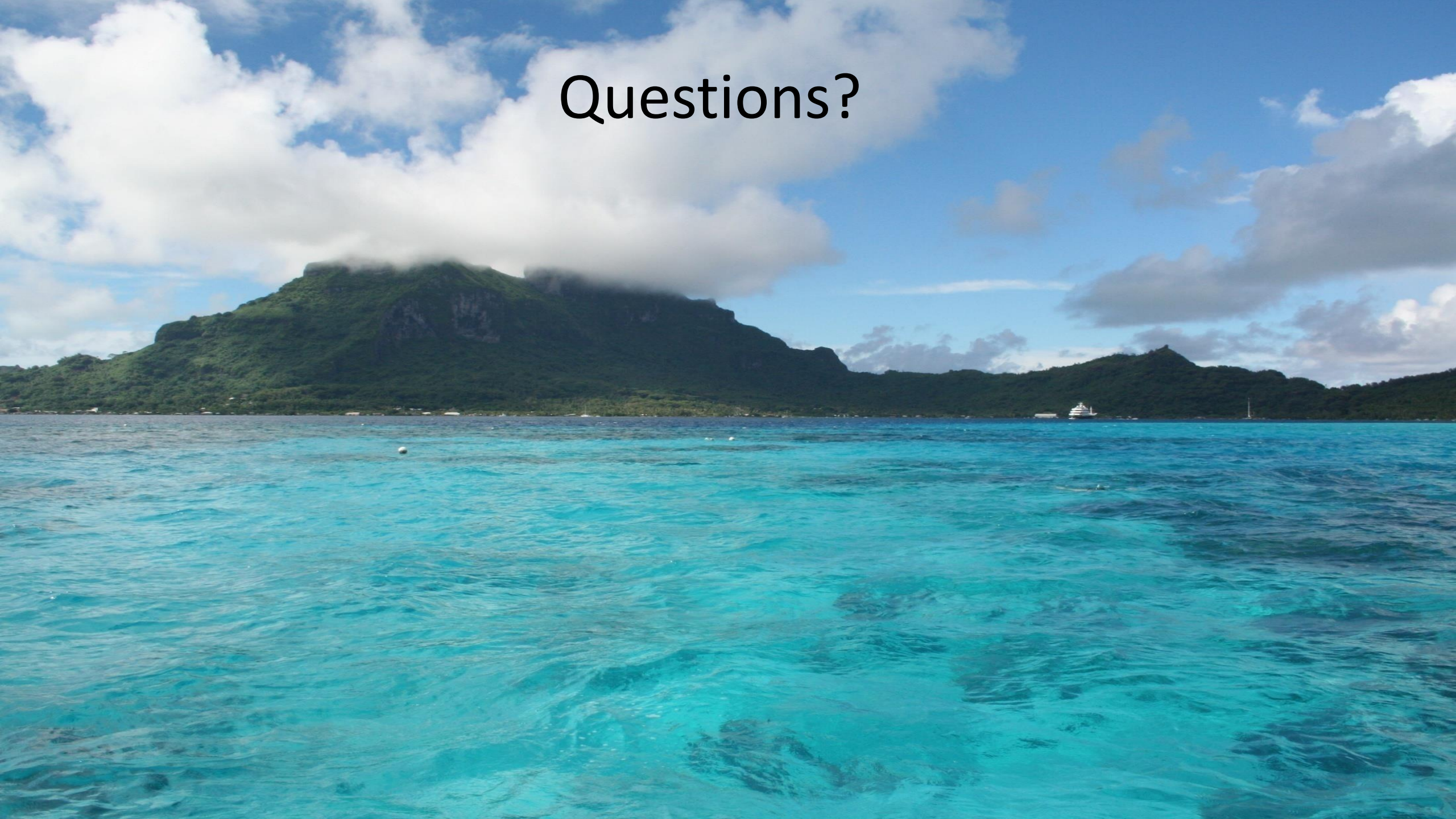
Questions?