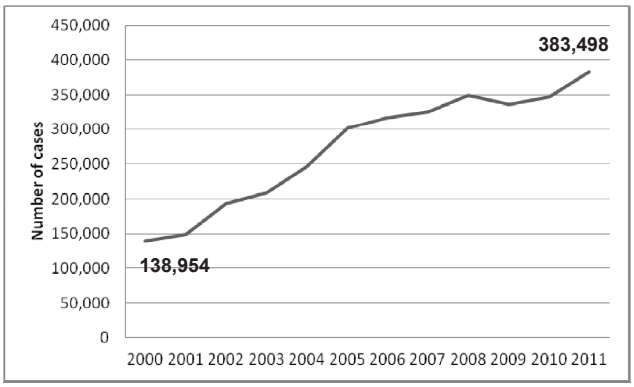
Epidemiological Trends in the Healthcare and Community Settings

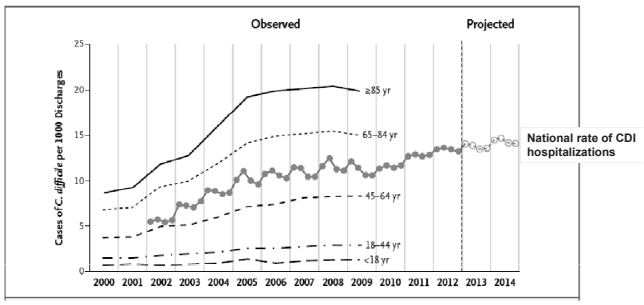
Stuart J. Johnson, MD, FIDSA, DTM&H
Professor, Department of Medicine
Stritch School of Medicine
Loyola University
Chicago, IL

Total Number of CDI Cases in U.S. Hospitals Nationwide Inpatient Sample (NIS)



Source: AHRQ HCUP data. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.

The Rate of *C. difficile* Infection is Predicted to Remain High



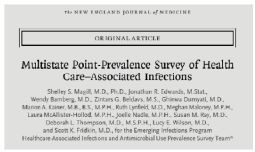
Steiner C et al. HCUP projections report #2014-01. Rockville MD: Agency for Healthcare Research and Quality 2014. [http://hcup-us.ahrq.gov/reports/projections/2014-01.pdf.]
Lessa FC, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S65-S70.
Leffler DA, Lamont TJ. *N Engl J Med.* 2015;372:1539-48.

C. difficile Infection (CDI) Recognized as a Top Priority

- **CDC:** urgent threat, EIP surveillance
- **NIH:** requests for applications for novel therapeutics
- **CMS:** publically reported, may impact hospital reimbursement

CDC Emerging Infections Program (EIP) Surveillance for CDI

Active population- and laboratory- based surveillance systems in selected counties in 10 U.S. states since 2009


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multistate Point-Prevalence Survey of Health Care–Associated Infections

Shelley S. Magill, M.D., Ph.D., Jonathan R. Edwards, M.Stat., Wendy Bamberg, M.D., Zintars G. Beldavs, M.S., Ghinwa Dumyati, M.D., Monroe A. Kainer, M.B., B.S., M.P.H., Ruth Lynfield, M.D., Meghan Maloney, M.P.H., Laura McAllister-Hollod, M.P.H., Joelle Nadle, M.P.H., Susan M. Ray, M.D., Deborah L. Thompson, M.D., M.S.P.H., Lucy E. Wilson, M.D., and Scott K. Fridkin, M.D., for the Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team*

← *C. difficile* is the most commonly identified health care-assoc. infection (HAI) – 12.1% of all HAIs
Magill SS, et al. *N Engl J Med.* 2014;370:198-208.


NAP1 Strain Type Predicts Outcomes From *Clostridium difficile* Infection

Isaac See,[1,2] Yi Mu,[1] Jessica Cohen,[1,2] Zintars G. Beldavs,[1] Lisa G. Winston,[3] Ghinwa Dumyati,[4] Stacy Holzbauer,[5] John Dunn,[6] Monica M. Farley,[7,8] Carol Lyons,[11] Helen Johnston,[12] Eric Phipps,[13] Rebecca Perlmutter,[14] Lydia Anderson,[1] Dale N. Gerding,[15,16] and Fernanda C. Lessa[1]

↑ NAP1 is the most prevalent strain (28.4%) & predicts severe disease, severe outcome & death
See I, et al. *Clin Infect Dis*. 2014;58:1394-400.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

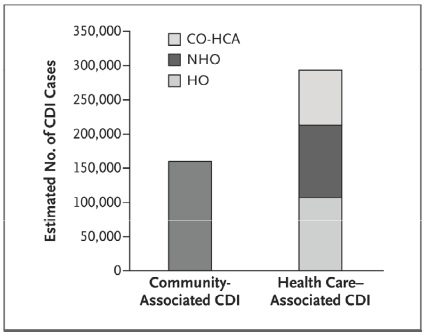
Burden of *Clostridium difficile* Infection in the United States

Fernanda C. Lessa, M.D., M.P.H., Yi Mu, Ph.D., Wendy M. Bamberg, M.D., Zintars G. Beldavs, M.S., Ghinwa K. Dumyati, M.D., John R. Dunn, D.V.M., Ph.D., Monica M. Farley, M.D., Stacy M. Holzbauer, D.V.M., M.P.H., James I. Meek, M.P.H., Erin C. Phipps, D.V.M., M.P.H., Lucy E. Wilson, M.D., Lisa G. Winston, M.D., Jessica A. Cohen, M.P.H., Brandi M. Limbago, Ph.D., Scott K. Fridkin, M.D., Dale N. Gerding, M.D., and L. Clifford McDonald, M.D.

↑ *C. difficile* was responsible for ~half a million infections & ~29,000 deaths in 2011
Lessa FC, et al. *N Engl J Med.* 2015;372:825-34

Estimated U.S. Burden of CDI

Number of cases according to the location of stool collection and inpatient healthcare exposure, 2011



HCA CDI: 293,000
-*CO-HCA*: 81,300
-*NHO*: 104,400
-*HO*: 107,600

CA CDI: 159,700
-82% had outpatient health care exposure

2/3 were HCA, but only 1/4 had onset during hospitalization

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

Still Much to Understand

- Diagnosis
  - Patient selection
  - Diagnostic assay
- Prevention
  - Better data needed
  - Challenge: *C. difficile* is ubiquitous
- Treatment
  - Prevent complications
  - Prevent recurrences

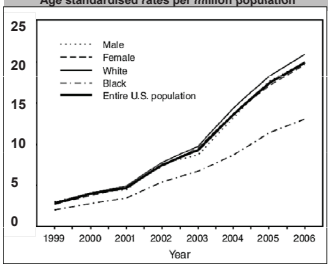
New Perspectives on CDI Pathogenesis and How this Translates to Therapy

Ciarán P. Kelly, MD
Professor of Medicine
Harvard Medical School
Director Gastroenterology Fellowship Training
Director Celiac Center
Beth Israel Deaconess Medical Center
Boston, MA

C. difficile Infection & Mortality

US CDI Death Rates*

*Age standardised rates per million population



CDC estimates**

>500,000 cases annually

29,000 CDI-related deaths

~100 deaths per million annually

"Urgent Hazard" [highest threat level]

In US, reported deaths related to CDI (according to death certificates) are:

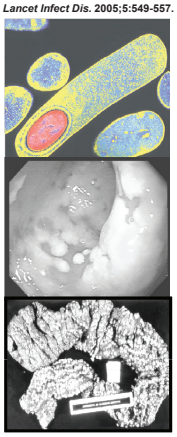
- ×4 deaths related to MRSA
- ×6 deaths related to all other enteric pathogens combined

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

CDI Pathogenesis & Novel Therapy

Aslam S et al. *Lancet Infect Dis.* 2005;5:549-557.

- Steps in the Pathogenesis of CDI
- New approaches to prevention & treatment
- Restoring colonization resistance
  - FMT (Fecal microbial therapy)
  - Other bacteriotherapies
- Immunity & immunization
  - Passive immunotherapy
  - Active vaccine



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Pathogenesis of *Clostridium difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora ⇐ "Dysbiosis"

(loss of colonization resistance)

↓

Colonization by *C. difficile* ⇐ Exposure

↓

Anti-toxin immunity — **Toxin A & Toxin B** ⇐ Toxin effects

↙ ↘

Symptomless carriage — **Diarrhea & colitis**

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.
Kyne L, et al. *Lancet.* 2001;357:189-93.

Pathogenesis of *Clostridium difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora ⇐ **"Dysbiosis"**

(loss of colonization resistance)

- Antimicrobials
- Chemotherapy
- Neonatal state
- Enteric infection
- IBD with colitis

↓

Colonization by *C. difficile*

↓

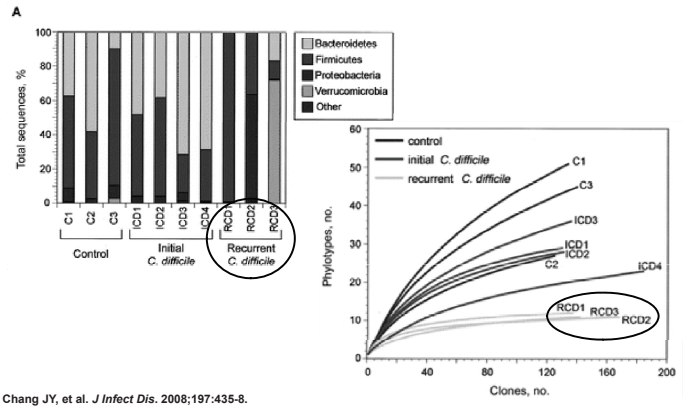
Toxin A & Toxin B

↙ ↘

Symptomless carriage **Diarrhea & colitis**

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Decreased Diversity of Fecal Microbiome in CDI



Chang JY, et al. *J Infect Dis*. 2008;197:435-8.

Antibiotics Predisposing to CDI:

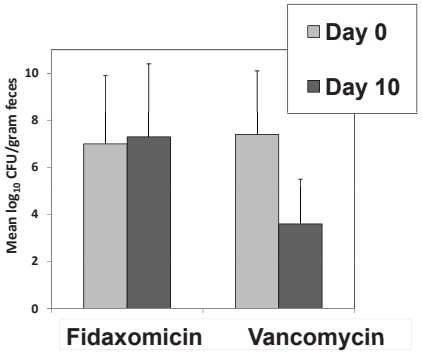
The good, the bad, and the ugly

Uncommonly Related	Less Commonly Related	Very Commonly Related
Aminoglycosides	Other penicillins	Clindamycin
Bacitracin	Sulfonamides	Ampicillin
Metronidazole	Trimethoprim	Amoxicillin
Teicoplanin	Cotrimoxazole	Cephalosporins
Rifampin	Macrolides	(2nd and 3rd generation)
Chloramphenicol		Fluoroquinolones
Tetracyclines		
Carbapenems		
Daptomycin		
Tigecycline		

Bouza E, et al. *Med Clin North Am.* 2006;90:1141-1163.
Loo VG, et al. *N Engl J Med.* 2005;353:2442-2449.

Fidaxomicin may Cause Less Intestinal Dysbiosis than Vancomycin

***Bacteroides* group counts in feces before and after 10 days of treatment with:**
Fidaxomicin (200 mg bid)
or
Vancomycin (125 mg qid)



Louie TJ, et al. *Clin Infect Dis.* 2012;55 Suppl 2:S132-142.

C. difficile Infection: Basic Principles of Management

- Suspect on clinical grounds
- **Discontinue non-essential antibiotics**
- Confirm presence of toxin-producing *C. difficile* by stool testing (usually PCR or EIA)
- Empiric treatment best avoided UNLESS:
  - Very high clinical index of suspicion
  - OR very severe illness

Non-*C. difficile* Antibiotics & Response to Therapy: New Data for an Old Rule

Outcome	No additional antibiotics	With additional antibiotics	
Time to resolution of diarrhea (median)	52 hours	96 hours	p<0.001
% Diarrhea NOT resolved at 10 days	7%	16%	p<0.001
% Sustained response and no recurrence	25%	34%	p=0.005

Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-7.

Novel Approaches: Turning to Nature's Cures for CDI

Antibiotic therapy

↓

Disturbed colonic microflora ← **Restore colonization resistance**

↓

C. difficile exposure & colonization

↓

Toxin A & Toxin B

↙ ↘

Symptomless carriage Diarrhea & colitis

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Probiotics to Restore Colonization Resistance and Prevent *C. difficile* Infection

Probiotics →

Antibiotic therapy

↓

Disturbed colonic microflora

↓

C. difficile exposure & colonization

↓

Toxin A & Toxin B

↙ ↘

Symptomless carriage Diarrhea & colitis

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

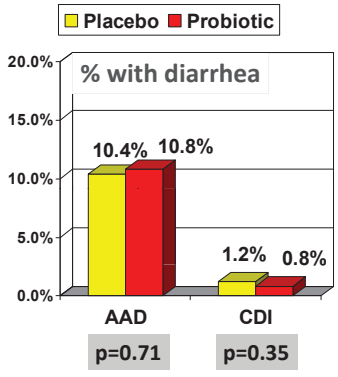
Lactobacilli and Bifidobacteria for Prevention of AAD and CDI

UK, National Health Service (NHS) prospective, multi-center, double-blind trial in ≥65-year-old inpatients receiving antibiotics

Randomized to 21 days of:

Probiotic (n=1,470)
$6x10^{10}$ organisms per day, multistrain lactobacilli & bifidobacteria mixture
or
Placebo (n=1471)

Primary outcomes:
AAD within 8 weeks
CDI within 12 weeks



Allen SJ, et al. *Lancet.* 2013;382:1249-57.

National Guidelines do not Recommend Oral Probiotics for CDI Prevention or Treatment

Episode of CDI	Treatment
First recurrence	• Metronidazole, vancomycin or fidaxomicin
Second recurrence	• Prolonged oral vancomycin (tapering and pulse-dosed) OR fidaxomicin
Third and subsequent recurrences	• Prolonged oral vancomycin (tapering and pulse-dosed) • Fidaxomicin • Vancomycin with rifaximin "chaser" • Fecal microbial transplant

Why?

- Few RCTs
- Most studies single-center
- Reproducibility not shown
- Different agents studied
- Therapeutic indication not always clear

"Not recommended" Cohen SH, et al. Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol.* 2010;31(5):431-55.
"insufficient evidence to support" - Debast SB, et al. European Society of Clinical Microbiology and Infectious Diseases. *Clin Microbiol Infect.* 2014;20(Suppl 2):1-26.
"Limited evidence for use ..." Surawicz CM, et al. Am College of Gastroenterol. *Am J Gastroenterol.* 2013;108(4):478-98.

FECAL ENEMA AS AN ADJUNCT IN THE TREATMENT OF PSEUDOMEMBRANOUS ENTEROCOLITIS

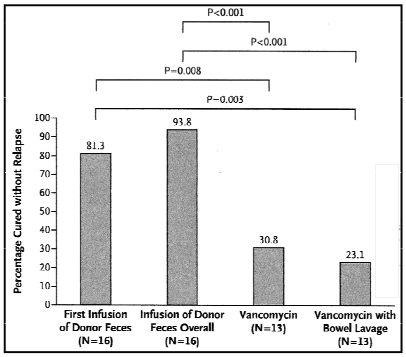
B. Eiseman, M.D., W. Silen, M.D., G. S. Bascom, M.D., and A. J. Kauvar, M.D., Denver, Colo.

(From the Departments of Surgery and Medicine, University of Colorado School of Medicine and the Veterans Administration Hospital)

- Fecal transplantation by enema for four patients with fulminant, life-threatening, pseudomembranous enterocolitis.
- Empiric therapy to "re-establish the balance of nature" within the intestinal flora to correct the disruption caused by antibiotic treatment.
- They reported "immediate and dramatic" responses and concluded that "this simple yet rational therapeutic method should be given more extensive clinical evaluation".

Eiseman B, et al. *Surgery.* 1958;44:854-9.

Duodenal Infusion of Donor Feces for Recurrent *C. difficile* Infection



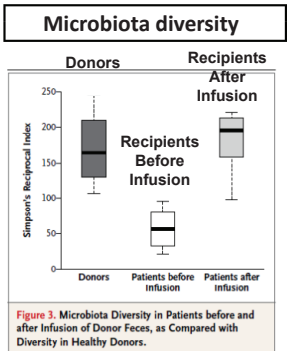


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

van Nood E, et al. *N Engl J Med.* 2013;368:407-15.
Kelly CP. *N Engl J Med.* 2013;368:474-5.

FMT Approaches:
Bringing Methods to the Madness

- Multiple methods of administration
  - Overall ~75% by colonoscopy or retention enema
  - ~25% by nasogastric tube or upper GI endoscopy
    - Reported efficacy >90% for lower versus >80% for upper routes
- Recent publications provide recommendations for:
  - Donor screening, processing of donor feces, and methods of administration
- "Stool banks" – improve access [academic, non-for-profit & commercial]

Bakken JS, et al. *Clin Gastroenterol Hepatol*. 2011;9:1044-9.
Hamilton MJ, et al. *Am J Gastroenterol*. 2012;107:761-7.
Youngster I, et al. *JAMA*. 2014;312:1772-8

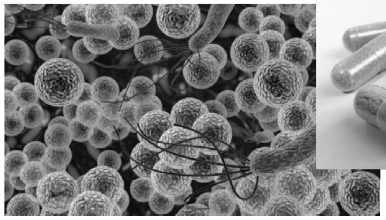
OpenBiome *(www.openbiome.org)*

- Established 2013
  - A "public stool bank" operated by the MIT Microbiome Health Research Institute (MHRI)
  - A nonprofit organization
  - Provides processed, frozen stool from rigorously-screened, healthy donors for use in FMT
  - ~$350 per unit (less than screening/processing cost)
  - Goal is to improve ease of access to FMT

Stool banking in your neighborhood

Beyond FMT – Oral Capsules

- Encapsulated feces
- Defined bacterial cultures
- Fecal spores preparation
- Non-toxigenic *C. difficile spores*



Youngster I, et al. *JAMA*. 2014;312(17):1772-8.

Beyond FMT

Bacteriotherapy with a Defined Culture

THE LANCET, MAY 27, 1989

TABLE II—EFFECT OF BACTERIAL STRAINS USED FOR BACTERIOTHERAPY ON GROWTH OF CL DIFFICILE STRAINS ISOLATED FROM PATIENTS AND VICE VERSA

Bacterial strain (registration number)	Patient					
	1	2	3	4	5	6
S faecalis (1108-2)	0	0	0	0	0	0
Cl innocuum (A27-24)	0	0	0	0	0	0
Cl ramosum (A31-3)	0	0	0	0	0	0
Bact ovatus (A40-4)	×	×	×	×	×	×
Bact vulgatus (A35-14)	×	×	×	×	×	×
Bact thetaiotaomicron (A33-12)	×	×	×	×	×	×
E coli (1109)	0	0	0	0	0	0
E coli (1108-1)	+	+	+	+	+	+
Cl bifermentans (A27-6)	+	+	+	+	+	+
P prodactus (1108-2)	+	+	+	+	+	+

0 denotes "no inhibition"
× denotes "test strain inhibited by *Cl difficile*"
+ denotes "*Cl difficile* inhibited by test strain.

Tvede M, Rask-Madsen J. *Lancet*. 1989;1(8648):1156-60.

THE LANCET, MAY 27, 1989

BACTERIOTHERAPY FOR CHRONIC RELAPSING CLOSTRIDIUM DIFFICILE DIARRHOEA IN SIX PATIENTS

M. TVEDE[1] J. RASK-MADSEN[2]

Department of Clinical Microbiology, Rigshospitalet, Statens Seruminstitut,[1] and Section of Gastroenterology, Department of Medicine G, Bispebjerg Hospital, University of Copenhagen, Denmark[2]

Summary Six patients with chronic relapsing diarrhoea caused by *Clostridium difficile* were treated with rectal instillation of homologous faeces (one patient) or a mixture of ten different facultatively aerobic and anaerobic bacteria diluted in sterile saline (five patients). The mixture led to a prompt loss of *Cl difficile* and its toxin from the stools and to bowel colonisation by *Bacteroides* sp, which had not been present in pre-treatment stool samples. Strains of *Escherichia coli*, *Cl bifermentans*, and *Peptostreptococcus productus* in the mixture inhibited the in-vitro growth of *Cl difficile*, which in turn inhibited the growth of *Bacteroides ovatus*, *Bacteroides vulgatus*, and *Bacteroides thetaiotaomicron*. The finding that *Bacteroides* sp had been absent during the patients' illness but was present after recovery suggests that the absence of *Bacteroides* sp may result in chronic relapsing *Cl difficile* diarrhoea, and that its presence may prevent colonisation by *Cl difficile*.

Non-toxigenic *C. difficile* is Not a Pathogen

Antibiotic therapy

↓

Disturbed colonic microflora

(loss of colonization resistance)

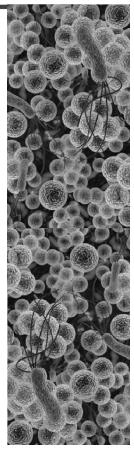
↓

Non-toxigenic *C. difficile*

↓

Toxin A Toxin B

Symptomless carriage **Diarrhea & colitis**



Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932-40.

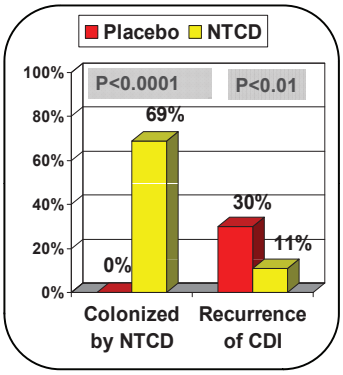
Non-toxigenic *C. difficile* Spores Nature's Tailor-made Probiotic?

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

Phase II trial:

All with CDI on oral vanco

- **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.

Turning to Nature's Cures for CDI

Antibiotic therapy

↓

Disturbed colonic microflora

↓

C. difficile exposure & colonization

↓

Toxin A & Toxin B

↙ Symptomless carriage

↘ Diarrhea & colitis

X **Most Probiotics**

Restore colonization resistance

- ✓ **FMT**
  - ✓ Infusion
  - ✓ Enema
  - ✓ Pills
- ✓ **Defined cultures**
- ✓ **Spore preps**
  - ✓ Fecal
  - ✓ Non-toxigenic CD

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Novel Approaches: Turning to Nature's Cures for CDI

Antibiotic therapy

↓

Disturbed colonic microflora

Restore colonization resistance

↓

C. difficile exposure & colonization

↓

Toxin A & Toxin B

↙ Symptomless carriage

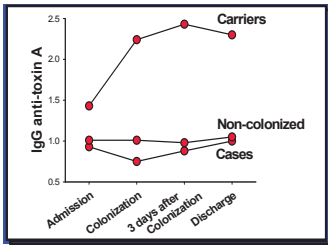
↘ Diarrhea & colitis

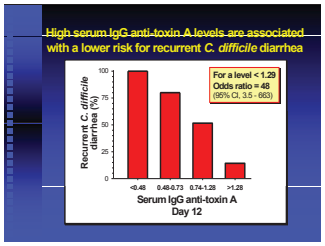
Immunize: Active vaccine or passive immunotherapy

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Anti-toxin Immunity Protects Against CDI

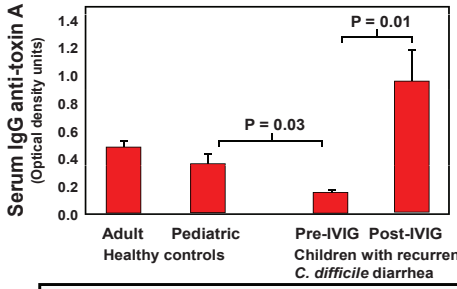
- High serum anti-toxin in symptomless carriers
- Serum anti-toxin response & protection against recurrent CDI





Kyne L, et al. *N Engl J Med.* 2000;342:390-397.
Kyne L, et al. *Lancet.* 2001;357:189-193.

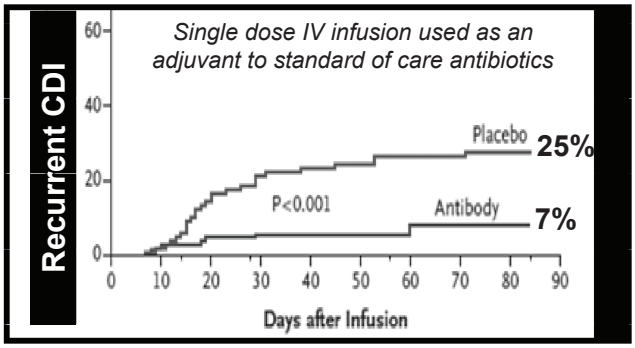
Intravenous Immunoglobulin Therapy for Recurrent *C. difficile* Diarrhea



Also used in severe refractory disease
Efficacy not proven – no RCT

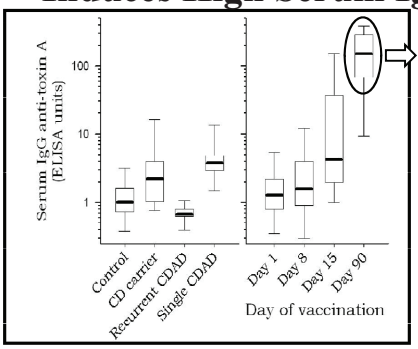
Leung DY, et al. *J Pediatr.* 1991;118:633-637.

Treatment with Monoclonal Antibodies Against *C. difficile* Toxins A and B Prevents Recurrence



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

A *C. difficile* Toxoid Vaccine (inactivated toxins A and B) Induces High Serum IgG Anti-toxin



50 times levels in patients with protective immunity

Young, healthy volunteers
90 days after first dose

Aboudola S, et al. *Infect Immun.* 2003;71:1608-1610.
Greenberg RN, et al. *Vaccine.* 2012:30;2245-9.

How Close are These Novel Treatments to Clinical Use?

Bacteriotherapy:

- FMT – already in use
- FMT by pill – already in use
- Defined bacterial mixtures – in development
- Spores of non-toxigenic *C. difficile* – in development

Restore colonization resistance

Immunization:

- Anti-toxin HuMabs – Phase III trials complete
- *C. difficile* vaccine – Phase III trial ongoing

Immunize: Active vaccine or passive immunotherapy

CDI: Case History

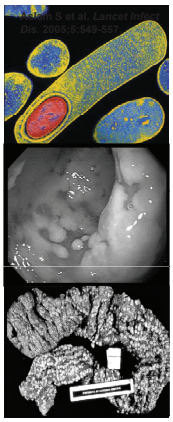
- Jackie, a 66-year-old woman
- Multiple medical problems (morbid obesity, type 2 diabetes mellitus, ischemic heart disease & recurrent urinary tract infections)
- Had been stable and feeling well for several months
- Developed oral pain
- Her dentist prescribed clindamycin for a possible dental infection
- Five days after completing the antibiotic she developed mild diarrhea and saw her PCP

CDI Case: Jackie (cont'd)
Which ONE statement is correct?

1. She probably has **simple antibiotic-associated diarrhea** and so no stool testing is indicated unless the diarrhea persists or worsens
2. If she **has not visited a hospital** or other healthcare facility recently, her risk for CDI is negligible
3. If stool testing shows the presence of toxigenic *C. difficile* but her **symptoms have resolved,** then treatment is not necessary
4. If stool testing shows the presence of toxigenic *C. difficile*, she should **avoid looking after or changing diapers for her 12-month-old twin grandchildren**
5. If stool testing shows the presence of toxigenic *C. difficile*, this indicates that **she was likely a *C. difficile* carrier** when she began clindamycin treatment

Take-Home Points

- Key events in CDI pathogenesis include:
  - Loss of colonization resistance
  - Exposure and colonization
  - Toxin production
  - Diarrhea and colitis if not immune
- Antibiotics differ in the degree to which they disrupt *C. difficile* colonization resistance
- Bacteriotherapies to restore colonization resistance are available and appear effective
- Agents for passive and active immunization are at late stages in development



Recognizing Factors Associated with Poor Clinical Outcomes in CDI

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

Back to the Patient

Jackie's diarrhea resolved without event. When seeing her PCP for a routine visit, she noted some vague side discomfort, but denied urinary urgency, dysuria, suprapubic tenderness or fevers. However, because of her history of UTI, a urine culture was sent. A pan-susceptible *E. coli* grew and the patient was started on ciprofloxacin.

On day 3 of ciprofloxacin, she developed diarrhea with severe abdominal cramping. She soon was unable the make it to the bathroom. She went to the emergency department. Stool was positive for *C. difficile* toxins, her WBC was 16,000/μL, and her serum creatinine 2.5 mg/dL.

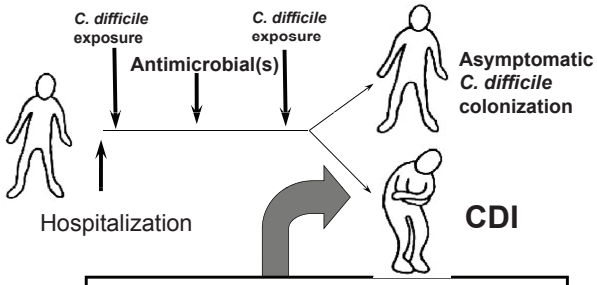
Which is correct?

1. Most patients diagnosed with UTI actually have a UTI. The cipro was appropriate.
2. The positive test for *C. difficile* toxin in stool likely represents asymptomatic carriage, not CDI.
3. CDI is no big deal. Metronidazole is an inexpensive and effective treatment.
4. It is possible to risk stratify patients with CDI to select treatments that will optimize patient outcomes.

Two Biggest Challenges in Treating CDI

- Severe CDI
  - Decrease morbidity and mortality
- Recurrent CDI
  - Decrease recurrences

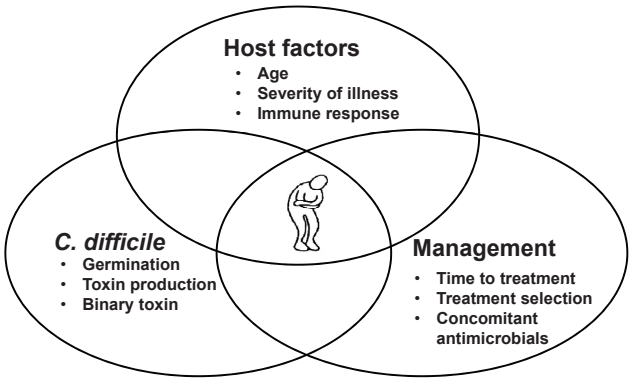
Current Pathogenesis Model for *C. difficile* Infection (CDI)



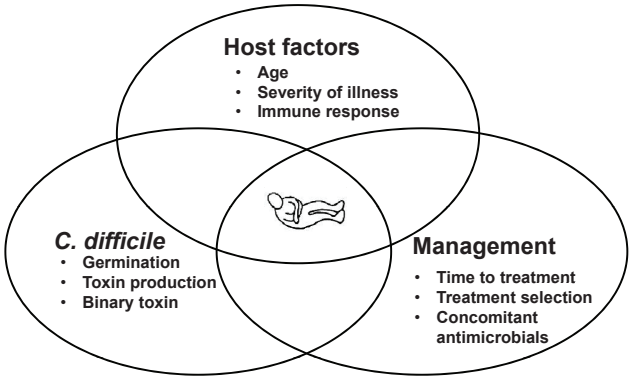
Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic antibody response results in CDI.

Johnson S, Gerding DN. *Clin Infect Dis.* 1998;26:1027-1036.
Kyne L, et al. *N Engl J Med.* 2000;342:390-397.

Factors that Contribute to Poor Outcomes



Factors that Contribute to Poor Outcomes



Patient Factors Associated with Death

Variable	Multivariable hazard ratio‡ (95% CI)
CDAD	1.23 (1.03–1.46)
Male sex	1.17 (1.08–1.27)
White race	1.22 (1.11–1.33)
Modified APS	
≤2	Reference
3–4	1.09 (0.96–1.24)
5–6	1.30 (1.14–1.49)
≥7	1.65 (1.46–1.87)
Albumin, g/dL§	
>3.5	Reference
2.5–3.5	1.62 (1.45–1.82)
<2.5	2.93 (2.52–3.42)
Liver disease	
None	Reference
Mild	2.37 (1.85–3.04)
Moderate to severe	3.76 (3.05–4.64)
Diabetes with chronic complications	1.49 (1.18–1.88)
Congestive heart failure	1.28 (1.15–1.42)
Cerebrovascular disease	1.62 (1.37–1.92)
Cancer, excluding leukemia or lymphoma	2.44 (2.15–2.76)
Leukemia or lymphoma	4.92 (3.98–6.08)
Metastatic solid tumor	4.41 (3.87–5.03)
HIV/AIDS	2.88 (2.12–3.91)
Paraplegia/ hemiplegia	1.53 (1.12–2.07)
Mechanical ventilation	3.17 (2.71–3.71)
ICU admission	1.31 (1.14–1.50)

Dubberke ER, et al. *Emerg Infect Dis*. 2008;14:1031-8.

C. difficile Strain and Outcomes

Severe CDI*

Risk Factors[a]	AOR (95% CI)
Cases with strain typing results (n = 2057)	
Age>65 y	1.69 (1.31–2.18)
Healthcare-associated epidemiologic classification[b]	1.75 (1.32–2.34)
Emergency department visit during 12 wk prior to infection	1.31 (1.01–1.69)
Charlson index	1.08 (.98–1.20)
Medications during 14 d prior to infection	
Immunosuppressive treatment	1.42 (1.05–1.92)
Any antibiotic	1.38 (1.08–1.76)
NAP1 strain	1.74 (1.36–2.22)

***Ileus, toxic megacolon, or WBC >15K**

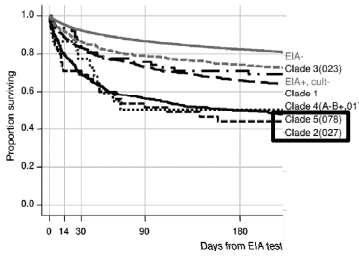
Severe Outcomes from CDI**

Risk Factors[a]	AOR (95% CI)
Cases with strain typing results (n = 2057)	
Age >65 y	1.71 (1.06–2.76)
White race	0.49 (.29–.85)
Healthcare-associated epidemiologic classification[b]	2.90 (1.63–5.19)
Charlson index	1.71 (1.38–2.13)
Any antibiotic during 14 d prior to infection	1.63 (1.04–2.56)
NAP1 strain	1.66 (1.09–2.54)

****ICU transfer, colectomy, death in 30 days**

See I, et al. *Clin Infect Dis*. 2014;58:1394-400.

C. difficile Strain and Death



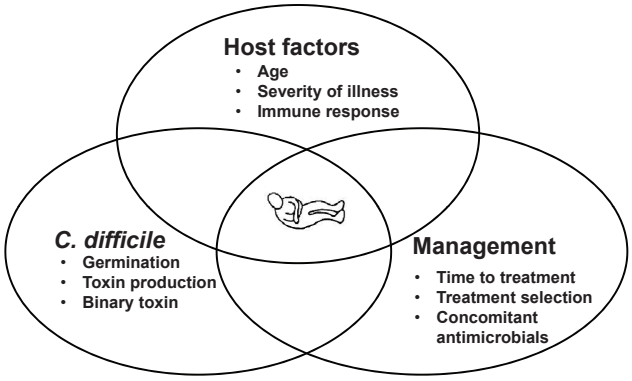
Death in 14 days

Risk Factors[a]	AOR (95% CI)
Cases with strain typing results (n = 2057)	
Age >65 y	2.98 (1.45–6.11)
White race	0.46 (.23–.95)
Epidemiologic classification	
Healthcare facility–onset	3.80 (1.62–8.94)
Community-onset healthcare facility–associated	2.33 (1.01–5.36)
Community-associated (reference)	
Charlson score	2.03 (1.44–2.86)
NAP1 strain	2.12 (1.22–3.68)

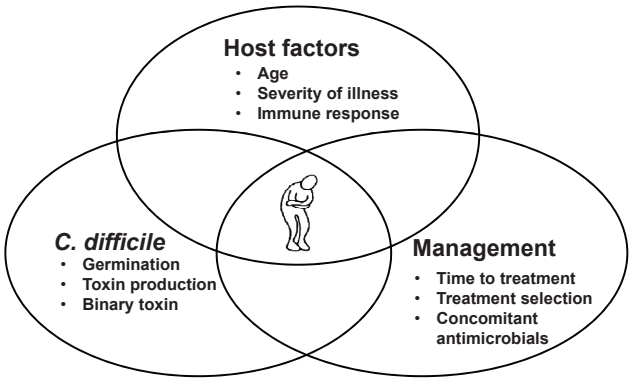
14 day mortality HR ~2.5 for clade 2

Walker AS, et al. *Clin Infect Dis*. 2013;56:1589-600.
See I, et al. *Clin Infect Dis*. 2014;58:1394-400.

Factors that Contribute to Poor Outcomes



Factors that Contribute to Poor Outcomes

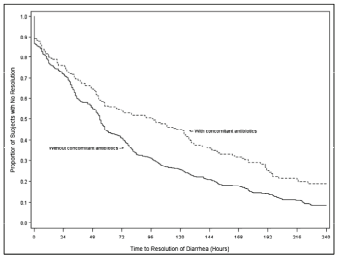


Back to the patient

Which statement is correct?

1. The ciprofloxacin is not indicated. Discontinuing it is an important component of her CDI management.
2. Outcomes of patients positive for toxin are worse than for patients that are toxin negative / PCR positive.
3. This patient has “severe” CDI. Treatment selection will impact her outcome.
4. All of the above.

Impact of Concomitant Antibiotics on Response to CDI Treatment



No CA	Fidaxo N=391	Vanco N=416	*P*
Clinical cure	92%	93%	0.80
Recurrence	12%	23%	<0.001
Sustained response	81%	69%	<0.001

CA	Fidaxo N=90	Vanco N=102	*P*
Clinical cure	90%	79%	0.04
Recurrence	17%	29%	0.05
Sustained response	72%	59%	0.02

CA = concomitant antibiotics

Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-7.

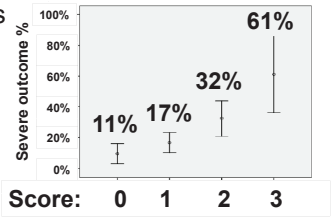
Risk Prediction for Severe Outcomes

Variable	Beth Israel (1995)	UPMC v1 (2005)	UPMC v2 (2008)	Calgary v1 (2006)	Calgary v2 (2007)	Hines VA (2007)	Illinois (Zar) (2007)	Temple (2009)
Age	X						X	
Concomitant abx	X							
Immunosuppressants	X		X					
Comorbidities	X		X					
Altered mental status	X		X					
Temperature				X		X	X	
Hypotension						X		
Abd pain / tender	X	X		X	X			
BM frequency				X	X			
Elevated WBC	X	X	X		X	X	X	X
Hypoalbuminemia	X		X				X	
Renal function	X						X	
Radiological findings		X	X			X		
Endoscopy findings							X	

Fujitani S, et al. *Infect Control Hosp Epidemiol.* 2011;32:220-8.

More Prediction Scores

- ATLAS: age, concomitant antimicrobials, albumin, WBC, creatinine
  - Predict response rate to CDI treatment
- Na: age, WBC, creatinine
  - Predict severe outcomes
- SHEA/IDSA Guidelines
  - WBC ≥15000
  - Cr ≥1.5 × pre-morbid



Miller MA, et al. *BMC Infect Dis.* 2013;13:148.
Na X, et al. *PLoS One.* 2015;10(4):e0123405.

Ultimate Goal: CDI Severity Scores and Improved Outcomes

- Illinois / Zar score
- Original study: metronidazole response 76% vs. vancomycin 97% (p=0.02)

	Before ($N = 144$)	After ($N = 112$)	*P* value
Mild to moderate CDI	$N = 85$	$N = 59$	
Refractory disease (*N*, %)	8 (9.41)	5 (8.47)	NS
Death during admission (*N*, %)	0 (0)	1 (1.7%)	NS
Length of stay, days (median, range)	11 (1–196)	11 (1–64)	NS
Severe CDI	$N = 59$	$N = 53$	
Refractory disease (*N*, %)	19 (32.20)	8 (15.09)	0.035
Death during admission (*N*, %)	8 (13.6%)	2 (3.77)	0.096
Length of stay, days (median, range)	17 (4–202)	15 (4–481)	NS

Zar FA, et al. *Clin Infect Dis.* 2007;45:302-7. Jardin CG, et al. *J Hosp Infect.* 2013;85:28-32.

Recurrent CDI

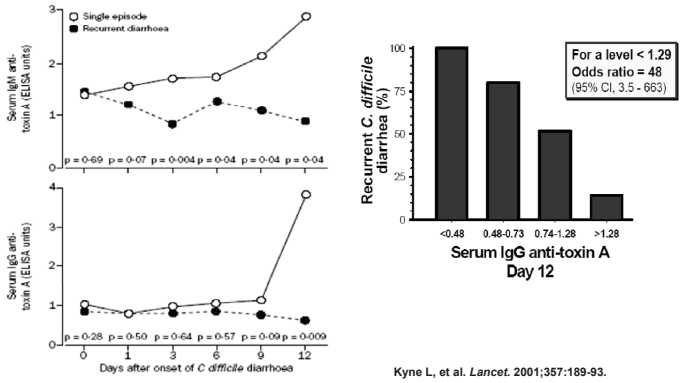
- Recurrence risk after first episode 15% to 30%
  - Risk increases with additional recurrences
- Associated with worse outcomes
  - Readmissions (RR = 2.5; 95% CI, 2.2–2.9)
  - Costs ($11,631; 95% CI, $8,937–$14,588)
  - Mortality (HR 1.3; 95% CI, 1.1–1.6)

Olsen MA, et al. *Am J Infect Control.* 2015;43:318-22.
Olsen MA, et al. *Clin Microbiol Infect.* 2015;21:164-70.
Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2014;35:1400-7.

Back to the Patient
Which statement is correct?

1. Infecting *C. difficile* strain is not associated with risk of recurrent CDI.
2. Anti-toxin antibody levels are not associated with risk of recurrent CDI.
3. It is not possible to identify patients at increased risk for recurrent CDI.
4. Recent exposure to ciprofloxacin may increase this patient's risk for recurrent CDI.

IgG Response Associated with Decreased Risk for Recurrent CDI



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

C. difficile Strain and Recurrent CDI

			Recurrence		
Variable	Test	Reference	OR	95% CI	*P* Value
REA group	BI group	Non-BI group	1.57	1.01–2.45	.046
	No isolate	Non-BI group	0.91	.57–1.47	.70
Age	≥65	<65	1.36	.93–1.98	.11
CDI history	One prior episode[b]	No prior episode	1.82	1.15–2.87	.01
Region	Canada	United States	1.37	.91–2.07	.13
	Europe	United States	0.78	.43–1.39	.14
Antibiotic history prior to CDI treatment	Yes	No	NA	NA	NA
CA during treatment period[a]	Yes	No	…	…	…
CA during treatment or follow-up period[b]	Yes	No	1.57	1.03–2.39	.04
Comorbidity[d]	Yes	No	NA	NA	NA
Treatment	Fidaxomicin	Vancomycin	0.45	.31–.65	<.0001

REA, restriction endonuclease analysis
Petrella LA, et al. *Clin Infect Dis.* 2012;55:351-7.

Difficult to Predict Recurrent CDI

- Risk for recurrence already high
- Risk may be influenced by local epidemiology/practices
- No commercially-available assays to measure anti-*C. difficile* antibody levels

Risk Factors for CDI and Recurrent CDI

Initial CDI

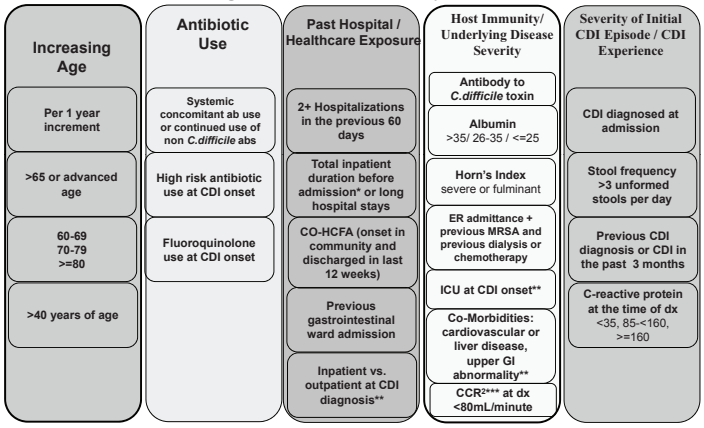
- Age
- Antimicrobials
- Severity of underlying illness
- Immune response

Recurrent CDI

- Age
- Antimicrobials
- Severity of underlying illness
- Immune response

Risk Factors Associated with CDI Recurrence

Findings from Selected Key Publications



* any past admission, >2-13 weeks, >13 weeks
** protective against CDI recurrence *** creatinine clearance rate

Prediction of *C. difficile* Recurrence

TABLE 2 Factors found to predict rCDI in the logistic regression model

Factor	*Odds ratio*	*95% CI*
Age (per 1 year)	1.21	1.04 - 1.40
CO-HCFA CDI (ref: HO-CDI)	1.71	1.32 - 2.22
2+ hospitalization in prior 60 days (ref: 0 hospitalizations)	1.49	1.08 - 2.06
New gastric acid suppression at the onset of iCDI	1.59	1.13 - 2.23
High-risk antibiotic at the onset of iCDIa	1.25	1.01 - 1.55
Fluoroquinolone at the onset of iCDI	1.31	1.04 - 1.65
ICU at the onset of iCDI	0.49	0.34 - 0.72

[a]High risk antibiotics included all cephalosporins, clindamycin, and penicillins.

The validated model had a C statistic of 0.63.

Zilberberg MD, et al. *J Hosp Med.* 2014;9:418-23.

Integrating the New with the Old when Managing CDI

Stuart J. Johnson, MD, FIDSA, DTM&H
Professor, Department of Medicine
Stritch School of Medicine
Loyola University
Chicago, IL

Overview

'Old':

- Current guideline recommendations
- Limitations of metronidazole and vancomycin

'New':

- Alternative approaches to therapy
- Emerging approaches in treating CDI and reducing the risk of recurrence

Case History, review

Chapter 1:

- 66-year-old woman with multiple medical problems
- Developed mild diarrhea 5 days after finishing a course of clindamycin for a dental infection
- ***Outcome*** *– resolved without specific treatment*

Chapter 2:

- She developed diarrhea with severe abdominal cramping 3 days after starting ciprofloxacin for a questionable UTI.
- Her WBC was 16,000 and serum creatinine 2.5
- ***Outcome*** *– symptoms resolved after receiving treatment based on severity stratified recommendations, vancomycin 125 mg 4 x daily for 10 days*

Case History, continued

Chapter 3:

- 9 days after successfully completing the vancomycin regimen, she again developed diarrhea with abdominal cramping
  - In review of her chart, the ciprofloxacin had been continued to finish a 10-day course of treatment for the 'UTI'
- She was then treated with vancomycin followed by a taper & pulse regimen
- Unfortunately, she again developed diarrhea 7 days after finishing the vancomycin taper/pulse

What would you recommend now?

1. Fecal microbiota transplant
2. Repeat vancomycin treatment followed by taper/pulse
3. Vancomycin 125 mg QID × 10 d followed by rifaximin 400 mg BID × 14 d
4. Fidaxomicin 200 mg BID × 10 d
5. Fidaxomicin 200 mg BID × 10 d followed by fidaxomicin 200 mg QD × 7 d, then once every other day for 2–3 weeks

History of CDI Guideline Recommendations & Clinical Practice

1970s: Vancomycin established as effective treatment for pseudomembranous colitis (*Tedesco F, et al. Lancet. 1978;2:226-8.)*

1980s: Metronidazole shown to be effective for CDI (*Teasley DG, et al. Lancet. 1983;2:1043-6.)*

1995: Hospital Infection Control Practices Advisory Committee (HICPAC):
- Reduce vancomycin use in hospitals (concern for emergence of vancomycin resistance in other pathogens) (*MMWR. 1995;44(RR-12):1-13.)*

1995: Society for Healthcare Epidemiology of America(SHEA) Position Paper on CDI:
- Vancomycin or metronidazole for 10 days is effective
- **Metronidazole may be preferred** (*Gerding DN, et al. ICHE 1995;16:459-77.)*

2010: SHEA/IDSA (Infectious Diseases Society of America) CDI guidelines:
- Vancomycin is the drug of choice (DOC) for severe disease
- **Metronidazole is DOC for mild-to-moderate CDI**
- 10–14 day course recommended (concern for slow response to metronidazole) (*Cohen SH, et al. ICHE 2010;31:431-55.)*

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010

- Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10–14 days (A-I)
- Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10–14 days (B-I)
- Vancomycin orally (and per rectum if ileus is present) with or without metronidazole IV...for severe, complicated CDI. Vancomycin is dosed at 500 mg (C-III)
- Consider colectomy in severely ill patients…(ideally before) serum lactate rises to 5 mmol/L and WBC rises to 50,000/μL (B-II)

Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010 – *Recurrent CDI*

- Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (C-III)
- Do not use metronidazole beyond first recurrence or for long-term chronic therapy (B-II)
- Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III)
- No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy (C-III)

Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

Limitations of Current Guidelines

- No mention of fidaxomicin
- Limited evidence for recommendations on severe, complicated CDI
- Limited evidence for recommendations on recurrent CDI
- Little mention of fecal microbiota transplant

Limitations of Metronidazole and Vancomycin

- Recurrent CDI after initially effective treatment
- Modest-to-low fecal concentrations of metronidazole
- Potential for resistance (MIC creep with metronidazole)
- Neither treatment directly addresses the main pathogenic mechanism of *C. difficile* (toxin production)

New Data on CDI Treatment Since Publication of the IDSA/SHEA Guidelines

- Fidaxomicin phase 3 trials, randomized substudy of patients with first CDI recurrence
- Randomized trial of FMT
- Findings from the largest and most rigorous randomized comparison of metronidazole and vancomycin (phase 3 trials of tolevamer)

Phase 3 Multicenter Trials of Tolevamer for CDI

randomized, double-dummy, double-blind, active-controlled, parallel-design

	Treatment Regimen		
	First dose	All subsequent doses	
Treatment arm	Day 1, single loading dose	Through day 10	Through day 14
Tolevamer (3.0 gm in 43 mL liquid)	129 mL (9.0 g) plus 1 placebo capsule	1 placebo capsule qid	43 mL (3.0 g) tid
Vancomycin (125 mg capsules)	Placebo liquid plus 1 capsule	1 capsule qid	Placebo liquid tid
Metronidazole (375 mg capsules)	Placebo liquid plus 1 capsule	1 capsule qid	Placebo liquid tid

Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

Results

- 1118 patients randomized between 2005 & 2007
  - Study 301, n=574 (91 sites in the US & Canada)
  - Study 302, n=544 (109 sites in Europe, Australia, & Canada)
  - 1071 included in the full analysis set (FAS)*
    - tolevamer, n=534
    - metronidazole, n=278
    - vancomycin, n=259
- Patients similarly matched across the 3 treatment arms, but differences noted between studies in terms of age, body weight, inpatient status, and concomitant antibiotic use

*FAS: all randomized patients who received any treatment and who had any post-dose evaluation

Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

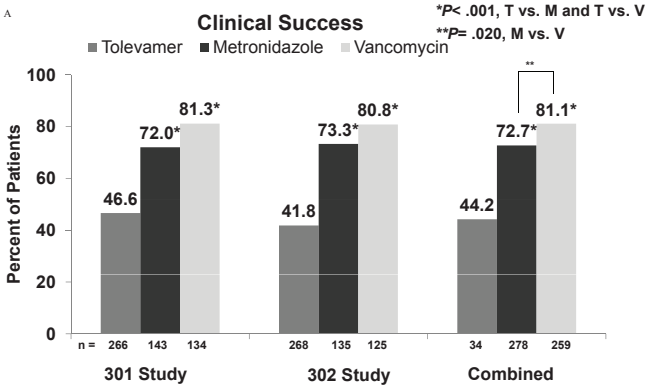
Baseline Characteristics

	Study 301 (n=543)	Study 302 (n=528)	P Value
Age	62 ± 17.7	68 ± 16.4	<.0001
Age group (>65 years)	46%	61%	
Gender (F)	52%	54%	
Body wt. (kg)	75 ± 24	68 ± 17	<.0001
Inpatient	56%	91%	<.0001
Treatment naïve (yes)	48%	55%	
CDI history (1º episode)	71%	83%	
Severe CDI	34%	24%	
Concomitant antibiotics (yes)	19%	26%	.044
Antibiotics during f/up (yes)	56%	60%	
CDI Strain (BI, aka RT 027)*	25%	8%	

**Prevalence of BI strain in study 301 > 302, but overall distribution of strains was not different*

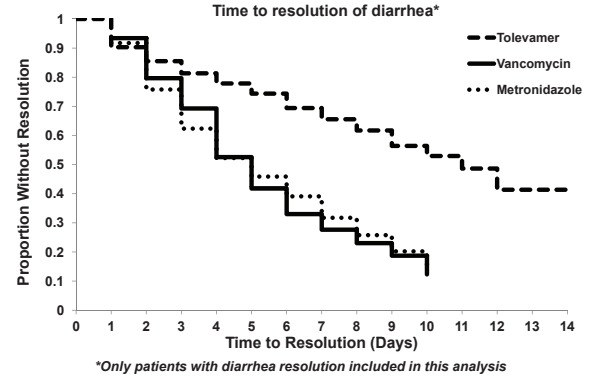
Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

Results: Clinical Success



Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

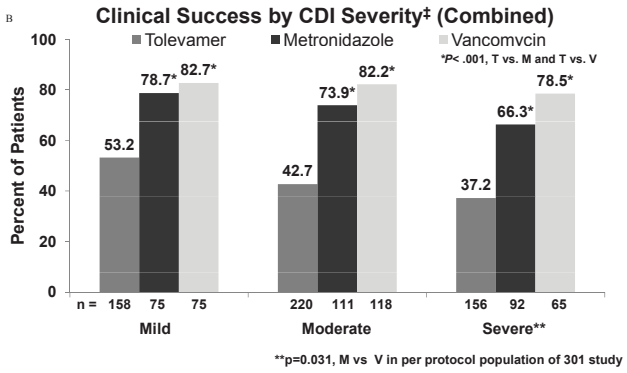
Results: Time to Resolution



**Only patients with diarrhea resolution included in this analysis*

Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

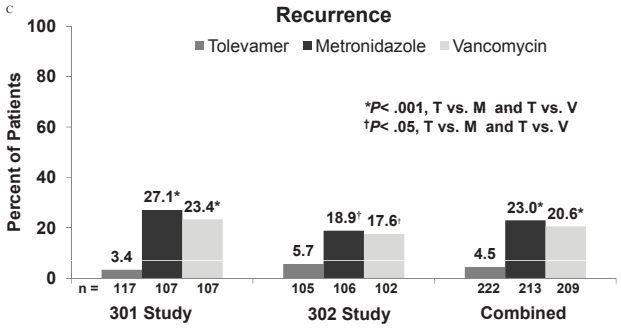
Results: Clinical Success by CDI Severity



**p=0.031, M vs V in per protocol population of 301 study

‡Disease severity was based on 3 criteria: stool frequency, white blood cell count, and presence of abdominal pain
Johnson S, et al. *Clin Infect Dis.* 2014;59:345-54.

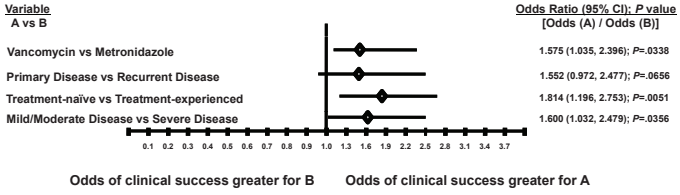
Results: CDI Recurrence



Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

Post-hoc Analysis of Vancomycin vs. Metronidazole

Multivariate logistic regression analysis of factors associated with clinical success



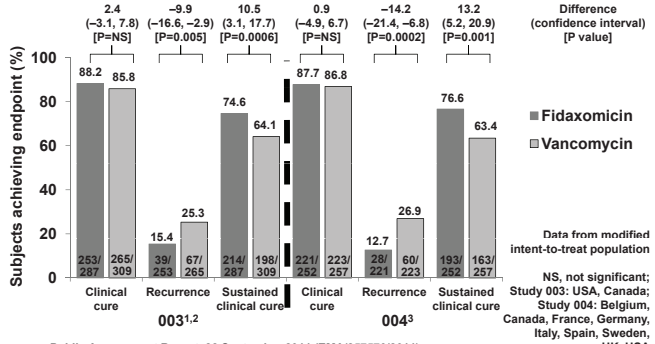
Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

Alternative Approaches to Therapy (Recurrent CDI)

- Switch treatment agent
- Tapering/pulsed treatment regimens
- Post-vancomycin chaser regimens
- Host microbiota replacement
- Immune approach

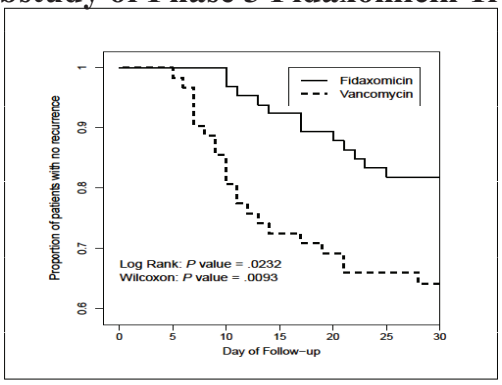
Phase 3 Trial Results of Fidaxomicin vs Vancomycin for CDI

Included patients with first and second CDI episodes



1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011).
2. Louie TJ, et al. *N Engl J Med*. 2011;364:422–31.
3. Cornely OA, et al. *Lancet Infect Dis*. 2012;12:281–9.

Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI: Randomized Substudy of Phase 3 Fidaxomicin Trials



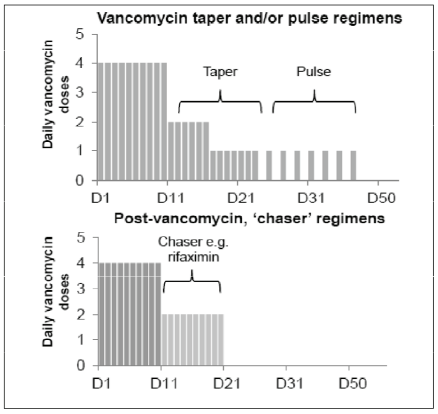
Cornely OA, et al. *Clin Infect Dis*. 2012;55(Suppl 2):S154-61.

Caution for Using a Standard Treatment Course of Fidaxomicin in Patients with Multiple CDI Recurrences

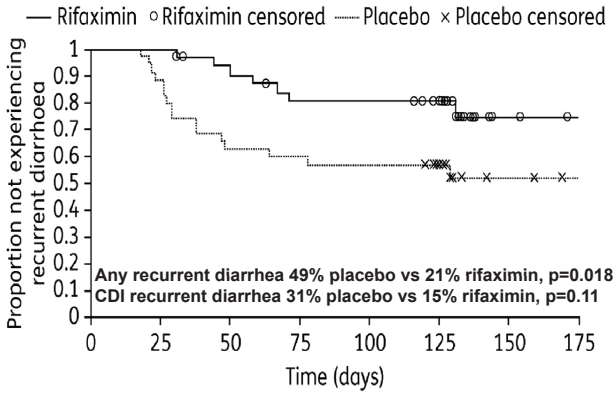
- Two patients with multiple recurrences given treatment doses of fidaxomicin with improvement but followed by symptomatic recurrence
- Prior regimens
  - 62-YOF: M × 14 d followed by Sb twice, V (many), V tapers (several)
  - 44-YOF: (M × 14 d twice); V × 10 d twice, rifaximin chaser

M, metronidazole; Sb, *Saccharomyces boulardii* therapy; V, vancomycin
Orenstein R. *Clin Infect Dis.* 2012;55:613-4.

Alternative Dosing Strategies for Treatment of Recurrent CDI



Randomized, Placebo-controlled Pilot Trial of Rifaximin Chaser Strategy



Garey KW, et al. *J Antimicrob Chemother.* 2011;66:2850-5.

Fidaxomicin Chaser

Patient	Age/Sex	No. of CDI episodes	Prior CDI Regimens	Duration of CDI treatment up to fidaxomicin chaser*	Outcome (Follow up)
1	67/M	4	M, M, V_t, V_t	8 mo (6 mo continuous V until FDX chaser)	Success (10 mo)
2	80/F	5	M, V, V, V_t, V&ivM followed by V_t	24 mo (5 mo of continuous V until FDX chaser)	CDI recurrence 3 mo later, but was treated for UTI just prior to recurrence
3	32/F	8	M, M, V_t, V_t, V/Rfx, V/Rfx, V_t (IVIG), V_t	30 mo (5 mo of continuous V until FDX chaser)	Success (9 mo)

*Following their last CDI episode, patients were 'maintained' on oral vancomycin (V) at a low dose until fidaxomicin (FDX) became available. Vancomycin was stopped and fidaxomicin 200 mg was given BID for 10 d.

Johnson S, Gerding DN. *Clin Infect Dis.* 2013;56:309-10.

68-year-old Woman Developed CDI Following Clindamycin Treatment for Infected Leg Wound (Oct'12)

Date	CDI episode/symptoms	Treatment
11/12/12*	1	Metronidazole × 10 days
12/06/12	2	Metronidazole × 10 days
12/21/12*	3	Vancomycin × 14 days, then taper (finished 2/27/12)
03/13/13	4	Vancomycin × 14 days, then fidaxomicin bid × 10 days *Fidaxomicin chaser*
04/23/13*	5 Symptoms started 17 days after completing fidaxomicin chaser (frequent, loose stools, became watery with urgency)	Fidaxomicin bid × 10 days, then daily × 7 days, then every other day × 14 days *Fidaxomicin taper*
• Clinic follow-ups in June and July: (patient reported mild, self-limited diarrhea episode 1 week after stopping fidaxomicin in May, none since)		

*Confirmed with positive stool *C. difficile* PCR assays

Alternative Fidaxomicin Dosing Regimens for Patients with Multiple CDI Recurrences

Symptom-free intervals (SFI) & subsequent recurrence rates

n	Age, mean±SD	Sex (F)	No. of CDI episodes, mean±SD	Longest SFI* prior to FDX regimen, median (IQR)	SFI* post FDX regimen median (IQR)	Subsequent recurrence rate
Fidaxomicin Chaser *(200 mg bid x 10d)*						
8	66.9±19	75%	5.5±2	57 (48)	278 (649)	38%
Fidaxomicin Taper *(200 mg daily x 7d, then q every other day x 26d)*						
12	63.6±16	58%	5.1±2	25 (30)	257 (280)**	18%

**SFI: Symptom-free interval, days*
***p=0.003, compared with non-fidaxomicin taper SFI, Mann-Whitney U test*
Treatments prior to the fidaxomicin regimens included:
metronidazole, vancomycin, rifaximin chaser, IVIG, fecal transplant, and vancomycin taper (all patients had at least 1 vancomycin taper [mean no.= 2.3])

Soriano MM. *Open Forum Infect Dis.* 2014;1(2): doi: 10.1093/ofid/ofu069.

Emerging Approaches in Treating CDI and Reducing the Risk of Recurrence

- Narrow-spectrum antibiotics
  - Several new antibacterial agents under study
- Microbial approaches
  - FMT (pre-screened donors, capsules)
  - Biotherapeutics (e.g., non-toxigenic *C. difficile* [NTCD])
- Toxin binders
  - Tolevamer or similar agent as adjunctive therapy?
- Immune approaches
  - Monoclonal antibodies to toxin A and B (actoxumab/bezlotoxumab*)*

CDI Antibacterial Agents in Clinical Trials: www.clinicaltrials.gov

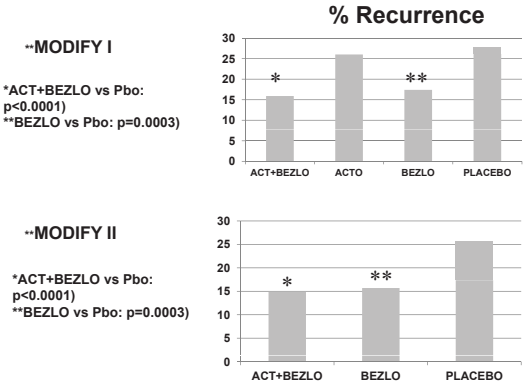
Drug	Sponsor	Drug Class	Clinical Status
CB-183,315 (surotomycin)	Merck & Co.	cyclic lipopeptide	Phase III
ACT-179811 (cadazolid)	Actelion	quinolonyl-oxazolidinone	Phase III
LFF571	Novartis	thiopeptide	Phase II
SMT19969	Summit	?	Phase II
CRS3123	NIAID	methionyl-tRNA synthetase inhibitor	Phase I

Phase 3 Trials of Actoxumab/Bezlotoxumab, mAbs as Adjunctive Therapy for CDI

- Patients receiving standard of care for primary or recurrent CDI randomly assigned to one IV infusion of
  - ACT+BEZLO 10 mg/kg each
  - ACT 10 mg/kg alone *(MODIFY I)*
  - BEZLO 10 mg/kg alone
  - Placebo
- 1º endpoint: recurrent CDI at 12 weeks
- MODIFY I
  - 1452 patients (19 countries); 1412 (97%) received study infusion
- MODIFY II
  - 1203 patients (17 countries); 1168 (97%) received study infusion

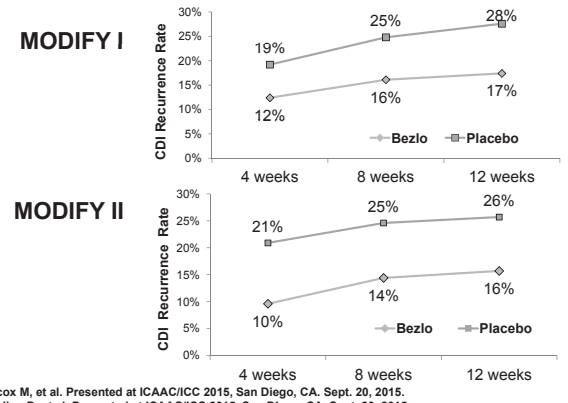
Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

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



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.

CDI Recurrence by Timepoint: Efficacy Sustained Over 12 Weeks



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.

Potential Therapeutic Role of Actoxumab/Bezlotoxumab mAbs

- Adjunctive therapy: both phase 2 and phase 3 studies of actoxumab/bezlotoxumab included standard antibiotic therapy for CDI; the potential for this as stand-alone therapy is unknown
- Initial vs. recurrent CDI?
  - Could make a case for use in both settings
- Mild/moderate CDI vs. Severe CDI?
  - Stand-alone therapy in mild cases and avoid any further host dysbiosis by antibiotics?
- Adjunctive therapy for Fulminant CDI?
  - Toxemia has been identified in CDI patients (Yu H, et al. *PLoS ONE*. 2015;10(4):e0124235); Could toxemia be involved in the often rapid deterioration of these patients?

Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin for treatment of CDI
- Vancomycin and fidaxomicin are similarly effective for primary CDI and fidaxomicin is superior for sustained response
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be used (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow-up
- Unresolved issues: In what setting should fidaxomicin and FMT be used?: Primary CDI, 1st , 2nd, 3rd or later recurrence?
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb)

Notes

Continuing Professional Development

Reflect | Plan | Do | Evaluate

Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

REFLECT

Consider my current knowledge and skills, and self-assess my professional development needs and goals in the area of *Clostridium difficile* infection.

PLAN

Develop a "Personal Learning Plan" to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.
List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.

Monitor progress regularly toward achievement of your goal.