Understanding *Clostridium difficile* Infections: Are We There Yet?

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Historical Perspective

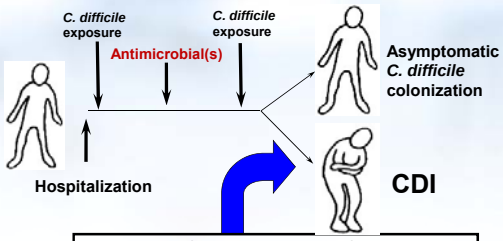
- 1935: *Bacillus difficilis* first described
- 1943 – 1978: Antibiotic associated colitis (AAC) / pseudomembranous colitis (PMC)
- 1978: *Clostridium difficile* identified as causative agent of AAC/PMC
  - Cytotoxicity cell assay developed
- 1981: Oral vancomycin FDA-approved for treatment of *C. difficile* infection (CDI)
- 1982: Oral metronidazole as effective as oral vancomycin
- 1984: Toxin EIAs approved

- 2000 – present: Increasing incidence and severity of CDI
- 2007: Surveillance definitions developed
- 2007: First double-blinded trial of CDI treatment published (Zar)
- 2009: Nucleic acid amplification tests approved
- 2011: Fidaxomicin FDA-approved
- 2011: First diagnostic assay comparison where patients prospectively evaluated and included regardless of diarrhea severity

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
- Ubiquitous: infants, pets, livestock, wild animals, food, water

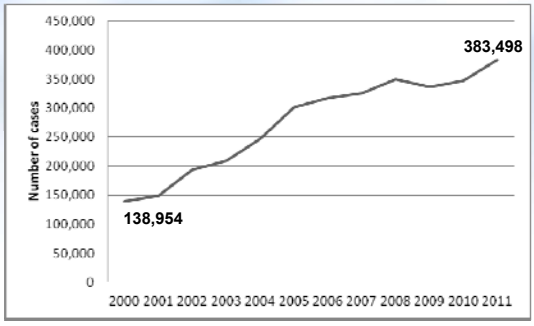
Current Pathogenesis Model for CDI



Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic immune response against toxins 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.

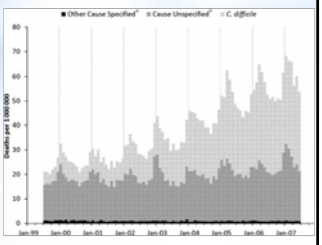
Total Number of Cases in U.S. Hospitals Nationwide Inpatient Sample (NIS)



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

Increasing CDI Severity

- Outbreaks of severe CDI in US, Canada, Ireland, England, Netherlands, France, Germany
- Sherbrooke, Quebec, Canada outbreak, 2003
  - 16.7% attributable mortality
- St. Louis, endemic, 2003
  - 5.7% attributable mortality
  - 2.2-times more likely readmitted
  - 1.6-times more likely discharged to nursing home



Pépin J, et al. *Can Med Assoc J.* 2005;173:1037-42.
Dubberke ER, et al. *Clin Infect Dis.* 2008;46:497-504.
Dubberke ER, et al. *Emerg Infect Dis.* 2008;14:1031-8.
Hall AJ, et al. *Clin Infect Dis.* 2012;55:216-23.

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)
- Attributable inpatient costs of recurrent CDI (2010 USD)
  - $11,631
  - Driven by readmissions
- Other costs not yet quantified
  - CDI outside of the hospital
  - Increase in transfers to skilled nursing facilities at hospital discharge
  - Lost time from work (patient and/or caregiver)

Kwon JH, et al. *Infect Dis Clin North Am.* 2015;29:123-34.
Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2014;35(Suppl 2):S48-65.

CDI is a Top Priority

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

Role of the Hospitalist

- ~50% of CDI cases are managed in the hospital
- Diagnose CDI
- CDI treatment
  - Cure now
  - Prevent recurrences in the future
- Prevention
  - Adherence to contact precautions
    - Gowns, gloves, stethoscope
    - Encourage/prompt others

Centers for Disease Control and Prevention. *MMWR.* 2012;61(9):157-62.

Still Much to Understand

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

Infection Control Measures to Prevent *C. difficile* Infection: What Really Works?

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University of Pittsburgh Medical Center, Presbyterian
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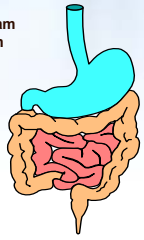


Ubiquity of Toxigenic *C. difficile*

Source	N	Toxigenic *C. difficile* (%)	concentration
Domestic animals	200	3 (1.5)	?
Farm animals	524	4 (0.8)	?
Fish	107	0	?
Soil	104	9 (8.6)	>2 cfu / 1gm
Hospitals	380	72 (18.9)	≥1 cfu / 24 cm^2
Nursing homes	275	4 (1.5)	?
Houses	350	3 (0.9)	?
Dorms	200	3 (1.5)	?
Water*	110	36 (32.7)	5 cfu/100 mL
Vegetables	300	5 (1.7)	?

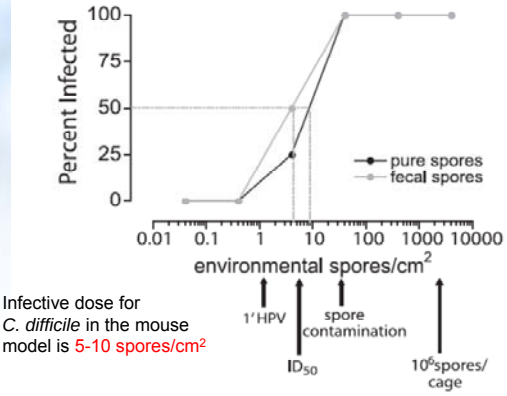
* Fresh water from lakes,rivers, seawater; no chlorinated tap water samples positive

al Saif and Brazier. *J Med Micro.*1996;45:133-7.

7/106 (6.7%) Healthy Subjects with Toxigenic *C. difficile* Allegheny County, PA 2012

Positive subject	Visit	Toxigenic culture	CFU/g	*C. difficile* NAAT (illlumigene)	tcdC genotype
1	1	POS	2.7 x 10^3	NEG	*tcdC 5*
	2	NEG			
	3	NEG			
2	1	POS	< 10		*tcdC 20*
	2	NEG			
3	1	POS	8.7 x 10^3	NEG	*tcdC 19*
	2	POS	4.9x10^4	POS	*tcdC 19*
4	1	POS	3.0 x 10^4	POS	*tcdC 14*
	2	NEG			
	3	NEG			
5	1	POS	<10		*tcdC 53*
6	1	POS	8.0x10^4	NEG	*tcdC 3*
	2	NEG			
7	1	POS	1.1x10^3	NEG	*tcdC 10*
	2	POS	1.6x10^6	POS	*tcdC 10*

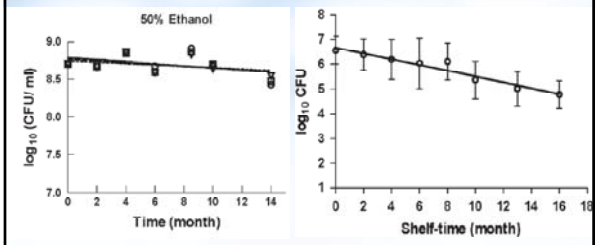
Galdys et al. *J Clin Microbiol* 2014 Jul; 52(7):2406-9.



Infective dose for *C. difficile* in the mouse model is 5-10 spores/cm^2

Lawley *et al. Appl Environ Microbiol.* 2010;76(20): 6895-6900.

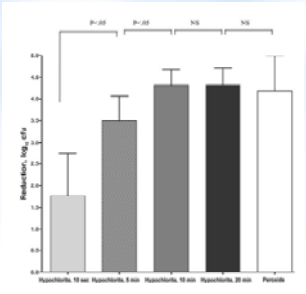
Longevity of *C. difficile* Spores



Viability of *C. difficile* spores stored in 50% ethanol (left) or dried on metal disks (right).

Perez *et al. J AOAC Int. 2011*;94(2):618-626.

C. difficile is Tough to Kill



Standard hospital disinfectants (NH3)

Isopropyl alcohol 70%

Ethanol 80%

INEFFECTIVE

Strong oxidizing agents:

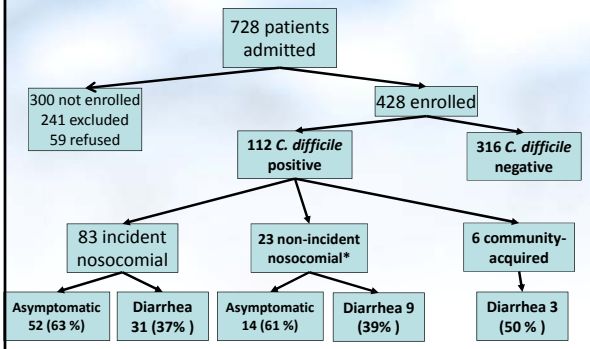
H_2O_2 10%

5000 ppm bleach

Prolonged contact time (10 minutes)

Wilcox et al, *ICHE*. 2008;28(8):921-25.

C. difficile as Nosocomial Infection



McFarland *et al. N Engl J Med.* 1989;320(4): 204-210.

CD Epidemiology: Background

- Widespread in environment
- Hospitals/clinics are major reservoirs
- Nearly indefinitely viable
- Difficult to disinfect
- Large reservoir of asymptomatic carriers
- Spread primarily on the hands of healthcare workers
- Transmitted by fecal-oral route

WHAT INTERVENTIONS ARE EFFECTIVE?

Community-acquired *C. difficile*?

setting	year	# cases	% cases	Rate per 100,000 person-years*	abx exposure (3 mos.)	exposed to healthcare facilities
Connecticut	2006	241	?	6.9	68%	29%
Manitoba	2005-6	275	27.3%	23.4	?	?
VA/Durham NC	2005	109	20%	21-46	51%	>50%
Reading, UK	2008-9	54	?	12.9	31.5%	27.8%

* Hospital-acquired disease ~0.1-50 cases/10,000 patient-days, i.e. 500-5000x higher incidence in hospital populations

MMWR 57(13);340-343, 2008.
Infect Control Hosp Epidemiol. 2009;30(10):945-51.
Emerg Infect Dis. 2010;16(2):197-204.
J Infect Public Health. 2010;3(3):118-23.

Prospective Study of *C. difficile* Contribution to Outpatient Diarrheal Illness

- All outpatients with acute diarrheal illnesses at Yale and Hopkins ER and clinics May 2001-Sept 2004
- 43/1091 (3.9%) participants with + EIA tests for CDI
  - Only 7 had no recognized risk factors
  - Only 3 (0.27%) had no risk factors and no co-infection (rotavirus, norovirus, *C. perfringens*)

"An evolving picture of widespread, frequent CDI among outpatients without risk factors should be tempered by these findings."

Hirshon et al. *EID.* 2011;17(10)1946-9.

CD in Hospitals

- CD is the most common cause of acute care HA diarrhea
  - accounts for ~15–30% of all abx-associated diarrhea
  - more than 300,000 cases/year.
- Reported incidence – 1 to 30/1,000 discharges
  - No real national benchmarks
- Severe disease occurs in ~3% of infected patients
  - Prolonged ileus
  - Toxic megacolon
  - Perforation
  - Colectomy
  - Death
- Relapses occur in 20%–30% of cases

	# CDI/1,000 discharges	#CDI/10,000 pt-days*
Target Rate	5	8
Alarming Rate	10	16
OMG Rate	>20	>33

* Based on a average LOS of 6 days

Barlett JG, et al. *Am J Clin Nutr*. 1980;33:2521-2526.
Gerding DN, et al. *Arch Intern Med*. 1986;146:95-100.
Fekety R, et al. *JAMA*. 1993;269:71-75.
Riley TV, et al. *Epidemiol Infect*. 1994;113:13-20.
Johnson D, et al. *Lancet*. 1990; 336:97-100.
George WL, et al. *J Clin Microbiol*. 1982;15:1049-1053.
Bartlett JG. *Clin Infect Dis*. 1992;15:573-581.
Kelly CP, et al. *N Engl J Med*. 1994;330:257-262.
McFarland LV, et al. *N Engl J Med*. 1989;320:204-210.
Brooks SE, et al. *Infect Control Hosp Epidemiol*. 1992;13:98-103.

Audience Question

Handwashing with soap and water for 30 seconds is as effective at preventing *C. difficile* transmission as wearing gloves.

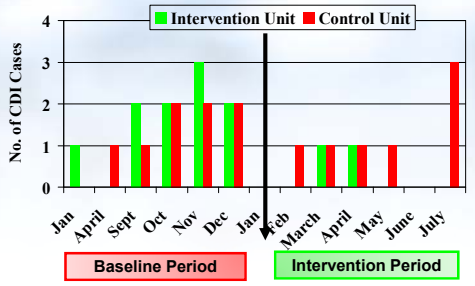
1. TRUE
2. FALSE
3. Beats me.

Answer: False!

- Handwashing = 2 $\log_{10}$ reduction in *C. difficile* CFU on palmar surfaces of volunteers, never in complete eradication
- Alcohol hand-rubs =no intervention
- Prospective controlled study of vinyl gloves vs. enhanced education for care of CDI patients
  - Incidence CDI fell from 7.7 to 1.5/1000 discharges on glove wards
  - Incidence fell from 5.7 to 4.2 cases/1000 discharges on control wards (p=0.015)

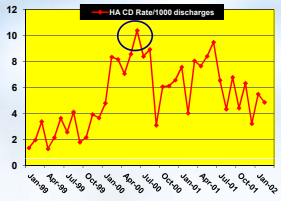
Bettin, K. et al. *Infect Control Hosp Epidemiol*. 1994 Nov;15(11):697-702.
Oughton et al. *Infect Control Hosp Epidemiol*. 2009 Oct;30(10):939-44.
Johnson S. et al. *Am J Med*. 1990 Feb;88(2):137-40.

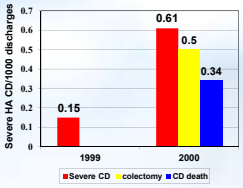
Effect of Glove-Wearing by Personnel on 2 Wards vs 2 Control Wards



Johnson S, et al. *Am J Med.* 1990;88:137-140.

The Pittsburgh Story





- Hospital-acquired (HA) CD infection (I) rate began increasing in 2000
- Peaked 6/00 at 10.4 cases/1000 discharges
- From "99 to "00 annual incidence increased significantly from 2.7 to 7.2 ($p<10^{-7}$; 95% CI=2.1–3.6)

- Accompanied by an increase in AE rate from 0.15 to 0.61 cases/1000 discharges
  (p=0.01; 95% CI 1.31–14.3)
  ~Half of the colectomy cases were associated with CD death

- No obvious changes in patient population, cleaning or infection control policies.
- The only formulary changes were switching ceftazidime to cefepime and cipro to levo

"The Epidemic Strain"

- REA type BI, Ribotype 027, PFGE type NAP-1, tcdC=1, MLST=1
  - In US (Chicago) pre-2001 isolates 0.3% BI/NAP1/027
  - Post-2001 outbreak isolates in US hospitals 10-75% BI/NAP1
  - Similar 2002-4 Quebec outbreak described
- Outbreak isolates associated with nonsense mutations in *tcd*C, negative regulator of toxin B
- Contain extra toxin outside PaLoc= binary toxin (*cdt*)
- Produces 16-20X toxin A and B *in vitro* during both growth phases.

McDonald LC, Killgore GE et al. *NEJM.* 2005;353: 2433-41.
Loo VG et al. *NEJM.* 2005;353: 2442-2449.
Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, and McDonald LC. *Lancet.* 2005;366: 1079-84.

Epidemic Strain *C. difficile* May Not be Associated with Worse Clinical Outcomes

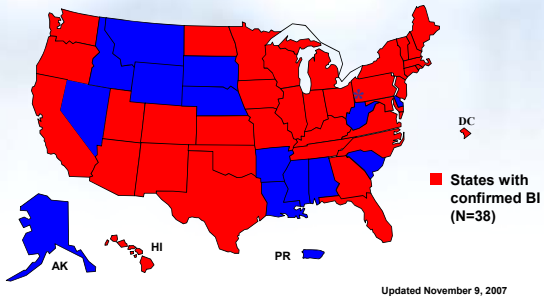
N (% epidemic)	year	endpoint	multivariate OR*	setting
236 (25)	**2004-6**	death, colectomy, or ICU admission	**0.74 (0.3-1.7)**	Boston
123 (41)	**2006**	Shock, colitis, ileus, PMC	**2.07 (0.6-6.8)**	England
205 (42)	**2001 2005**	Attributable death, colectomy	**2.10 (0.6-6.9)**	UPMC
478 (57)	**2005**	death or CDI-attributable death	**2.1 (0.98-4.6)**	Québec

*odds ratio for severe outcome associated with epidemic strain

Cloud J et al. *Clin Gastroenterol Hepatol.* 2009 Aug;7(8):868-873.
Morgan OW et al. *PLoS One.* 2008 Mar 19;3(3):e1812.
Curry SR, unpublished data
Hubert B et al. *Clin Infect Dis.* 2007 Jan 15;44(2):238-44.

The Pittsburgh CD Story

Unlike Vegas, What Happens in Pittsburgh Doesn't Stay in Pittsburgh



Updated November 9, 2007

What We Knew

- **Hospitals are major reservoirs**
  - **~20% to 40% of hospitalized patients become colonized**
- **Iatrogenic Risk Factors – Things we do to the patient**
  - **Antibiotics, Antibiotics, Antibiotics, especially… PCN, clindamycin, and cephalosporins**
  - **Prolonged hospital/long-term care stay**
  - **Sharing a room with an infected patient**
  - **Gastrointestinal surgery or manipulation**
    - **Repeated enemas**
    - **Prolonged NG insertion**
    - **Decreased stomach acidity – PPIs/H2 Blockers**
- **Spread primarily on the hands on HCWs**
- **Transmitted by fecal-oral route**

***C. difficile* spores have been recovered from:**
hospital toilets/commodes metal bedpans floors thermometers
Spores can exist on surfaces for months

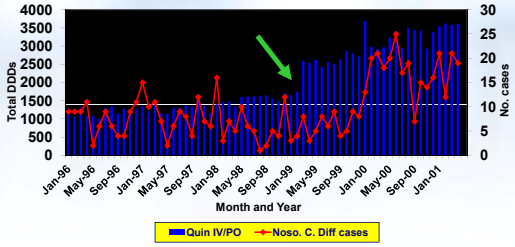
Bignardi GE. *J Hosp Infect.* 1998;40:1-15.
CDC Fact Sheet, August 2004 (updated 7/22/05).

Action Plan

Stop and Think!

- Review of Literature
- Multidisciplinary Team Assembled
  - Infection Control
  - Pharmacy
  - Microbiology
  - Environmental Services
  - Administration/ Clinical leadership
  - Clinical Staff
    - MDs
    - Nursing
    - Respiratory Care
    - Ancillary Care
  - Risk management
- What changed?
  - Patients
  - The bug
  - The HCWs
- Set Benchmarks

Antibiotic Trend Analysis Results Total DDDs for Quinolones* and Incidence of HA CD cases, 1/96–4/01



The quinolone formulary change was accompanied by a significant increase in quinolone use ($p<0.001$) which preceded the *C. difficile* outbreak by 9 months.

Cephalosporin and clindamycin use did not change significantly (data not shown)

*Cipro, oflox, and levo (combined)

Study Components

1. Matched case-control study
   - To characterize a CDI outbreak
   - Identify associated risk factors
   - 203 case-control sets
2. Inpatient antibiotic utilization trends
   - To determine whether the outbreak coincided with changes in antibiotic consumption
3. A microbiologic component
   - Assess for resistant strains
   - Molecular subtyping to evaluate for horizontal transmission

Muto CA, et al. *Infect Control Hosp Epidemiol.* 2005;26:273-280.

Matched Case-Control Study Results - Multivariate Analysis

8 variables in the final model were significant

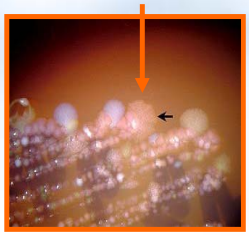
Variable	Cases (%)	Controls(%)	OR	95% CIs
Age	*Continuous variable*		1.02/y	1.006-1.037
DM	83 (40.9)	59 (29.1)	2.1	1.2-3.6
Transplant	44 (21.7)	18 (8.9)	5.8	2.3-14.6
Ceftriaxone	21 (10.3)	8 (3.9)	5.4	1.8-15.8
Levofloxacin	120 (59.1)	83 (40.9)	2.0	1.2-3.3
Clindamycin	32 (15.8)	13 (6.4)	4.8	1.9-12.0
H2 Blockers	159 (78.3)	141 (69.5)	2.0	1.1-3.5
Proton PI	78 (38.4)	54 (26.6)	2.4	1.3-4.4

- Like historical studies, exposure to ceftriaxone and clindamycin were independent RFs.
- Additionally, levofloxacin was found to be significant
- Levofloxacin was the most widely prescribed abx during the study period (59% of cases)

Muto CA, et al. *Infect Control Hosp Epidemiol.* 2005;26:273-280.

Microbiology

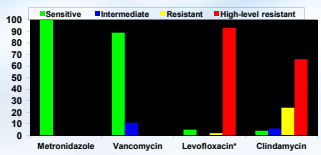
C. difficile colony



- CD isolates
  - In addition to CD toxin testing, began CD culturing 3/2001
    - Very labor-intensive process
    - TAT- 5 days
- On average, ~300 cultures were done per month
  - Positivity rate of 10% to 20%
- CD isolate collection
  - >7000 of CD isolates have been collected and stored

Had The Bug Changed?

REA Patterns of HA CD isolates



No Resistance

Significant Resistance

135 *C. difficile* isolates were typed
- REA types 2 and 4, differed from each other by a single band
  - Represent ~55% of all HA CD isolates (Outbreak strain)

A subset of isolates underwent additional testing and were consistent with the epidemic BI strain

Clabots CR, et al. *J Clin Microbiol.* 1993;31:1870-1875.
* McDonald LC et al.. *N Engl J Med.* 2005;353:2433-41.

What to Do?
What Works?

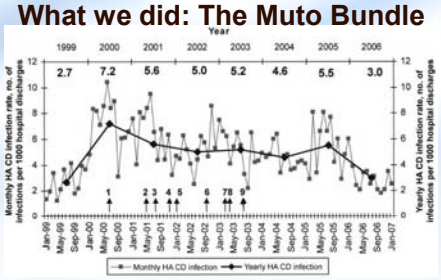
Infection Control Preventative Measures

IC Measure	Intervention efficacy
Barrier precautions	
Gloves[1]	Proven
Handwashing[2,3]	Probable
Private room/isolation[4-6]	Probable
Environmental cleaning	
Rooms[7-10]	Proven
Commodes	Untested
Single-use rectal thermometers[11]	Proven
Endoscope disinfection[12,13]	Probable
Other	
Antibiotic restriction[14,15]	Proven
Metronidazole tx for asymptomatic carriers[4,16]	Ineffective

Adapted from Gerding DN, et al. *Infect Control Hosp Epidemiol*. 1995;16:459-477.

1. Malamou-Ladas H, et al. *J Clin Pathol*. 1988;6:88-92.
2. McFarland LV, et al. *N Engl J Med*. 1989;320:204-210.
3. Bettin K, et al. *Infect Control Hosp Epidemiol*. 1994; 15:697-702.
4. Bender BS, et al. *Lancet*. 1986;2(8497):11-13.
5. Nolan NPM, et al. *Gut*. 1987;28:1467-1473.
6. Olson MM, et al. *Infect Control Hosp Epidemiol*. 1994;15:371-381.
7. Struelens MJ, et al. *Am J Med*. 1991;91:138S-144S.
8. Kaatz GW, et al. *Am J Epidemiol*. 1988;127:1289-1294.
9. Delmée M, et al. *Eur J Clin Microbiol*. 1987;6:623-627.
10. Mayfield JL, et al. *Clin Infect Dis*. 2000;31:995-1000.
11. Brooks SE, et al. *Infect Control Hosp Epidemiol*. 1992;13:98-103.
12. Hughes CE, et al. *Gastrointest Endosc*. 1986;32:7-9.
13. Rutala WA, et al. *Infect Control Hosp Epidemiol*. 1993;14:36-39.
14. Pear S, et al. *Ann Intern Med*. 1994;120:272-277.
15. Brown E, et al. *Infect Control Hosp Epidemiol*. 1990;11:283-290.
16. Johnson S, et al. *Ann Intern Med*. 1992;117:297-302.

What we did: The Muto Bundle



1. CD education module/RN test authority/CD email alerts/1:100 NaOCl cleaning/isolation precautions
2. CD management team (SWAT team)
3. Monitoring of isolation compliance
4. Computer flagging to enhance cohorting CD patients
5. First year of isolates collected by micro
6. Antibiotic management team piloted
7. Hand washing for CD patients (no EtOH)
8. Real-time lab alerts to floor for isolation
9. Full implementation of AMP/ 1:10 NaOCl cleaning

Muto *et al.* CID 45:1266-73, 2007.

CDC Summary of Prevention Measures

Core Measures

- Contact precautions for duration of illness
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system
- CDI surveillance
- Education

Supplemental Measures

- Prolonged duration of contact precautions*
- Presumptive isolation
- Evaluate and optimize testing
- Soap and water for HH upon exiting CDI room
- Universal glove use on units with high CDI rates
- Bleach (sporicide) for environmental disinfection
- Antimicrobial stewardship program

* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions

CONTACT PRECAUTIONS

(IN ADDITION TO STANDARD PRECAUTIONS)

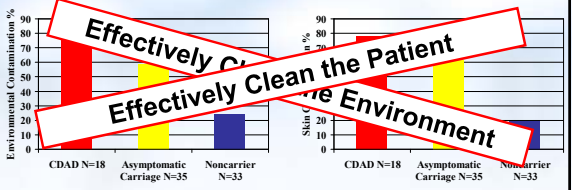
- **Private Room**
  - A private room is indicated; however patients infected with the same organism may share a room if necessary.
- **Gloves**
  - Wear gloves for contact with the patient and/or environment. Change gloves after contact with infective material. Remove gloves before leaving the patient's environment.
- **Gown**
  - Wear if you anticipate that your clothes will have contact with the patient, environmental surfaces, or items in the patient's room. Remove gown before leaving the patient's environment.
- **Wash Hands**
  - With antiseptic product immediately after glove removal and before leaving the patient's environment.
- **Transport**
  - Limit the movement/transport of patients to essential purposes only. During transport, ensure that all precautions are maintained at all times.
- **Equipment**
  - Dedicate the use of patient -care equipment to a single patient. If common equipment is used, clean and disinfect between patients.

Rationale for Soap and Water: Lack of Efficacy of Alcohol-Based Handrub Against *C. difficile*

Interventions compared		Mean log reduction (95% CI), $\log_{10}$ CFU/mL
Intervention 1	Intervention 2	
Warm water and plain soap	No hand hygiene	2.14 (1.74–2.54)
Warm water and plain soap	Alcohol-based handrub	2.08 (1.69–2.47)
Cold water and plain soap	No hand hygiene	1.88 (1.48–2.28)
Cold water and plain soap	Alcohol-based handrub	1.82 (1.43–2.22)
Warm water and plain soap	Antiseptic hand wipe	1.57 (1.18–1.96)
Warm water and antibacterial soap	No hand hygiene	1.51 (1.12–1.91)
Warm water and antibacterial soap	Alcohol-based handrub	1.46 (1.06–1.85)
Cold water and plain soap	Antiseptic hand wipe	1.31 (0.92–1.71)
Warm water and antibacterial soap	Antiseptic hand wipe	0.94 (0.55–1.34)
Warm water and plain soap	Warm water and antibacterial soap	0.63 (0.23–1.02)
Antiseptic hand wipe	No hand hygiene	0.57 (0.17–0.96)
Antiseptic hand wipe	Alcohol-based handrub	0.51 (0.12–0.91)
Cold water and plain soap	Warm water and antibacterial soap	0.37 (−0.03 to 0.76)
Warm water and plain soap	Cold water and plain soap	0.26 (−0.14 to 0.66)
Alcohol-based handrub	No hand hygiene	0.06 (−0.34 to 0.45)

Oughton, Matthew T., Vivian G. Loo, Nandini Dendukuri, Susan Fenn, and Michael D. Libman. "Hand Hygiene with Soap and Water Is Superior to Alcohol Rub and Antiseptic Wipes for Removal of Clostridium Difficile." Infection Control & Hospital Epidemiology 30.10 (2009): 939-44.

Environmental and Skin Contamination Asymptomatic Carriage



Asymptomatic carriers had significantly higher rates of environmental and skin contamination than did noncarriers but < patients with CDAD
Carriers of epidemic and nonepidemic CD strains had similar skin and environmental contamination (67% vs. 55%; *p*=0.78 and 55% vs. 62%; *p*=0.52 respectively)

Newest Bundle Component

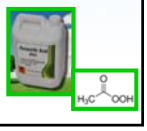
Clean patients with antimicrobial soap - CHG in ICU, Triclosan in non-ICU

Riggs MM, et al. *Clin Infect Dis.* 2007:45;992-8.

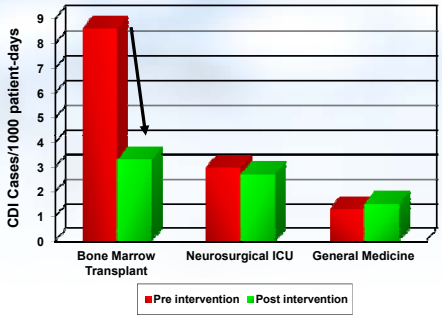
Environmental Cleaning: Options

- **Sodium hypochlorite/bleach (B) – 5500 ppm**
  - Caustic to the environment
    - Furniture, mattresses, equipment, etc.
    - Leaves a salt precipitate upon evaporation

- **H_2O_2 +/- Peracetic/Peroxyacetic acid (PA)**
  - EPA approval for use in healthcare settings
  - Decreased contact time with addition of PA: ≤5 minutes
    - Disrupts cell wall permeability
  - Use has been limited because of its vinegar odor



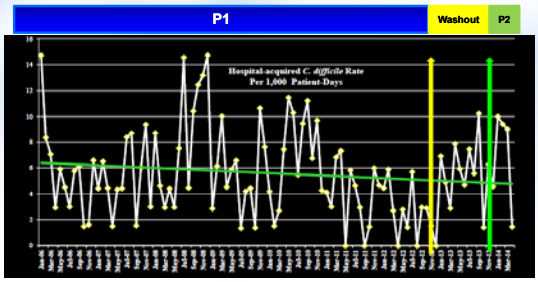
Effect of Environmental Disinfection with 1:10 Hypochlorite on CDI Rates



Mayfield JL, et al. *Clin Infect Dis.* 2000;31:995-1000.

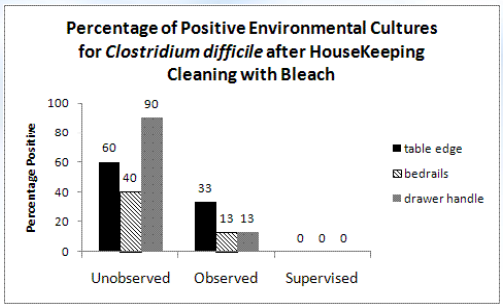
Sporicidal Switch

Sodium hypochlorite/bleach → H_2O_2 +Peraectic/Peroxyacetic acid (PA)



1. No change in CDI rates
2. Promotion of the "NEW SMELL OF CLEAN" was instrumental.
3. No damage to furniture or equipment
4. Staff were particularly fond of the one-step cleaning

Real-World Bleaching…



Guerrero DM, et al. Presented at SHEA Decennial, Atlanta, GA 2010.

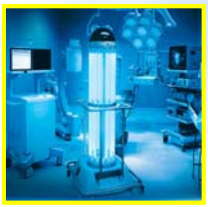
Assess Environmental Cleaning

- Ensure that environmental cleaning is adequate and high-touch surfaces are not being overlooked
- Fluorescent environmental marker to assess cleaning showed:
  - 47% of high-touch surfaces in 3 hospitals were cleaned
  - Sustained improvement in cleaning of all objects, especially in previously poorly-cleaned objects, following educational interventions with the environmental services staff
- The use of environmental markers is a promising method to improve cleaning in hospitals

Carling PC, et al. *Clin Infect Dis*. 2006;42:385-8.

Tru-D SmartUVC
Adjunct to Terminal Cleaning

- UV-C utilizes short-wavelength radiation that is germicidal
- Destroys 99.9% to 99.99% of targeted pathogens
  - 3–4 $\log_{10}$ disinfection
- Targets surfaces and shadows
- Automated and safe
- Remote activation
- Sensor and Lock on Door
- Cannot transmit through glass



UVC Disinfection

- Room Decontamination with UV radiation
- Evaluation of an Automated UVC Device for Decontamination of CD and Other HCA Pathogens in Hospital Rooms
- Rapid Hospital Room Decontamination Using Ultraviolet (UV) Light with a Nanostructured UV-Reflective Wall Coating
- Decontamination of Targeted Pathogens from Patient Rooms Using an Automated UVC-Emitting Device
- Terminal Decontamination of Patient Rooms Using an Automated Mobile UV Light Unit
- Decontamination with Ultraviolet Radiation to Prevent Recurrent CDI in Two Roommates in a Long-Term Care Facility

Rutala WA, et al. *Infect Control Hosp Epidemiol.* 2010; 31:1025-1029.
Nerandzic MN, et al. *BMC Infect Dis.* 2010, 10:197.
Rutala WA, et al. *Infect Control Hosp Epidemiol.* 2013;34:527-529.
Anderson DJ, et al. I*nfect Control Hosp Epidemiol.* 2011,;32:737-42.
Sitzlar B, et al. *Infect Control Hosp Epidemiol.* 2012;33:533-536.

Enhanced IC Measures

- Expanded duration of contact isolation to entire LOS - July 2000
- Require bleach cleaning for CD+ patient rooms
  - 1:100 dilution – May 2001
  - 1:10 dilution – July 2003
- Routine monitoring of isolation compliance - July 2001
- Require handwashing with soap and water (not alcohol-based sanitizers) for care of CD+ patients
  - Implemented May 2003
  - Room Signage

HANDWASHING,
WITH SOAP AND WATER,
IS REQUIRED PRIOR TO LEAVING
THIS ROOM

Increased Case Finding Early Identification

- Expanded CD ordering authorization to RNs – Implemented 7/00
- CD Alert - Email sent by the Medical Director to clinicians requesting consideration of CD testing on high-risk patients
  - Previous CDI
  - Extended antibiotic use
  - Leukocytosis, leukopenia or bandemia
    - Patient readmitted within 14 days with a WBC >10,000
    - A LOS >7 days and WBC >10,000 or <2000 and bandemia >10%
      - » 13,302 alerts have been sent through 9/05

Informatics Tools

- Electronic flagging of CD+ patients
  - To assure maintained isolation during entire inpatient stay
  - Implemented *November 2001*
- Automatic real-time CD+ notification
  - Generated from Laboratory Information System directly to the patient care unit
    - Fax, email, and digital page available, soon phone voice message
    - Patient CD+ result and need for Contact Precautions.
    - Requirements for CD isolation at our facility listed on the fax and email.
  - Implemented *March 2003*
- Linked comment to all CD+ lab results stating isolation requirements
  - Implemented *March 2003*

Example of a Unit Fax Report
Isolation Summary of Positive Cultures Detected
Review for Institution PRESBYTERIAN UNIVERSITY HOSPIT
Report Date:03/25/2003
Unit Location: MUH 5 South MIC9
Notified: Mode: Time:

MRN - 999999999 [Clostridium difficile] Pat: NANCY M DUCK
CollDate: 03/22/2003 Acc: X58570 Ord Loc: MIC9;1 Resist: N/A
Time: 23:30 Site: Stool
Isolation: Contact
Glossary of Isolation Actions

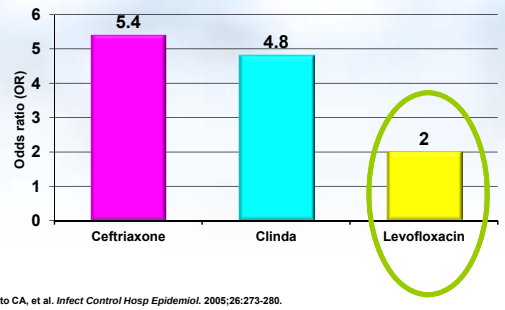
CONTACT
Barriers : Gown and Gloves. In addition to Standard Precautions, wear a gown and gloves when entering the room.

Patient Placement - Place the patient in a private room. When a private room is not available, place the patient in a room with a patient(s) who has active infection with the same microorganism, but with no other infection (cohorting).

Patient Transport - Limit the movement and transport of the patient from the room to essential purposes only. If transport or movement is necessary, minimize risk of transmission by placing a gown on the patient.

UPMC PUH

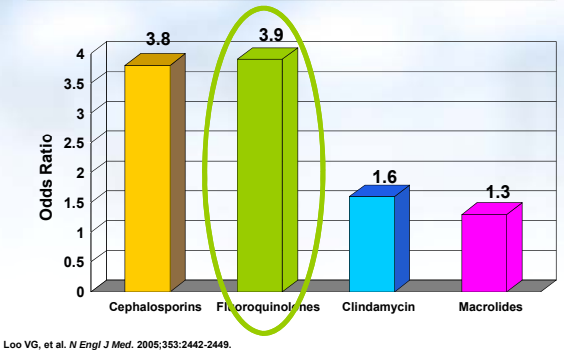
Risk of CD Diarrhea According to Antibiotic Class



Muto CA, et al. *Infect Control Hosp Epidemiol.* 2005;26:273-280.

Canadian Experience

Risk of CD Diarrhea According to Antibiotic Class



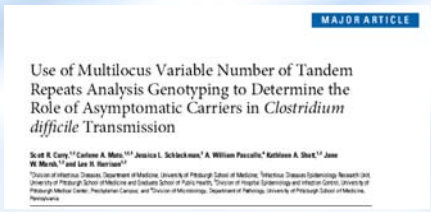
Loo VG, et al. *N Engl J Med*. 2005;353:2442-2449.

Targeted Antibiotic Restriction

- Levofloxacin, clindamycin and ceftriaxone were found to be associated with increased risk of HA CD in our case-control study.
- Require prior approval for inpatient use
  - Implementation began *October 2002*
  - *Fully implemented by July 2003*
- Antibiotic usage
  - Defined daily doses (DDDs)/per 100 patient-days are calculated monthly and annually
  - Individual antibiotics and class usage is followed

The Antibiotic Management Team achieved significant reductions of all antibiotics identified as high risk

2004: Quinolones - 50%; Clindamycin - 75%; Ceftriaxone - 35%
2006: Quinolones - 38%; Clindamycin - 68%; Ceftriaxone - baseline



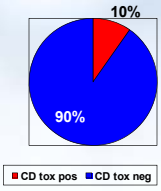
MAJOR ARTICLE

Use of Multilocus Variable Number of Tandem Repeats Analysis Genotyping to Determine the Role of Asymptomatic Carriers in *Clostridium difficile* Transmission

- 3006 high-risk patients at UPMC screened
  - 314 (10.4%) positive for *C. difficile*
  - 226 (7.5%) found only on screening tests
  - 56 HA-CDI cases during screening
    - 17 (30%) linked to known CDI patients by MLVA
    - 16 (29%) linked to carriers by MLVA
    - Balance of cases of unknown origin

Asymptomatic Toxigenic CD Positivity Rate

Positivity rate for patients



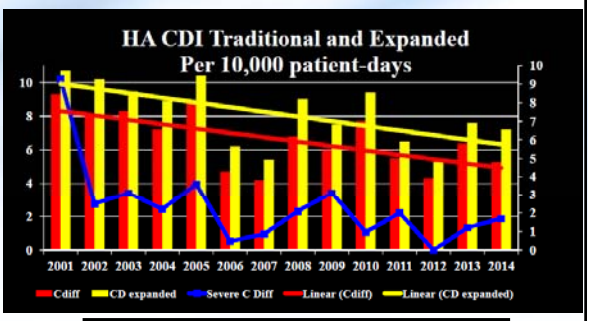
- CD was cultured 292/3003 (10%) patients
- 210/3003 (7.0%) of patients with no known CD history were positive
  - CD identified 7.5 days prior to discharge (945 un-isolated pt-days)

Where did they get it?

- Toxigenic CD was recovered from 5/6 rooms sampled at 15/30 sites.
- In 4/5 patients – At least 1 environmental isolate matched the patient's perirectal swab
- Effective universal bleach cleaning may interrupt transmission to the next room occupant

Curry SR et al, *Clin Infect Dis.* 2013 Oct;57(8):1094-102.

DID IT WORK?



Peak – 2000
CD Bundle was implemented over time
CD HAI rate significantly↓
(OR = 1.6, CI = 1.3-2.0, p=0.00003)
By 2007 - 64% reduction from peak

Conclusions

- A new epidemic CD strain has emerged worldwide, causal role not established
- Traditional risk factors like age, cephalosporin and clindamycin use still play a role
  - Newer risk factors like fluoroquinolone and PPI use have also been identified
  - Newly described at-risk populations have been identified
- Infection Control Measures associated with reduction in HA CDI rates
- Unknown which components were necessary and sufficient:
  - Antimicrobial restriction
  - Enhanced environmental cleaning
  - Glove use
  - Hand hygiene
  - Patient isolation
- Future directions
  - Technical advances in environmental cleaning
  - Enhanced vertical controls (such as for VRE/MRSA)

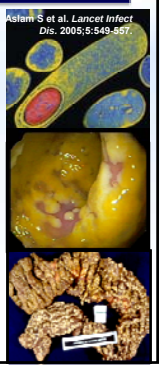
Preventing CDI

Recognizing Patient Risk Factors for *C. difficile* Infection, Recurrence, and Complications

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

CDI: Understanding Patient Risk for Complications and Recurrence

- Pathophysiology of *Clostridium difficile* infection (CDI)
- Risk factors that predict severe complications of CDI
- Features of severe and of severe complicated (fulminant) CDI
- Management of fulminant CDI
- Pathophysiology of recurrent CDI
- Risk factors that predict recurrent CDI



Pathogenesis of *C. difficile* Infection (CDI)

Antibiotic therapy ← Prime risk factor

↓

Disturbed colonic microflora (loss of colonization resistance) ← Other sources of dysbiosis

↓

C. difficile exposure & colonization ← Highest risk in healthcare facilities

↓

Toxin A & Toxin B ← Chemotherapy, Neonatal state, Enteric infection, IBD with colitis

↙ Symptomless carriage ↘ Diarrhea & colitis

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

Antibiotics Predisposing to CDI:

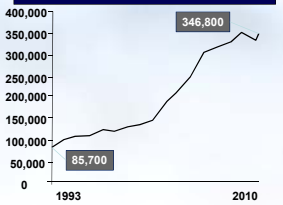
The good, the bad, and the ugly

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

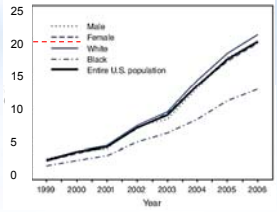
Bouza E, et al. *Med Clin North Am.* 2006;90:1141-1163.
Loo VG, et al. *N Engl J Med.* 2005;353:2442-2449.

Marked Increases in Severe CDI in the US

US Annual CDI-Related Hospitalizations



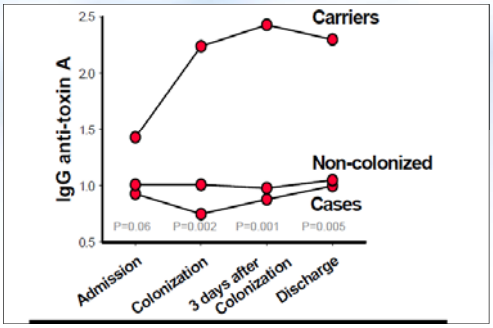
US CDI Death Rates
Age-standardized rates per million population



- 14,000 deaths per annum in US per CDC estimate
- x 4 annual deaths related to MRSA
- x 6 annual deaths related to all other enteric pathogens combined

AHRQuality. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf. US (CDC) mortality statistics.

Immunity to *C. difficile* Toxins is Associated with Symptomless Carriage



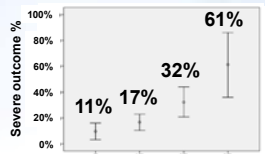
Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

Predicting Severe Complications of CDI

- Derivation cohort –
  263 CDI subjects in Boston
- Validation cohort –
  CDI subjects in Houston (n=225) & Dublin (n=150)

Severe outcomes – CDI-related
ICU admission and/or
Colectomy and/or Death.

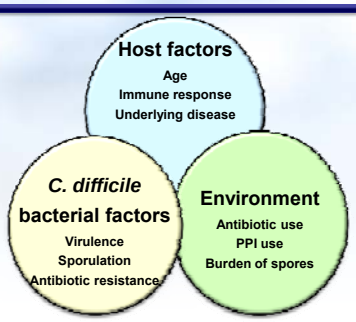
Prediction score
1 for Age ≥65 years
1 for WBC ≥20,000 cells/μL
1 for Creatinine ≥2 mg/dL



Score: 0 1 2 3
(73% accurate)

Na X, et al. Clinical Prediction Tool for Severe *Clostridium difficile* Infection. *PlosONE*. (under review).

C. difficile Infection: Factors Contributing to Increased Incidence and Severity



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932–40.
Bauer MP, et al. *Clin Microbiol Infect.* 2009;15:1067–79.
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431–55.

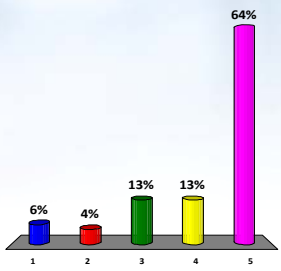
Severe CDI: Case Presentation

- 87-year-old man undergoes hip replacement surgery following fractured femur
- Medical history: diabetes mellitus, COPD & severe CAD with congestive heart failure
- POD #6: diarrhea. Stool test positive for toxigenic *C. difficile*
- WBC 18,200 cells/μL, creatinine 1.9 mg/dL (baseline 1.2)
- Treated with oral vancomycin 125 mg q6h
- 36 hours later, he develops nausea, abdominal distension and hypotension.
- His WBC is now 34,700 cells/μL and creatinine is 2.7 mg/dL

Audience Question

How would you change his management at this time?

1. Increase **oral vancomycin dose to 500 mg** q6h
2. Discontinue oral vancomycin as it is not effective and change to **oral metronidazole 500 mg** q8h
3. Continue **oral vancomycin 125 mg** q6h and add **oral metronidazole 500 mg** q8h
4. Increase **oral vancomycin dose to 500 mg** q6h and add **IV metronidazole 500 mg** q8h
5. Increase **oral vancomycin dose to 500 mg** q6h, **add IV metronidazole 500 mg** q8h AND request a **surgery consultation**



CDI: SHEA – IDSA Treatment Guidelines

CDI Severity	Treatment
1. Mild to moderate	**Metronidazole** 500 mg 3 times per day PO 10–14 days
2. Severe	**Vancomycin** 125 mg 4 times per day PO 10–14 days
3. Severe, complicated (fulminant)	**Vancomycin** 500 mg 4 times per day PO or by nasogastric tube or enema plus **Metronidazole** 500 mg q8h **IV**

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-55. Debast SB, et al. *Clin Microbiol Infect*. 2014;20 Suppl 2:1-26. Surawicz CM, et al. *Am J Gastroenterol*. 2013;108(4):478-98.

CDI: Determining Disease Severity

Severe

- **Marked leukocytosis**
  - **>15,000 in severe CDI**
  - **>25,000 increased fatality**
- **High** (>1.5 mg/dL) **or rising** (50% increase) **serum creatinine**
- Severe diarrhea
  - >10 bowel movements/day
- Severe abdominal pain or distension
- Fever >101ºF
- Low serum albumin (<2.5)

Fulminant
(Severe complicated)

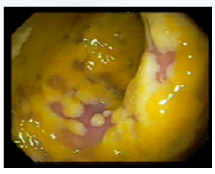
- **Not responding to therapy**
- **Toxic megacolon**
- **Hemodynamic instability**
- **Organ failure**
- Ileus
- CT with
  - Colonic thickening
  - Ascites
- Pseudomembranes on colonoscopy

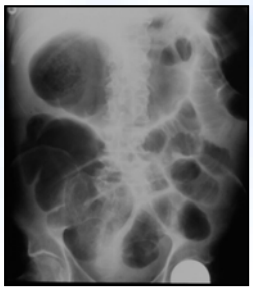
Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932-40. Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-55. Debast SB, et al. *Clin Microbiol Infect*. 2014;20 (Suppl 2):1-26. Surawicz CM, et al. *Am J Gastroenterol*. 2013;108(4):478-98.

Colonic Distension and Small Bowel Ileus in Fulminant *Clostridium difficile* Colitis

Severe / fulminant CDI may present as an acute abdomen and/or small bowel and colonic ileus (mimicking acute colonic pseudo-obstruction)

- **Little or no diarrhea**
- **Sigmoidoscopy usually diagnostic**





Kelly CP, et al. *Gastrointestinal Pharmacotherapy*. W. B. Saunders, 1993; pp.199-212.

When Standard Therapy Fails in Fulminant CDI: Unproven Adjunctive Treatments

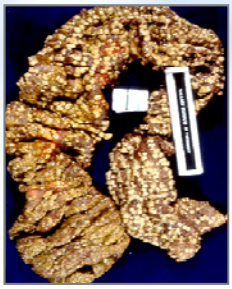
1. **Tigecycline**
   - Loading dose of 100 mg IV
   - Then 50 mg two times per day
2. **IVIG** (Intravenous immunoglobulin infusion)
   - 400 mg/kg body weight x 1
3. **FMT** (Fecal microbiota transfer)

Kelly CP, LaMont JT. *N Engl J Med*. 2008;359:1932-40.
Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-55.
Debast SB, et al. *Clin Microbiol Infect*. 2014;20(Suppl 2):1-26.
Eiseman B, et al. *Surgery*. 1958;44:854-9.

Diverting Loop Ileostomy and Colonic Lavage:

An alternative to total abdominal colectomy in refractory CDI

Colectomy versus:



- **Loop ileostomy**
- Intraoperative **colonic lavage** with warmed polyethylene glycol 3350/ electrolyte via the ileostomy
- Post-op antegrade **vancomycin instillation** via ileostomy

42 patients
- **83%** by laparoscopy
- **93%** colon preserved
- **19%** mortality
  - *versus* **50%** mortality in historical controls (odds ratio, 0.24; p=0.006).

Neal MD, et al. *Ann Surg*. 2011;254:423–429.

Severe CDI: Case Presentation

- **87-year-old man undergoes hip replacement surgery following fractured femur**
- **Medical history: diabetes mellitus, COPD & severe CAD with congestive heart failure**
- **POD #6: diarrhea. Stool test positive for toxigenic *C. difficile***
- **WBC 18,200 cells/μL, creatinine 1.9 mg/dL (baseline 1.2)**
- **Treated with oral vancomycin 125 mg q6h**
- **36 hours later he develops nausea, abdominal distension and hypotension**
- **His WBC is now 34,700 cells/μL and creatinine is 2.7 mg/dL**

Back to Audience Question

How would you change his management at this time?

1. Increase **oral vancomycin dose to 500 mg** q6h
2. Discontinue oral vancomycin as it is not effective and change to **oral metronidazole 500 mg** q8h
3. Continue **oral vancomycin 125 mg** q6h and add **oral metronidazole 500 mg** q8h
4. Increase **oral vancomycin dose to 500 mg** q6h and add **IV metronidazole 500 mg** q8h
5. Increase **oral vancomycin dose to 500 mg** q6h, **add IV metronidazole 500 mg** q8h AND request a **surgery consultation**

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40. Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-55. Debast SB, et al. *Clin Microbiol Infect.* 2014;20(Suppl 2):1-26. Eiseman B, et al. *Surgery.* 1958;44:854-9.

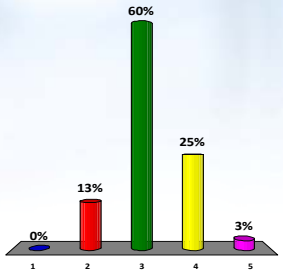
Recurrent CDI: Case Presentation

- **Our 87-year-old patient with severe complicated CDI responded to intensive medical management.**
- **He was transferred to rehab where he completed 14 days of oral vancomycin and was treated for a UTI with ciprofloxacin.**
- **Five days later, he developed diarrhea, nausea, vomiting, abdominal distension and his WBC was elevated at 17,200 cells/µL.**
- **He was transferred back to the acute care hospital where he responded well to aggressive treatment for recurrent CDI (oral vancomycin and intravenous metronidazole).**
- **Prior to transfer he asks if there is a risk for yet another recurrence of CDI.**

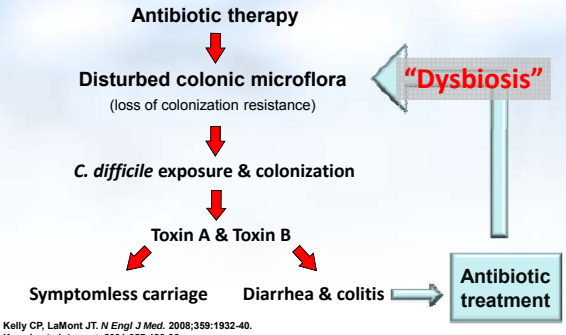
Audience Question

What is his risk for a second recurrence?

1. **Less than 10%**
2. **10 to 20%**
3. **20 to 30%**
4. **30 to 70%**
5. **Greater than 70%**



Recurrent *C. difficile* Infection
An Antibiotic-Perpetuated Cycle



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

Recurrent *Clostridium difficile* Infection

- Common: ~25% of patients treated with metronidazole or vancomycin suffer a recurrence
  - Recurrence rates after fidaxomicin lower (~15%)
- Mechanisms of recurrence:
  - NOT primarily due to antimicrobial resistance
  - Instead, antimicrobial therapy perpetuates dysbiosis
- Same strain as initial episode (relapse) or a new strain (re-infection)
- Several patient risk factors for CDI recurrence have been identified

Cohen MB. *J Ped Gastroenterol Nutr.* 2009;48(Suppl. 2):S63–5. Kyne L, et al. *Lancet* . 2001;357:189–93. Bauer MP, et al. *Clin Microbiol Infect.* 2009;15:1067–79. Bauer MP, et al. *Lancet.* 2011;377:63–73. Hu MY, et al. *Gastroenterology* 2009;136:1206–14. McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769–75. Do AN, et al. *Clin Infect Dis* 1998;26:954–9. Bauer MP, et al. *Clin Microbiol Infect.* 2011;17(Suppl. 4):A1–4. Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7.

Risk Factors for Recurrent CDI

- Previous episode of recurrent CDI
- Additional antibiotic use (perpetuates dysbiosis)
- Aged 65 years or over
- Impaired immune response to *C. difficile* toxins
- Prolonged hospitalization
- Severe underlying disease
  - ICU admission
  - Immunocompromised
  - Renal impairment
- Acid anti-secretory medication?

Cohen MB. *J Ped Gastroenterol Nutr.* 2009;48(Suppl. 2):S63–5. Kyne L, et al. *Lancet* . 2001;357:189–93. Bauer MP, et al. *Clin Microbiol Infect.* 2009;15:1067–79. Bauer MP, et al. *Lancet.* 2011;377:63–73. Hu MY, et al. *Gastroenterology* 2009;136:1206–14. McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769–75. Do AN, et al. *Clin Infect Dis* 1998;26:954–9. Bauer MP, et al. *Clin Microbiol Infect.* 2011;17(Suppl. 4):A1–4. Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7.

Meta-analysis of Risk Factors for Recurrent CDI

Risk factor	Odds ratio	95% CI	P
Non-*C. difficile* antibiotics after diagnosis of CDI	4.23	2.10–8.55	<0.001
Acid antisecretory medications	2.15	1.13–4.08	0.019
Older age	1.62	1.11–2.36	0.0012

Factors were evaluated only if studied in at least 3 publications that met the quality inclusion criteria:
Fewer than 3 studies evaluated:
- ***Disease severity (Horn's index)***
- ***Anti-toxin immune response***

Garey KW, et al. *J Hosp Infect.* 2008;70:298–304.

GASTROENTEROLOGY 2009;136:1206–1214

Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent *Clostridium difficile* Infection

MARY Y. HU,* KIANOOSH KATCHAR,* LORRAINE KYNE,‡ SEEMA MAROO,* SANJEEV TUMMALA,* VALLEY DREISBACH,* HUA XU,* DANIEL A. LEFFLER,* and CIARÁN P. KELLY*

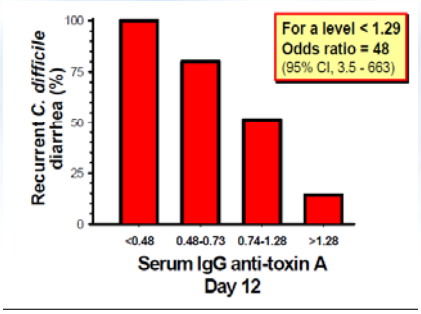
Predictors of recurrence:
1 for **Age >65 y**
1 for **Severe underlying disease** (Horn's index)
1 for **Additional antibiotic** use

Score	Recurrence rate (validation cohort)
0	0%
1	17%
2	31%
3	67%

Predictive accuracy (in validation cohort): **72%**
Score of 0 or 1 versus 2 or 3 [95% CI: 59.2 to 82.4%]

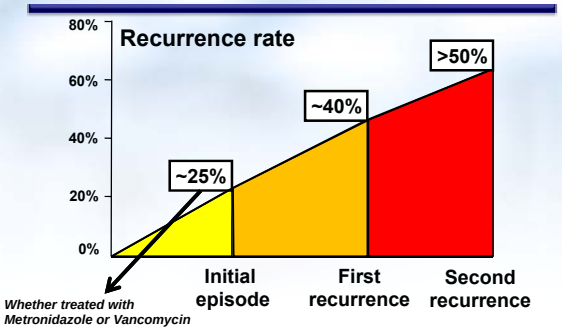
Hu MY, et al. *Gastroenterology* 2009;136:1206–14.

High Serum IgG Anti-toxin A Levels are Associated with a Lower Risk for Recurrent *C. difficile* Diarrhea



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

Prior CDI Recurrence and Recurrence Risk



McFarland LV, et al. *JAMA*. 1994;271:1913–8.
Pépin J, et al. *Clin Infect Dis.* 2005;40:1591–7.
McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769–75.

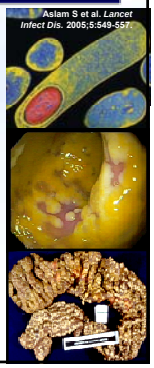
Back to Audience Question

What is his risk for a second recurrence?

1. Less than 10%
2. 10 to 20%
3. 20 to 30%
4. **30 to 70%**
5. Greater than 70%

Refractory and Fulminant (CDI): Key Points

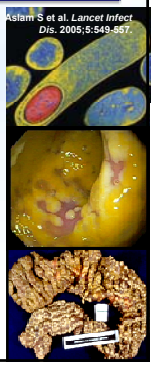
- CDI has become an increasingly common and lethal infection (usually nosocomial & iatrogenic).
- Factors that predict severe outcomes in CDI include older age (>65 years), high WBC (≥20,000 cells/μL) and high creatinine (≥2 mg/dL).
- Severe complicated (fulminant) CDI can result in SIRS (systemic inflammatory response syndrome), hypotension, organ failure and toxic megacolon.
- Vancomycin therapy is indicated in severe CDI – metronidazole is not an appropriate sole therapy.
- In refractory CDI, timely surgical intervention can be lifesaving.



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

Risk Factors for Recurrent CDI: Key Points

- Antibiotic treatment for antibiotic-induced CDI perpetuates dysbiosis and predisposes to recurrence.
- Recurrent CDI is common.
  - ~25% after a 1st CDI episode
  - ~35% after a 2nd CDI episode
  - ~50% after a 3rd or subsequent CDI episode
- Host immune responses (anti-toxin antibody production) can protect against recurrent CDI.
- Factors that predict a higher risk for recurrence include prior recurrences, additional (concomitant) antibiotic use, older age, and severe underlying disease.


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

A Patient-Centered Approach for Managing CDI: Balancing the Old with the New

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

Barnes-Jewish Hospital | Washington University in St. Louis Physicians
NATIONAL LEADERS IN MEDICINE

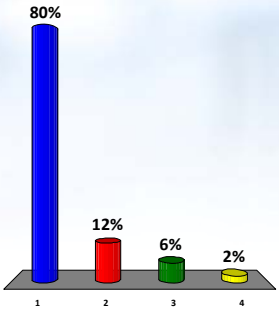
Case

- 70-year-old female nursing home resident
  - Developed diarrhea: six Bristol 7 stools/day
  - Completed ciprofloxacin for a UTI 5 days prior
- In ED noted to be dehydrated
  - IV fluids started
  - WBC = 13.5K cells/µL
- Stool positive for *C. difficile* toxin

Audience Question

What do you do?

1. Start metronidazole 500 mg PO q8h
2. Start vancomycin 125 mg PO q6h
3. Start fidaxomicin 200 mg PO q12h
4. Feces, feces, feces



CDI Treatment

- Historically two main treatments
  - Metronidazole
  - Oral vancomycin (not intravenous)
- Response rates equal until 2000
  - Initial cure in 85% to 95%
  - Recurrence in 15% to 30%

Increased Reports of Metronidazole Failures

Study	Response	Recurrence
Fernandez	61/99 (62%)	Not reported
Musher	161/207 (78%)	47/161 (29%)
Pépin	323/435 (74%)	109/323 (34%)
Belmares	72/102 (71%)	Not reported

Fernandez A, et al. *J Clin Gastroenterol.* 2004;38:414-418.
Musher DM, et al. *Clin Infect Dis.* 2005;40:1586-1590.
Pépin J, et al. *Clin Infect Dis.* 2005;40:1591-1597.
Belmares J, et al. *J Infect.* 2007;55:495-501.

Vancomycin vs. Metronidazole for Severe CDI

- **First double-blind trial of metronidazole vs. vancomycin**

Disease severity	No. of patients cured/ no. of patients treated (%)			
	Mtz group	Vm group	Total	*P*[a]
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

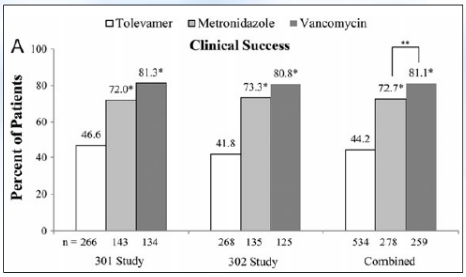
Zar FA, et al. *Clin Infect Dis*. 2007;45:302-7.

CDI Treatment Stratified by Severity

Clinical scenario	Supportive clinical data	Recommended treatment
Mild to moderate	**Leukocytosis (WBC <15,000 cells/μL) or SCr level <1.5 times premorbid level**	**Metronidazole 500 mg 3 times per day PO for 10–14 days**
Severe	**Leukocytosis (WBC ≥15,000 cells/μL) or SCr level ≥1.5 times premorbid level**	**Vancomycin 125 mg 4 times per day PO for 10–14 days**
Severe, complicated	**Hypotension or shock, ileus, megacolon**	**Vancomycin 500 mg 4 times per day PO or by nasogastric tube *plus* metronidazole 500 mg IV q8h**

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

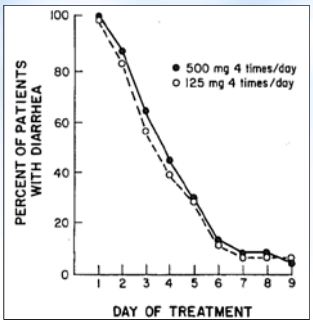
Metronidazole Also Inferior For Non-Severe CDI



Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354.

A Word on Vancomycin Dose

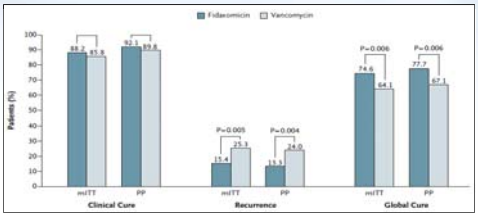


- Vancomycin concentration at 125 mg QID >100 times higher than MIC for *C. difficile*
- Time-dependent killing
  - No additional benefit beyond 4–10× MIC
- Higher concentrations may kill more "non-susceptible" bacteria

Fekety R, et al. *Am J Med*. 1989;86:15-9.

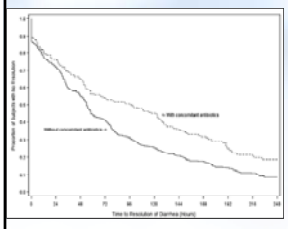
Fidaxomicin

- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram-negatives
  - Sparing of *Bacteroides* spp., bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Patients with multiple recurrences were excluded



Louie TJ, et al. *N Engl J Med*. 2011;364:422-31.

Impact of Concomitant Antibiotics on Response to CDI Treatment



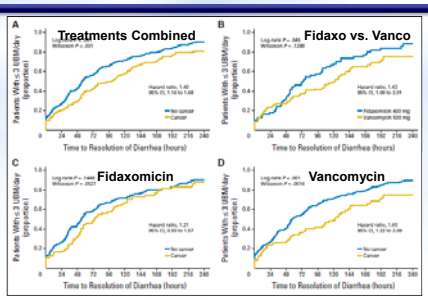
No CA	Fidaxo N=391	Vanco N=416	*P*
Clinical cure	92%	93%	0.80
Recurrence	12%	23%	<0.001
Sustained response	81%	69%	<0.001

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.

Fidaxomicin in Oncology Patients



Clinical cure: fidaxomicin 85%, vancomycin 74% (p=0.065)
Recurrence: fidaxomicin 14%, vancomycin 30% (p=0.018)
Sustained clinical response: fidaxomicin 74%; vancomycin 52% (p=0.003)

Cornely OA, et al. *J Clin Oncol*. 2013;31:2493-2500.

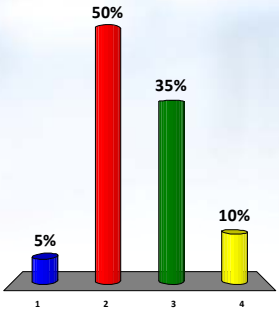
Case Continued

- **The patient responded to the 10-day course of vancomycin you prescribed**
  - **Diarrhea recurred 7 days later, stool was positive for *C. difficile*, responded to metronidazole at the nursing home**
- **Diarrhea recurred 5 days after metronidazole stopped**
  - **Ten Bristol 7 stools/day**
  - **Transferred back to the ED**
  - **Stool positive for *C. difficile* toxin**

Audience Question

What do you do?

1. **Metronidazole 500 mg PO q8h for 60 days**
2. **Vancomycin 125 mg PO q8h for 10 days then taper over several weeks**
3. **The pharmacy will finally let me prescribe fidaxomicin: fidaxomicin 200 mg PO q12h for 10 days**
4. **More feces**



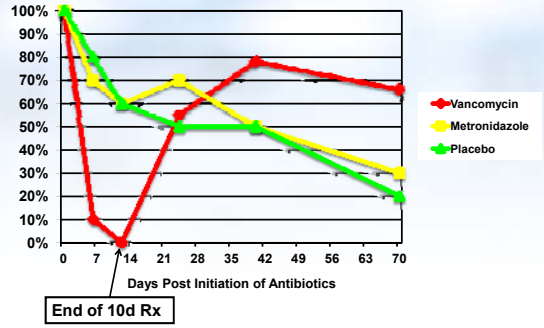
Management of Recurrent CDI

- CDI recurrence is a significant challenge
- Rates of recurrent CDI:
  - 20% after first episode
  - 45% after first recurrence
  - 65% after two or more recurrences

Clinical scenario	Recommended treatment
First recurrence	Treat as first episode according to disease severity
Second recurrence	Treat with oral vancomycin taper and/or pulse dosing

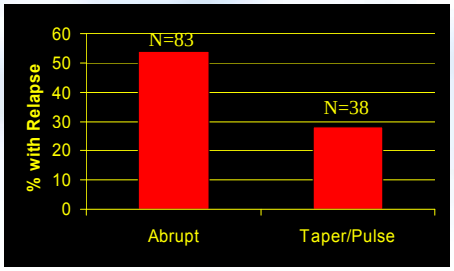
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.

First Step: Educate and Confirm Symptoms are from CDI



Johnson S, et al. *Ann Intern Med.* 1992;117: 297-302.

Abrupt Stop vs. Taper or Pulse of Vancomycin



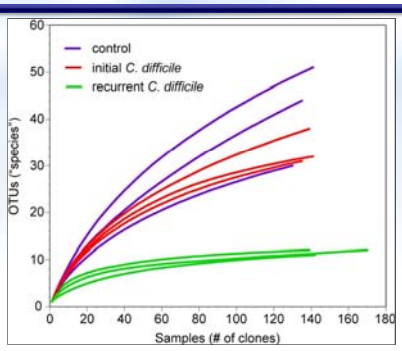
- Mean number of CDI episodes 3 ± 2.1 (range 1–14)
- Relative Risk of Relapse = 0.51 (95% CI: 0.29–0.90)

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

Alternative/Adjunctive Therapies

- Probiotics: **RCTs of *Lactobacillus* and *Saccharomyces boularii* without benefit**
- Cholesterol binders: **No better than placebo**
- Rifaximin: **Initial treatment and "Chaser" to prevent recurrence; *caution – rapid development of resistance***
- Nitazoxanide: **Non-inferior to metronidazole and vancomycin in small trials; no clear advantage**
- Tigecycline: **Case reports for severe CDI; mixed results**
- IVIG: **Severe or recurrent infections; mixed results**

Tens Days of Fidaxomicin May Not Be Enough for Recurrent CDI: Potential Role for Chaser or Taper



Chen X, et al. *Gastroenterology*. 2008;135:1984-1992.

Fecal Microbiota Transplant (FMT)

- **Theory: Restoration of fecal flora and colonization resistance**
- **First report in 1958**
- **Several recent reviews of published reports**

Method	Resolution
Colonoscope	55/62 (88.7%)
Enema	105/110 (95.4%)
Gastric or duodenal tube	55/72 (76.4%)
Rectal catheter	44/46 (95.6%)
>1 method	19/21 (90.5%)
Not reported	6/6 (100%)

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

Recent FMT Trial

- At least one relapse
- Open label
  - 4 to 5 days of vancomycin, bowel prep, FMT (duodenal tube)
  - 14 days of oral vancomycin
  - 14 days of vancomycin with bowel prep at day 4 to 5

Method	Number prior episodes	Resolution
Single infusion of feces	3 (1–5)	13/16 (81%)
Vancomycin only	3 (1–4)	4/13 (31%)
Vancomycin and lavage	2 (1–9)	3/13 (23%)

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

FMT: The Devil is in the Details

(and hopefully not in the stool)

- Sounds simple
  - Poop is readily available
  - All you have to do is mix it with saline, filter it, and infuse away
- FDA/IRB
  - IND no longer required, but patients must be informed FMT is experimental therapy , not all risks are known, and sign a consent form
  - Whether IRB approval is needed is up to local IRB
- Donor screening
  - Consent prudent: if determined to be not eligible, recipient will know the donor has an excluding condition, such as HIV
  - Not covered by insurance: Charges may approach $2000
- Stool prep/delivery
  - Body fluids must be handled like biohazard level 2 substance – prepared in biohazard hood
  - Good manufacturing practice
  - Fresh versus frozen
- Cleaning of materials to process stool

Investigational Therapies: Surotomycin

- Non-absorbed antimicrobial
  - Lipopeptide
- Phase 2 study
  - 250 mg BID with 50% reduction of recurrent CDI compared to vancomycin
    - 17% versus 35%; p<0.035
- Phase 3 studies ongoing

Investigational Therapies: LFF571

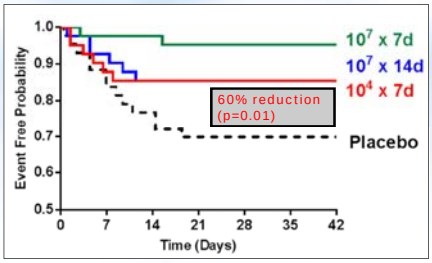
- Non-absorbed antimicrobial
  - Thiopeptide
- Phase 2 study
  - 200 mg QID versus vancomycin 125 mg QID

Population	Time point	Proportion (no.) of patients with cure using: LFF571	Vancomycin
Per protocol	End of therapy	0.91 (32)	0.78 (23)
	End of study	0.57 (30)	0.65 (20)
mITT	End of therapy	0.85 (46)	0.80 (25)
	End of study	0.59 (46)	0.60 (25)

Population	Proportion (no.) of patients with recurrences using: LFF571	Vancomycin
Per protocol		
Clinical definition	0.37 (27)	0.31 (16)
Toxin confirmed	0.19 (27)	0.25 (16)
mITT		
Clinical definition	0.31 (39)	0.30 (20)
Toxin confirmed	0.15 (39)	0.25 (20)

Mullane K, et al. *Antimicrob Agents Chemother*. 2015;59:1435-40.

Investigational Therapies: Nontoxigenic *C. difficile* (NTCD)

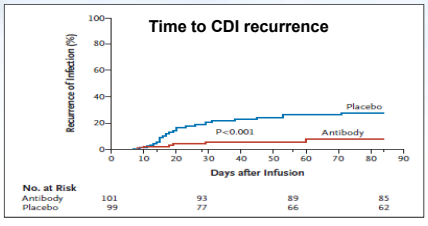


- Recurrence rate if became colonized with NTCD: 2%
- Recurrence rate if not colonized with NTCD: 31%

Villano SA, et al. Presented at IDWeek 2013.

Investigational Therapies: Monoclonal Antibodies (mAbs)

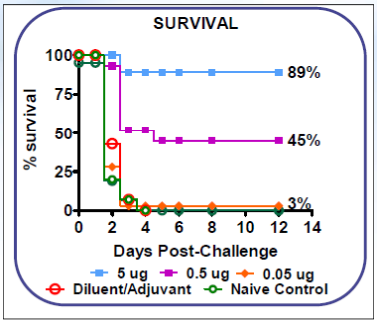
- Study of mAbs in 200 CDI patients receiving metronidazole or vancomycin
- Recurrence rates:
  - 7% in mAb group vs. 25% in placebo group



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

Investigational Therapies: *C. difficile* Toxoid Vaccine

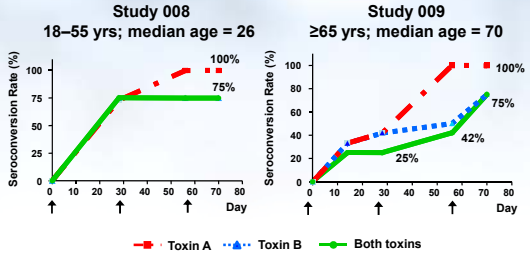
Dose response relationship with survival



Anosova NG, et al. Presented at the 4th International *Clostridium difficile* Symposium (ICDS). Bled, Slovenia, 2012.

Investigational Therapies: *C. difficile* Toxoid Vaccine

- **Seroconversion rates in young vs. elderly healthy subjects (50 µg dose)**



Foglia G, et al. Anaerobe Society of Americas 2010; Abstract CD 1093.

Conclusions: CDI Treatment

- **Initial episode**
  - Enthusiasm for metronidazole quickly waning
  - Vancomycin remains highly efficacious for initial episode
  - Role of fidaxomicin: potential populations
    - Risk for recurrence
    - Risk for decreased treatment response
- **Recurrent CDI**
  - Potential approach: vancomycin taper → fidaxomicin taper → FMT
- **Many agents being investigated**
  - Initial treatment
  - Prevent recurrence
  - Primary prevention