Epidemiological Trends in the Healthcare and Community Settings

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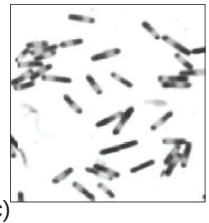
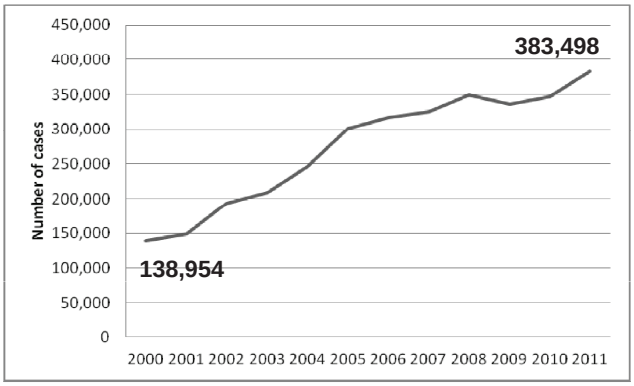
Clostridium difficile

- Gram-positive, spore-forming rod
- Obligate anaerobe
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
  - *C. difficile* infection (CDI, formerly CDAD)
    - Toxigenic *C. difficile* in stool ≠ CDI



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.

URGENT THREAT

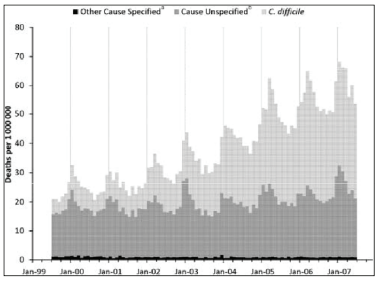
Pathogen	All Health Care–Associated Infections (N = 504)†	
	no. (%)	*rank*
Clostridium difficile	61 (12.1)	1
Staphylococcus aureus	54 (10.7)	2
Klebsiella pneumoniae or K. oxytoca	50 (9.9)	3

Type of Infection	Rank	No. of Infections	Percentage of All Health Care–Associated Infections (95% CI)
Pneumonia†	1 (tie)	110	21.8 (18.4–25.6)
Surgical-site infection	1 (tie)	110	21.8 (18.4–25.6)
Gastrointestinal infection	3	86	17.1 (14.0–20.5)

Magill SS, et al. *N Engl J Med*. 2014;370:1198-208.
Lessa FC, et al. *N Engl J Med*. 2015;372:2369-70.

Increasing CDI Severity

- Outbreaks of severe CDI in US, Canada, Ireland, England, Netherlands, France, Germany
- Sherbrooke, Quebec, Canada, outbreak, 2003
  - 16.7% attributable mortality
- 5% to 10% attributable mortality
  - Over 29,000 deaths in US



Pépin J, et al. *Can Med Assoc J*. 2005;173:1037-42.
Kwon JH, et al. *Infect Dis Clin North Am*. 2015;29:123-34.
Hall AJ, et al. *Clin Infect Dis*. 2012;55:216-23.
Lessa FC, et al. *N Engl J Med*. 2015;372:2369-70.

Costs of CDI

- Attributable inpatients costs of initial CDI (2012 USD)
  - $3,327 to $9,960 per episode (limited to studies with more robust methodology)
- Other costs not yet quantified
  - CDI outside of the hospital
  - Increase in transfers to skilled nursing at hospital discharge
  - Lost time from work (patient and/or caregiver)

Kwon JH, et al. *Infect Dis Clin North Am*. 2015;29:123-34.

CDI is a Top Priority

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

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

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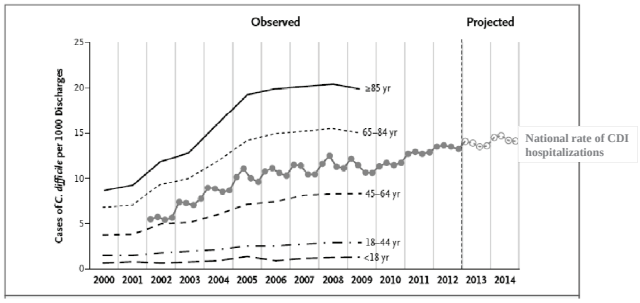
Department of Microbiology, Immunology and Infectious Diseases
University of Calgary
Calgary, Canada

New Appreciation of *C. difficile* as a Formidable Foe

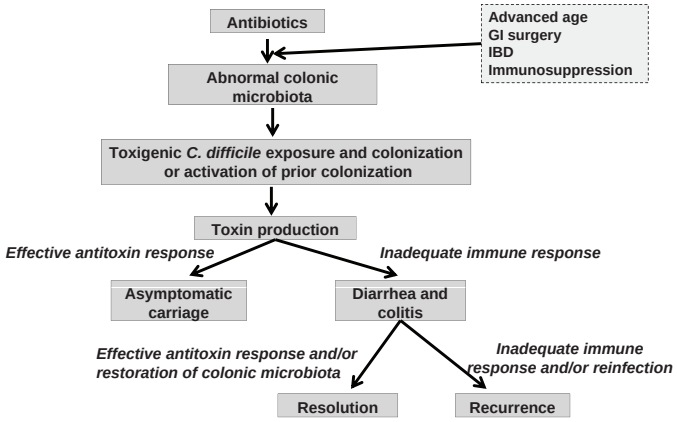
- Next-generation sequencing clarifies epidemiology and pathogenesis
  - Shows that this organism is an extraordinarily fit, versatile, and agile pathogen
- New insights into mechanisms of protection conferred by antibodies, antimicrobial action, and microbiome restoration as potential solutions

C. difficile Case Rates are Predicted to Remain High

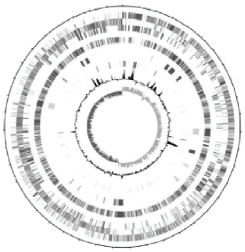


Steiner C et al. HCUP projections report #2014-01. Rockville MD: Agency for Healthcare Research and Quality 2014. [http://hcup-us.ahrq.gov/reports/projections/2014-01.pdf.]
Lessa FC, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S65-S70.
Leffler DA, Lamont TJ. *N Engl J Med.* 2015;372:1539-48.

Pathogenesis of *C. difficile* Infection is Complicated



Whole Genome Sequencing Reveals that *C. difficile* is a Formidable, Versatile, and Highly Adaptive Pathogen



- Genome 4.3 Mb, 42% larger than other clostridia
- High proportion of mobile genetic elements [bacteriophage, introns, insertion sequences, CRISPR-cas, transposable and conjugative elements]
- 'open genome', hyper-adaptable
- Low percentage conserved genome
- Homologous recombination

Sebaihia M ,et al. The multidrug-resistant human pathogen *Clostridium difficile* has a highly mobile, mosaic genome. *Nat Genet.* 2006;38:779-786. http://dx.doi.org/10.1038/ng1830.

Knight D, et al. *Clin Micro Rev*. 2015;28:721-41.

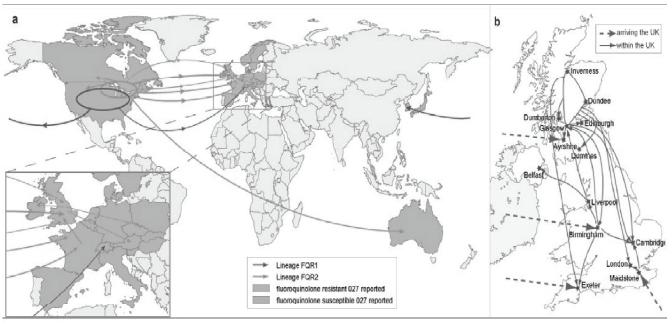
Evolutionary History of the *Clostridium difficile* Pathogenicity Locus

Dingle KE, et al. *Genome Biol Evol*. 2014;6:36-52.

Knight D, et al. *Clin Micro Rev*. 2015;28:721-41.

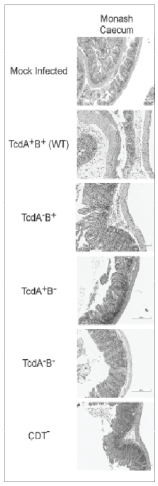
Origin of the Hypervirulent *C. difficile* Strain

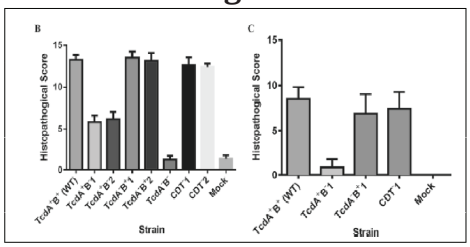
Two independent fluoroquinolone-resistant lineages of epidemic *Clostridium difficile* 027/BI/NAP1 emerged in North America and spread globally.



He M, et al. *Nat Genet*. 2013;45:109-113.

Role of Toxin A and Toxin B in Pathogenesis





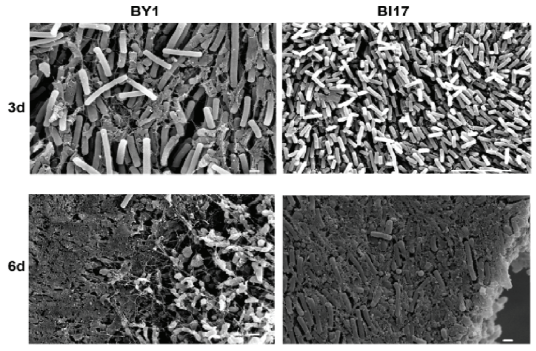
- Isogenic mutants of toxin A or B or both of *C. difficile* is tested in different animal models at 2 centers
- Toxin B is more virulent, and is associated with tissue damage in gut and organs.

Carter GP, et al. *Mbio*. 2015;6(3):e00551-15.

Has CDI Epidemiology Impacted Your Clinical Practice?

- Is NAP 1/BI/ribotype 027 a common strain at your hospital, state/province/region?
- Would a high prevalence (e.g. 40%) of quinolone-resistant *C. difficile* strains reduce quinolone use in your practice, as part of an antibiotic stewardship initiative?
- Has there been less use of metronidazole as first-line therapy due to hypertoxigenic strain infection?

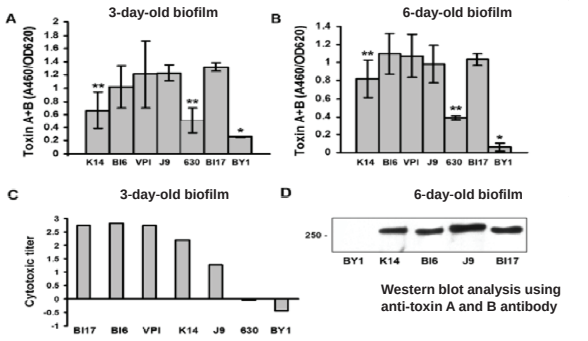
C. difficile Biofilm State: Impact on Pathogenesis?



Scanning electron microscopic analysis of *C. difficile* biofilms

Semenyuk E, et al. *PLoS One*. 2014;9(1):e87757.

Toxin Production Continues for *C. difficile* Strains in Biofilm State

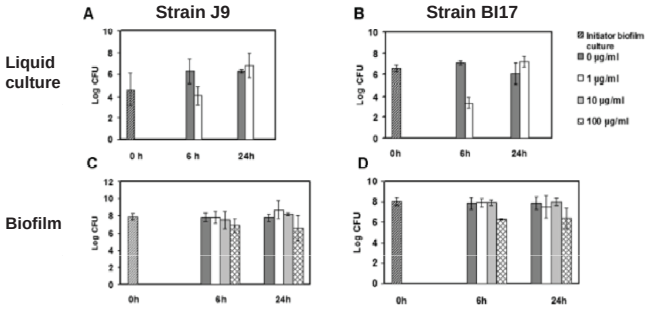


Western blot analysis using anti-toxin A and B antibody

- Toxin A and B are produced and accumulate in *C. difficile* biofilms
- Cytotoxicity correlates with toxin production

Semenyuk E, et al. *PLoS One.* 2014;9(1):e87757.

C. difficile in Biofilm State are Non-susceptible to Metronidazole



- In biofilm-cultured cells, no detectable growth inhibition at metronidazole levels up to 10 µg/mL
- In liquid-cultured cells, 100-fold growth inhibition with 1 µg/mL metronidazole

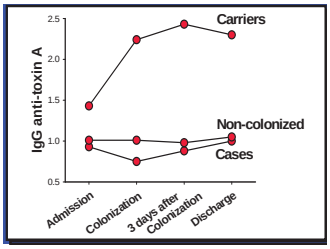
Semenyuk E, et al. *PLoS One.* 2014;9(1):e87757.

The Impact of Biofilm State on *C. difficile* Pathogenicity

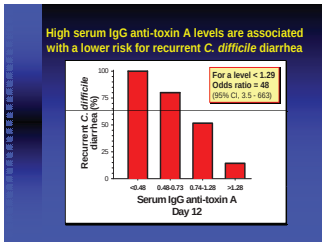
- Is this a possible explanation of failure to respond to antimicrobial therapy?
- Is this a factor accounting for recurrences?
- Findings partially justify maintaining the high concentrations of intraluminal vancomycin measured during vancomycin treatment of *C. difficile* infection?

Role of Antibodies in CDI Pathogenesis

- High serum anti-toxin in symptomless carriers

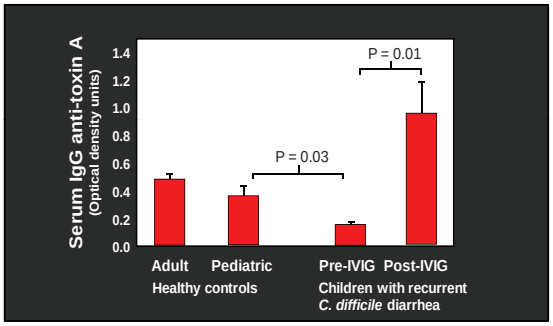


- Serum anti-toxin response & protection against recurrent CDI



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

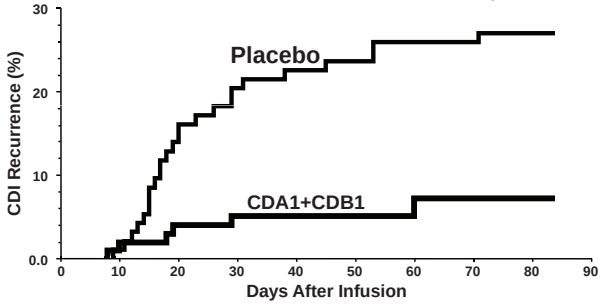
Intravenous Immunoglobulin Therapy for Recurrent *C. difficile* Diarrhea



All 5 children given IVIG had clinical resolution of GI symptoms and clearing of *C. difficile* cytotoxin B from stool.

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

Phase 2 Trial of Anti-Toxin A/B Monoclonal Antibodies as Adjunctive Therapy for CDI: CDI Recurrence Rates Over Study Period

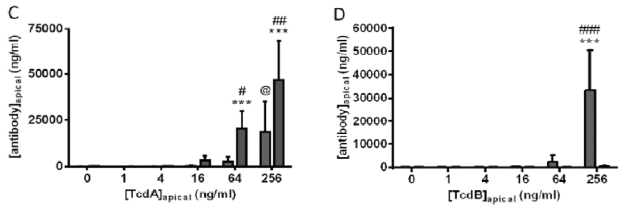


No. at Risk	Day 0	7	28	56	84
CDA1+CDB1	101	100	96	93	92
Placebo	99	95	93	89	87

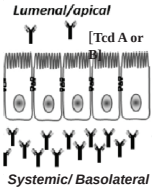
Lowy I, et al. *N Engl J Med*. 2010;362:197-205..

What mechanism allows systemically administered antibodies to act locally at the mucosal level?

Toxin-mediated Paracellular Transport of Antitoxin Antibodies Facilitates Protection Against CDI

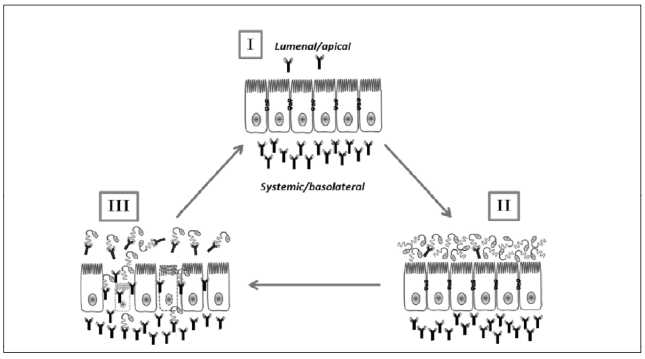


Antibody [actoxumab or bezlotoxumab] placed in basolateral side of 2 dimension MDCK cell culture system 48 hrs prior, followed by instillation of increasing toxin concentrations x 24 h in apical chamber.



Zhang Z, et al. *Infect Immunity.* 2015;83:405-16.

Toxin-mediated Paracellular Transport of Antitoxin Antibodies Facilitates Protection Against CDI



Zhang Z, et al. *Infect Immunity.* 2015;83:405-16.

Antimicrobials Predisposing to CDI

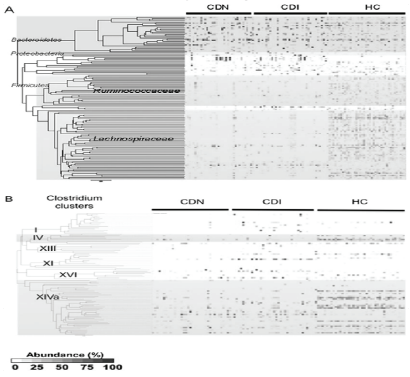
Very Commonly Related	Less Commonly Related	Uncommonly Related
Clindamycin	Other penicillins	Aminoglycosides
Ampicillin	Sulfonamides	Bacitracin
Amoxicillin	Trimethoprim	Metronidazole
Cephalosporins	Cotrimoxazole	Teicoplanin
Fluoroquinolones	Macrolides	Rifampin
		Chloramphenicol
		Tetracyclines
		Carbapenems
		Daptomycin
		Tigecycline
Ugly	**Bad**	**Good**

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

Role of Host Microbiome in the Pathogenesis of CDI

Marked decrease in microbial diversity and species richness observed in those with CDI

Proportions of bacterial taxa in each sample, as inferred from 16S rRNA gene sequence data

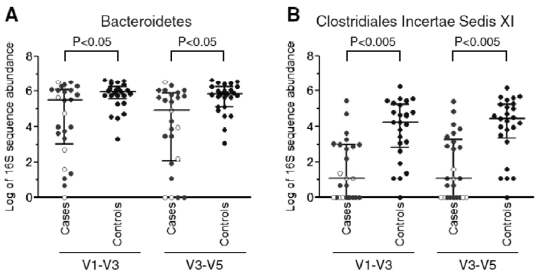


CDN, *C. difficile* negative; CDI, *C. difficile* infection; HC, healthy controls

Antharam VC, et al. *J Clin Microbiol*. 2013;51:2884-2892.

Reductions in Intestinal Clostridiales Precede the Development of Nosocomial CDI

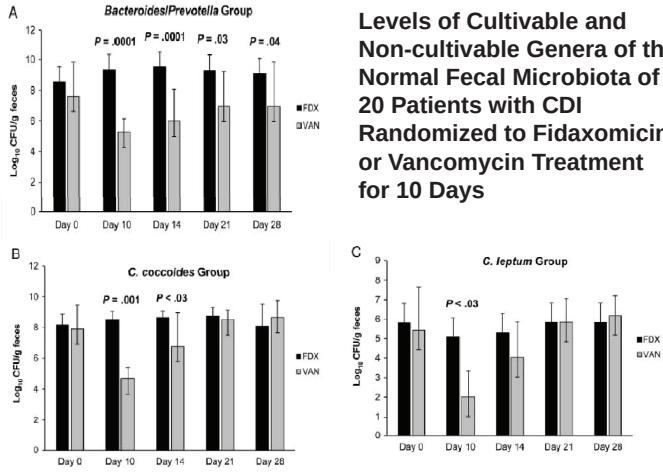
Fecal samples collected before onset of first CDI episode for 25 patients and compared to 25 age- and sex-matched controls



- **Reduction in the abundance of Clostridiales Incertae Sedis XI is associated with risk of nosocomial CDI**
  - **Potential target to prevent CDI?**

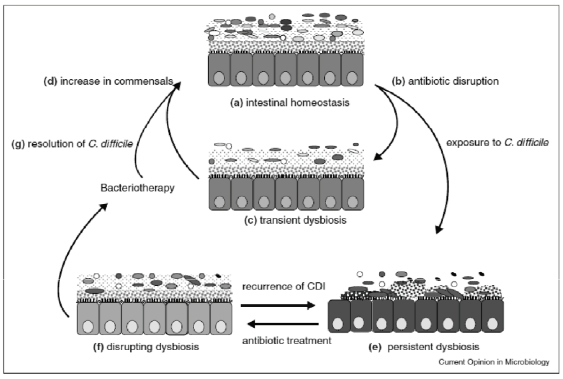
Vincent C, et al. *Microbiome*. 2013;1(1):18.

Levels of Cultivable and Non-cultivable Genera of the Normal Fecal Microbiota of 20 Patients with CDI Randomized to Fidaxomicin or Vancomycin Treatment for 10 Days



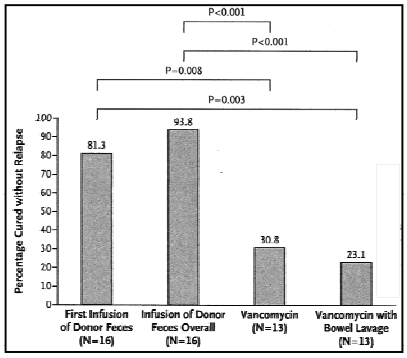
Louie T, et al. *Clin Infect Dis*. 2012;55 (S2):S132-42.

Bacteriotherapy for the Treatment of CDI

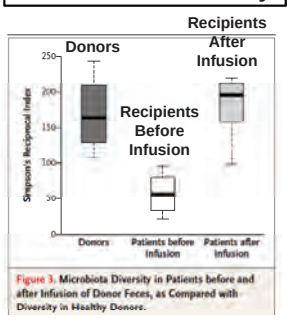


B. Adamu, Lawley TD. *Curr Opin Microbiol*. 2013;16:596-601.
Lawley TD, et al. *PloS Pathog*. 2012:8(10):e1002995.

Restoring the Fecal Microbiome: Duodenal Infusion of Donor Feces for Recurrent *C. difficile* Infection



Microbiota diversity



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

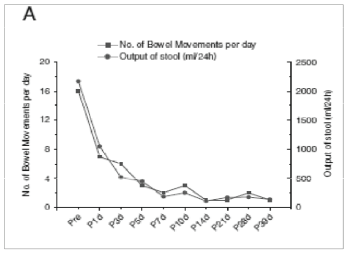
FMT Approaches:

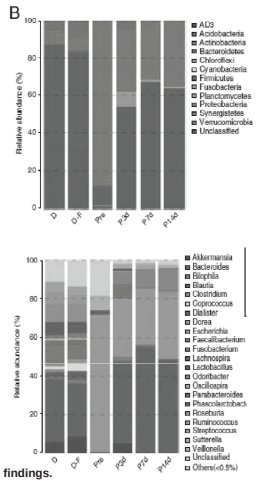
Bringing methods to the madness

- 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, methods of administration
- "Stool banks" – improve access [academic, not-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

Freeze-dried, Capsulized Fecal Microbiota Transplantation for Relapsing CDI

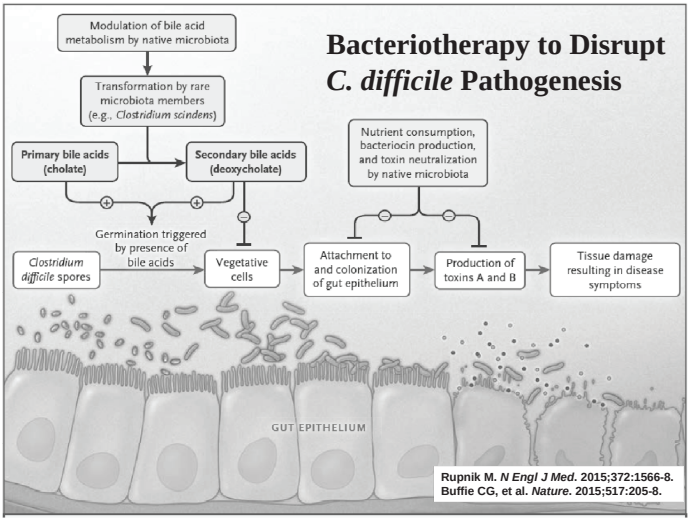




Comment: first case of an RCT, representing a lot of pressure to publish findings.

Tian H, et al. *J Clin Gastroenterol*. 2015;49:537-8.

Bacteriotherapy to Disrupt *C. difficile* Pathogenesis



Rupnik M. *N Engl J Med*. 2015;372:1566-8.
Buffie CG, et al. *Nature*. 2015;517:205-8.

Non-toxigenic *C. difficile* for Prevention of Recurrent CDI

CDI recurrence within 6 weeks as defined by diarrhea criteria and by investigator decision to re-treat for recurrent CDI

Events in Intention-to-Treat Safety Population	Placebo (n = 43)	NTCD-M3 Dosage 10^4 Spores/d for 7 d (n = 41)	10^7 Spores/d for 7 d (n = 43)	10^7 Spores/d for 14 d (n = 41)	All (n = 125)
CDI recurrence, No. (%)	13 (30)	6 (15)	2 (5)	6 (15)	14 (11)
Unadjusted comparison with placebo, *P* value[a]		.09	.002	.09	.003
Adjusted comparison with placebo[b]					
Odds ratio (95% CI)		0.4 (0.1-1.2)	0.1 (0.0-0.6)	0.4 (0.1-1.2)	0.28 (0.11-0.69)
P value		.11	.01	.10	.006
CDI recurrence based on NTCD colonization, No./total (%)[c]					
Colonized with NTCD	0/4 (0)	1/26 (4)	1/31 (3)	0/29 (0)	2/86 (2)[d]
Not colonized with NTCD	13/39 (33)	5/15 (33)	1/12 (8)	6/12 (50)	12/39 (31)[d]

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

Evolution of Bacteriotherapy (FMT)

Whole fecal microbes delivered by enema, NG/NJ, colonoscopy

Whole fecal microbes in condensed form given orally, fresh, frozen, freeze dried

Modified whole fecal microbes...some components inactivated

Defined microbial mixtures of 4–33 strains

Single strains: NTCD, *C. scindens*?

Conclusions

- *C. difficile* is a survivor organism, adaptive, persists in many ecosystems, is capable of rapid change on a needs basis, and has multiple means of remaining with us.
- Interplay of host (*e.g., anti-toxin antibodies*), pathogen properties, antimicrobial agents, and microbiome predict outcomes
- Bacteriotherapy (FMT) is rapidly evolving and should have a major impact in general medicine.

Recognizing Factors Associated with Poor Clinical Outcomes in CDI

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Director, Section of Transplant Infectious Diseases
Washington University School of Medicine
St. Louis, MO

Patient Case

- A 74-year-old female nursing home resident with recurrent UTIs developed left toe itching
  - She was started on ciprofloxacin for a UTI
- On day 3 of cipro, she developed diarrhea with severe abdominal cramping
- She soon was unable the make it to the bathroom
- She was sent to the emergency department
- Stool was positive for *C. difficile* toxins, her WBC was 16,000/mm^3, and her serum creatinine was 2.5 mg/dL

Audience Response Question

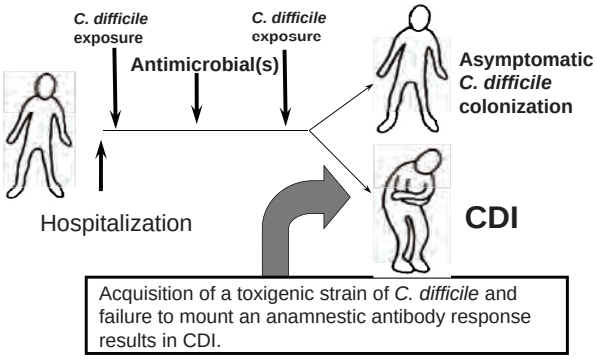
Which is correct?

1. Most patients diagnosed with UTI actually have a UTI. The cipro was appropriate. Kudos to the nursing home for astute clinical acumen.
2. The positive test for *C. difficile* toxin in stool likely represents asymptomatic carriage, not CDI.
3. CDI is no big deal. Metronidazole is 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

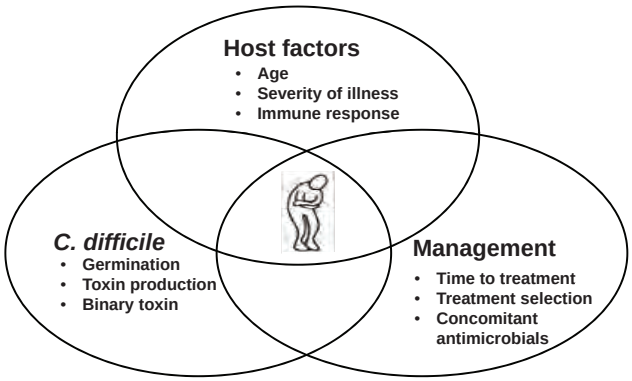
- Severe CDI
  - Decrease morbidity and mortality
- Recurrent CDI
  - Decrease recurrences

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

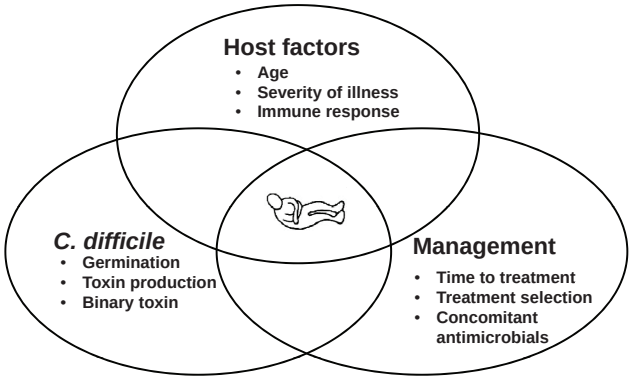


Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-1036.
Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

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**

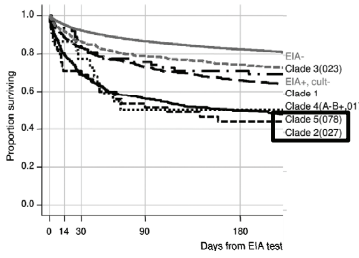
Severe Outcomes from CDI**

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



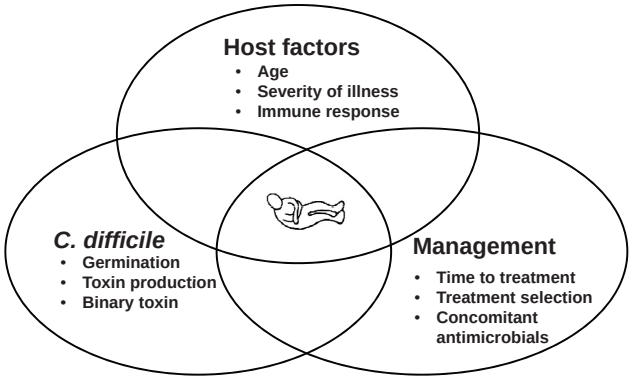
Death in 14 days

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)

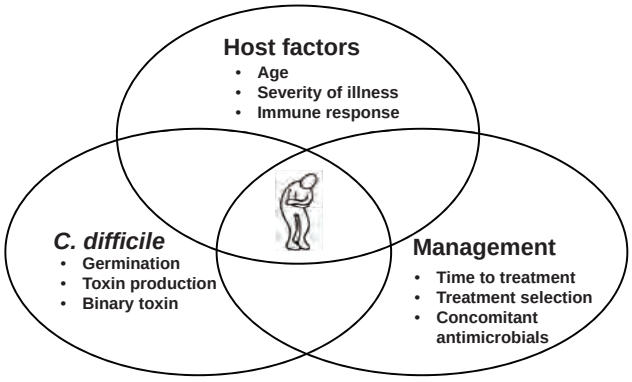
14 day mortality HR ~2.5 for clade 2

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

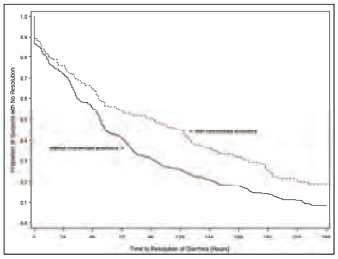


Audience Response Question

Back to the Patient Case…

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.

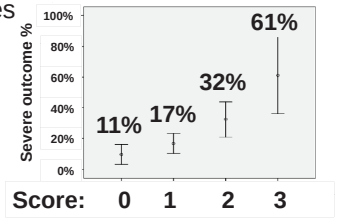
Risk Prediction for Severe Outcomes

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							
Immunosuppresants	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



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 10% 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)

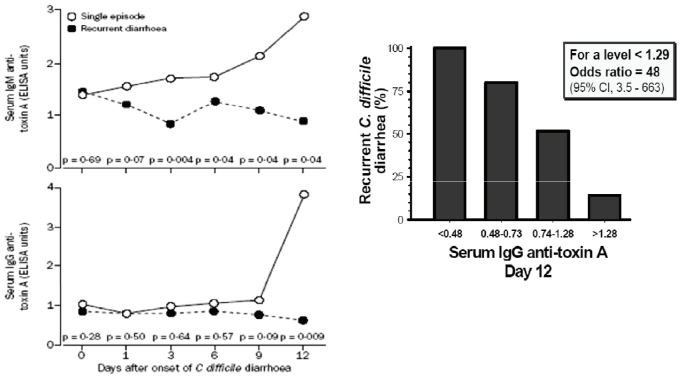
Olsen MA, et al. *Am J Infect Control*. 2015;43:318-22.
Olsen MA, et al. *Clin Microbiol Infect*. 2015;21:164-70.
Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2014;35:1400-7.

Audience Response Question

Back to the Patient Case…

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 Recurrent CDI



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

C. difficile Strain and Recurrent CDI

Variable	Test	Reference	Recurrence		
			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

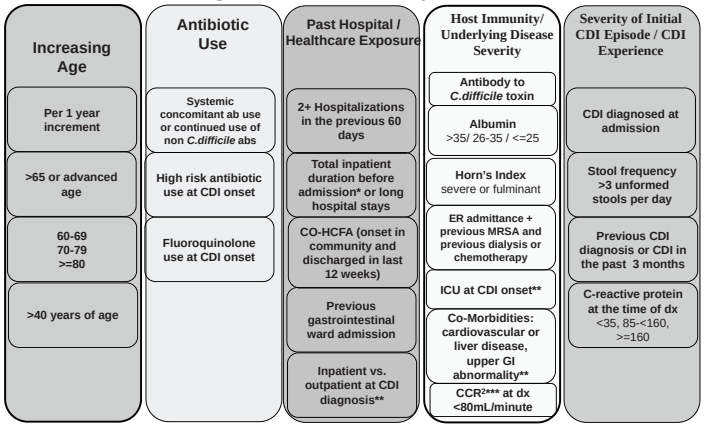
- Age
- Antimicrobials
- Severity of underlying illness
- Immune response

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

courtesy from S. Gupta

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.

Recurrent CDI Score with Outcomes Data

No. of Risk Factors	Points for Each Risk Factor: Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	Predicted Risk of Recurrence: FDX	VAN
(A) Score sheet for people with no prior episode					
No risk factors	0	0	0	10%	18%
1 Risk factor					
Age	1	0	0	13%	24%
UBM	0	1	0	13%	24%
Cr	0	0	2	17%	29%
2 Risk factors					
Age and UBM	1	1	0	17%	29%
Age and Cr	1	0	2	21%	35%
UBM and Cr	0	1	2	21%	35%
3 Risk factors					
Age, UBM, and Cr	1	1	2	28%	44%

No. of Risk Factors	Points for Each Risk Factor: Age ≥75 y	UBM ≥10/d	Cr ≥1.2 mg/dL	Predicted Risk of Recurrence: FDX	VAN
(B) Score sheet for people with prior episode					
No risk factors	0	0	0	14%	25%
1 Risk factor					
Age	1	0	0	19%	32%
UBM	0	1	0	19%	32%
Cr	0	0	2	24%	39%
2 Risk factors					
Age and UBM	1	1	0	24%	39%
Age and Cr	1	0	2	29%	45%
UBM and Cr	0	1	2	29%	45%
3 Risk factors					
Age, UBM, and Cr	1	1	2	37%	54%

The validated model had a C statistic of 0.59.

D'Agostino RB Sr, et al. *Clin Infect Dis*. 2014;58:1386-93.

Conclusions

- CDI epidemiology continues to evolve
- Several unmet needs
  - Validated severity/recurrence scores needed
  - Data to support how score can be used to improve outcomes
  - Optimal management of severe, complicated CDI
- Significant financial burden
  - Data remain focused on inpatient costs
- Treatment landscape evolving
  - Current and future treatments

Integrating the New with the Old when Managing CDI

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Stritch School of Medicine
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Overview

- Current guideline recommendations
- Limitations of metronidazole and vancomycin
- Alternative approaches to therapy
- Emerging approaches in treating CDI and reducing the risk of recurrence

Patient Case Study

A 65-year-old woman was admitted for community-acquired pneumonia and treated with a fluoroquinolone plus a macrolide. While in the hospital, she develops CDI and over the next 2 months, she experiences a total of 3 episodes of CDI. Her treatment regimen for each episode are as follows:

- Episode 1: Metronidazole 500 mg TID × 10 d
- Episode 2: Vancomycin 125 mg QID × 10 d
- Episode 3: Vancomycin 125 mg QID × 10 d followed by taper/pulse

Patient Case Study (cont'd)

The patient now develops a fourth episode of CDI. How would you treat this latest episode?

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 × 14d
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/mm^3 (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 patient who received any treatment and who had any post-dose evaluation

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

Baseline Characteristics

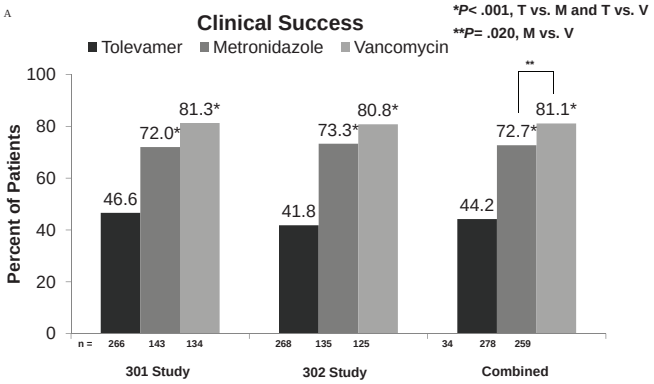
	Study 301 (n=543)	Study 302 (n=528)	P Value
Age	62 ± 17.7	68 ± 16.4	<.0001
Age group (>65)	46%	61%	
Gender (F)	52%	54%	
Body wt. (kg)	75 ± 24	68 ± 17	<.0001
Inpatient	56%	91%	<.0001
Treatment naïve (yes)	48%	55%	
CDI history (1^0 episode)	71%	83%	
Severe CDI	34%	24%	
Concomitant antibiotics (yes)	19%	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.

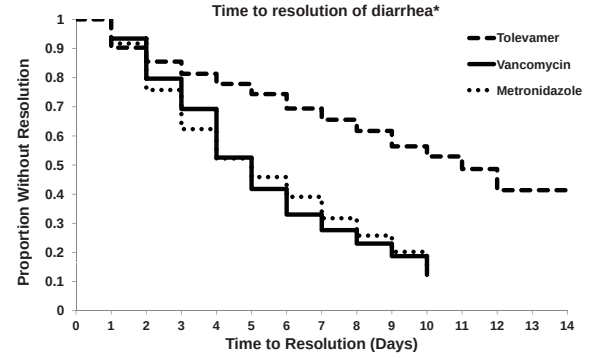
Results: Clinical Success

A



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

Results: Time to Resolution

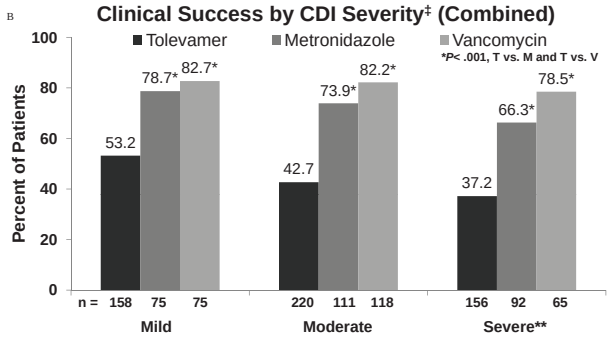


**Only patients with diarrhea resolution included in this analysis*

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

Results: Clinical Success by CDI Severity

B

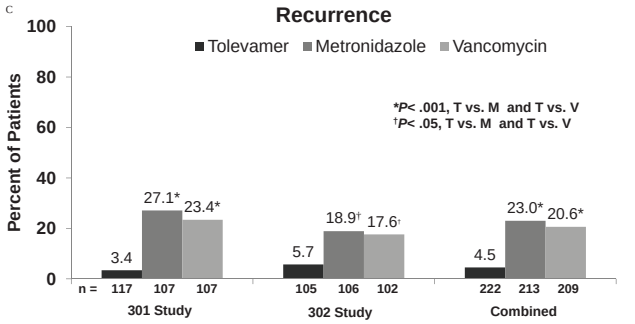


**p=0.031, M vs V in per protocol population of 301 study

‡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.

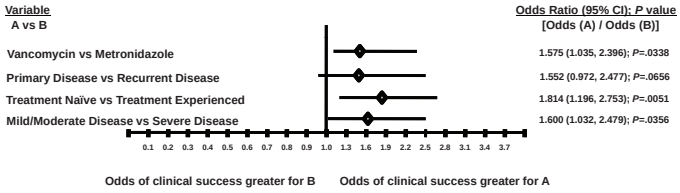
Results: CDI Recurrence



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

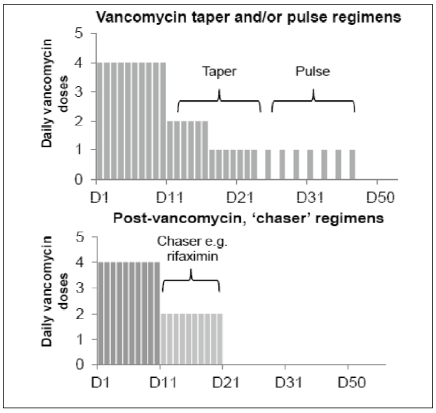


Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

Alternative Approaches to Therapy (Recurrent CDI)

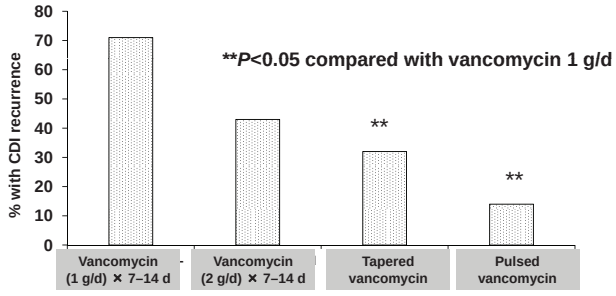
- Switch treatment agent
- Tapering/pulsed treatment regimens
- Post-vancomycin chaser regimens
- Host microbiota replacement
- Immune approach

Alternative Dosing Strategies for Treatment of Recurrent CDI



Vancomycin Regimens for Recurrent CDI

Post-Hoc Analysis From Two Trials (*n*=163)



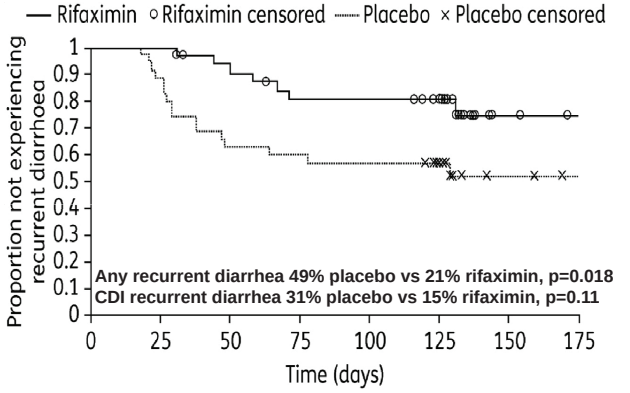
McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769-75.

Interruption of Recurrent CDI by Serial Therapy with Vancomycin and Rifaximin (the "Rifaximin Chaser")

- Eight women with multiple CDI recurrences
  - Mean age: 72 ± 15.3 years
  - Mean previous CDI episodes: 5.8 ± 1.5
  - Mean time to recurrence between episodes: 10.5 ± 12.9 d
- Regimen: rifaximin (400 bid for 2 weeks) immediately after completing the last course of vancomycin and before recurrence of symptoms
- Seven of the eight patients had no further diarrhea recurrence
- One patient had a symptomatic recurrence 10 days after stopping rifaximin, but responded to a second course of rifaximin without subsequent recurrence
  (CD isolate recovered after 2nd course showed high-level resistance to rifaximin in vitro)

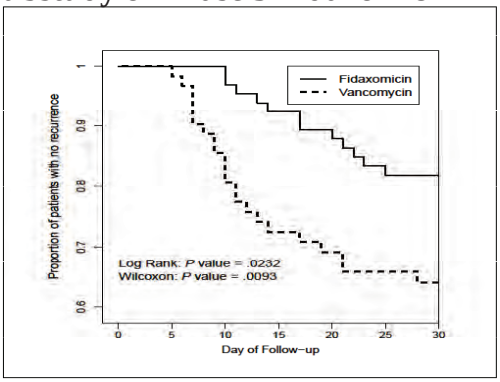
Johnson S, et al. *Clin Infect Dis.* 2007;44:846-8.

Randomized, Placebo-controlled Pilot Trial of Rifaximin Chaser Strategy



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

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.

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
  - Biotherapeutics (e.g., non-toxigenic *C. difficile*)
- Toxin binders
  - Tolevamer or similar agent as adjunctive therapy?
- Immune approaches
  - Monoclonal antibodies to toxin A and B

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

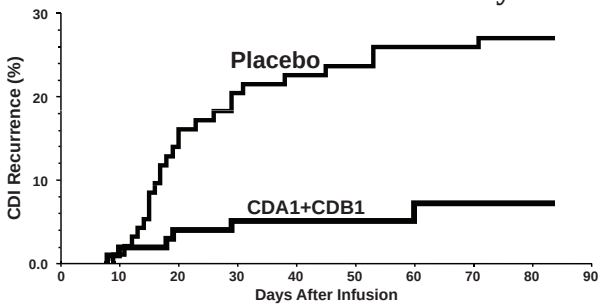
Drug	Sponsor	Drug Class	Clinical Status
CB-183,315 (surotomycin)	Cubist	cyclic lipopeptide	Phase III
ACT-179811 (cadazolid)	Actelion	quinolonyl-oxazolidinone	Phase III
LFF571	Novartis	thiopeptide	Phase II
SMT19969	Summit	?	Phase II
CRS3123	NIAID	methionyl-tRNA synthetase inhibitor	Phase I

Non-toxigenic *C. difficile* (NTCD) Following Standard CDI Treatment: Phase 2 Trial Results

- 168 patients randomized to:
  - 7 days of low-dose non-toxigenic CD (10^4 spores),
  - 7 days of high-dose non-toxigenic CD (10^7 spores),
  - 14 days of high-dose non-toxigenic CD (10^7 spores), or
  - Placebo
- Colonization with non-toxigenic CD (primary endpoint)
  - 54% treated with low dose
  - 79% treated with high dose
- Recurrent CDI (secondary endpoint)
  - reduced by ≥50% over placebo
- The CDI recurrence rate was 2% (2/86) among those that were successfully colonized with non-toxigenic CD

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

Phase 2 Trial of Anti-toxin A/B Monoclonal Antibodies as Adjunctive Therapy for CDI: CDI Recurrence Rates Over Study Period



No. at Risk	Day 0	7	28	56	84
CDA1+CDB1	101	100	96	93	92
Placebo	99	95	93	89	87

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

Potential Therapeutic Role of Actoxumab/Bezlotoxumab, mAbs Directed Against TcdA/TcdB

- 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?

Potential Therapeutic Role of Actoxumab/Bezlotoxumab Phase III Clinical Trial Results

To be presented during the "*Clostridium difficile* Prevention and Treatment Session", Sunday morning (8:30–11:00 AM): Meeting Room 6B Upper Level (Session 151)

- **Wilcox M, et al. Phase 3 double-blind study of actoxumab (ACT) & bezlotoxumab (BEZ) for prevention of recurrent *C. difficile* infection (rCDI) in patients on standard of care (SoC) antibiotics (MODIFY II).**
- **Gerding D, et al. Phase 3 double-blind study of bezlotoxumab (BEZ) alone & with actoxumab (ACT) for prevention of recurrent *C. difficile* infection (rCDI) in patients on standard of care (SoC) antibiotics (MODIFY II).**

Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin in the 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 CDI recurrence? 2nd recurrence? 3rd or later recurrence?
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb)