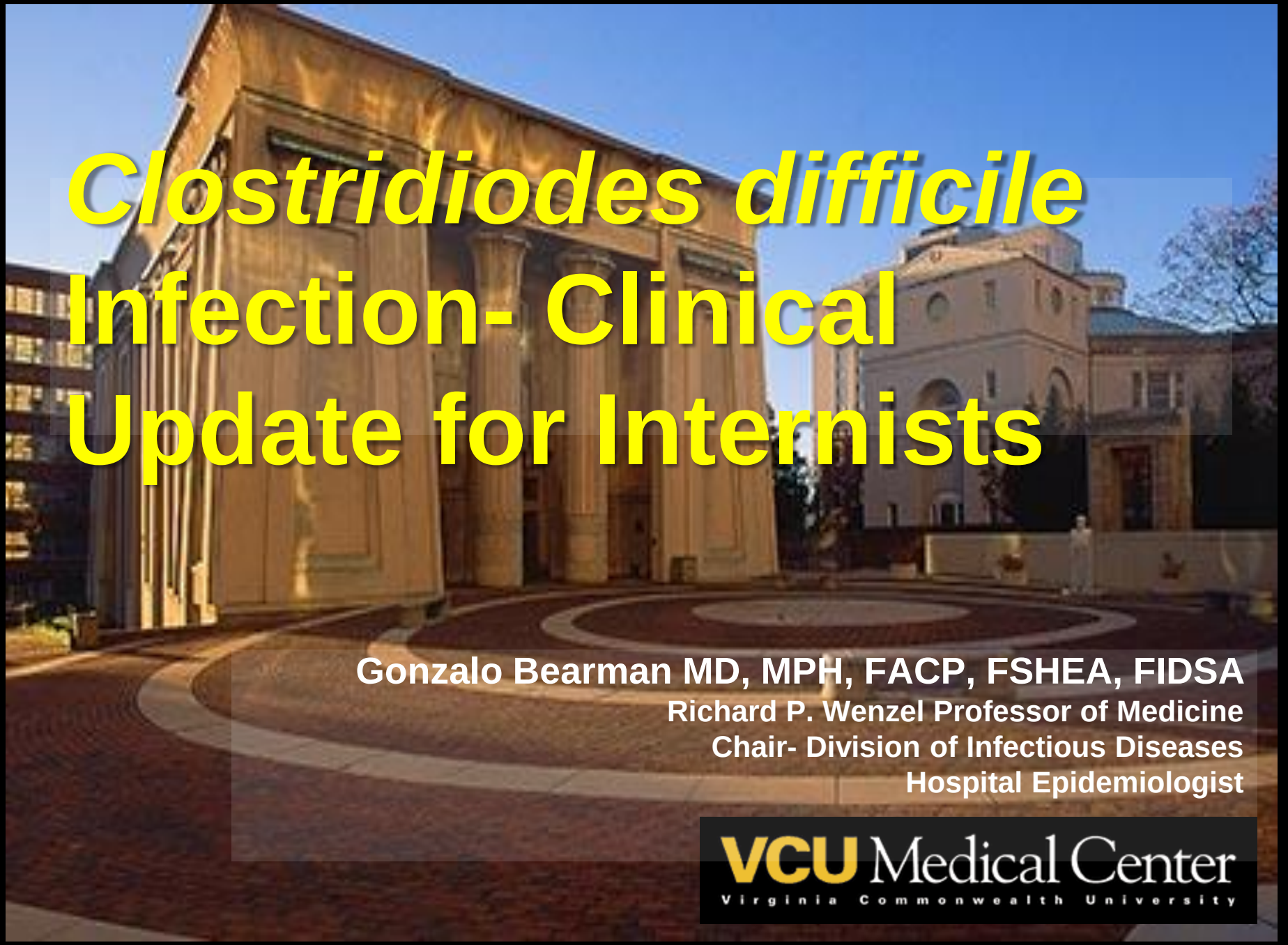

Clostridiodes difficile Infection- Clinical Update for Internists

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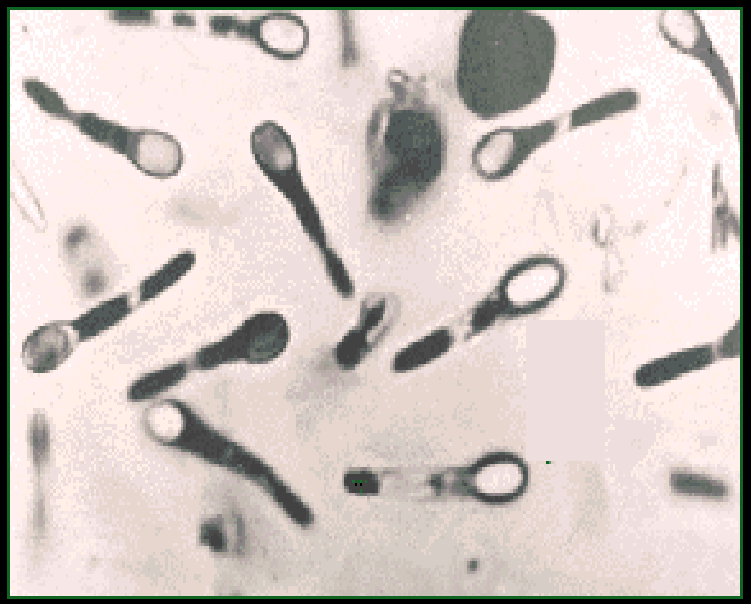
Disclosures

- Prior research grants from:
  - Pfizer Pharmaceuticals
  - Biovigil LLC
  - Vestagen Technologies
  - Cardinal Healthcare
  - Molnlycke Health Care
  - AO (Orthopedic) Foundation Grant

Epidemiology

Clostridioides difficile

- *Clostridioides difficile* is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhea and colitis



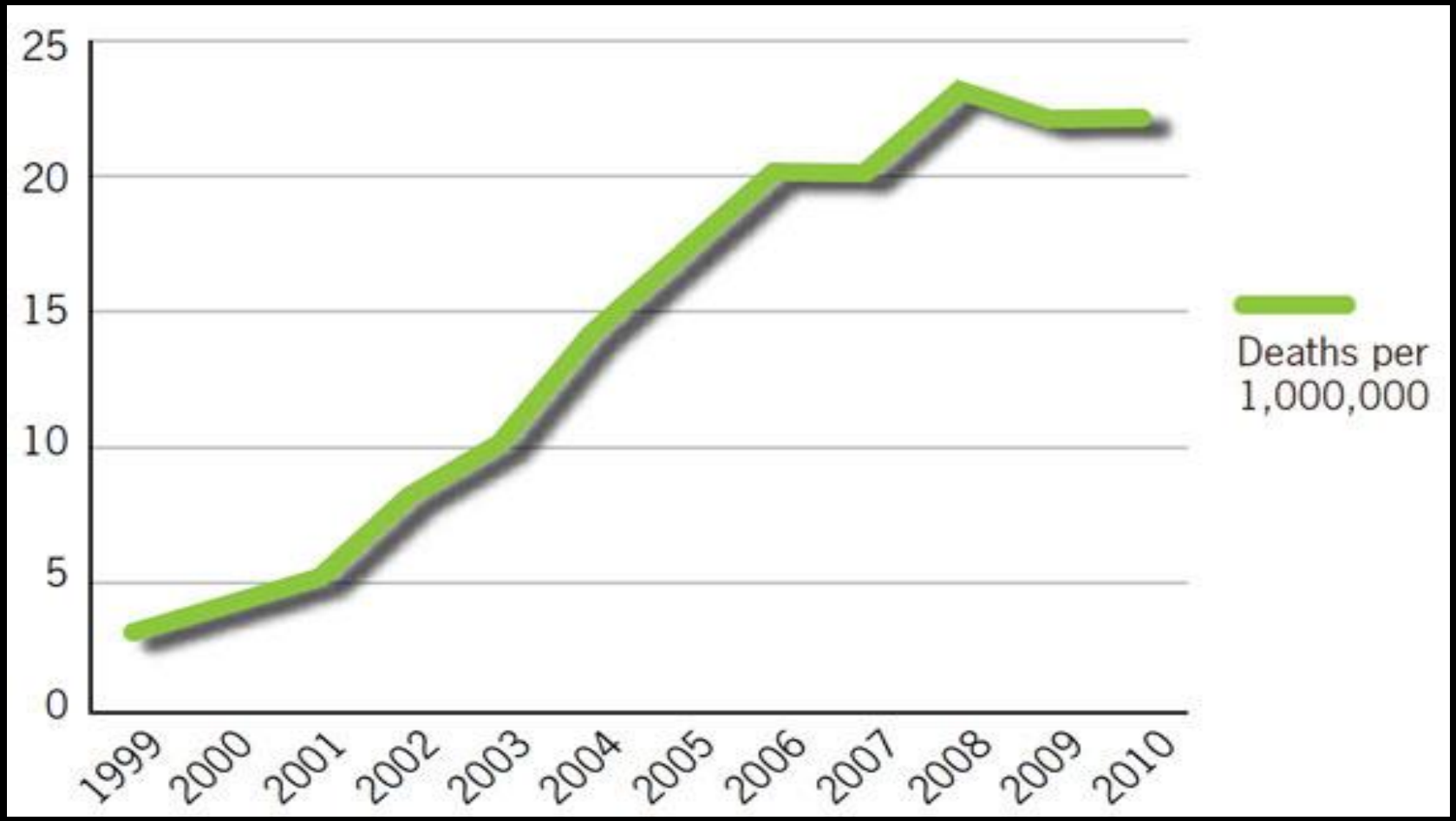
Epidemiology

- *C. difficile* cultured from the stool of 3% of healthy adults and up to 80% of healthy newborns and infants
- Stool carriage of *C. difficile* reaches 16–35% among hospital inpatients.
- *C. difficile* persists in the stools of 10–40% of patients with CDI
- Contaminated environmental surfaces, other patients with CDI and hand carriage on the part of healthcare personnel are important reservoirs for cross transmission

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

Mcfarland LV et al*. N Engl J Med* 1989; 320: 204–210.

Increasing CDI Mortality in USA



CDI is increasingly recognized disease in the community

- Data from the US, Canada and Europe suggest that ~20%-27% of all CDI cases are community associated
  - Incidence 20-30 per 100,000 population
- Outpatient antimicrobial exposure and PPI use associated with increased risk

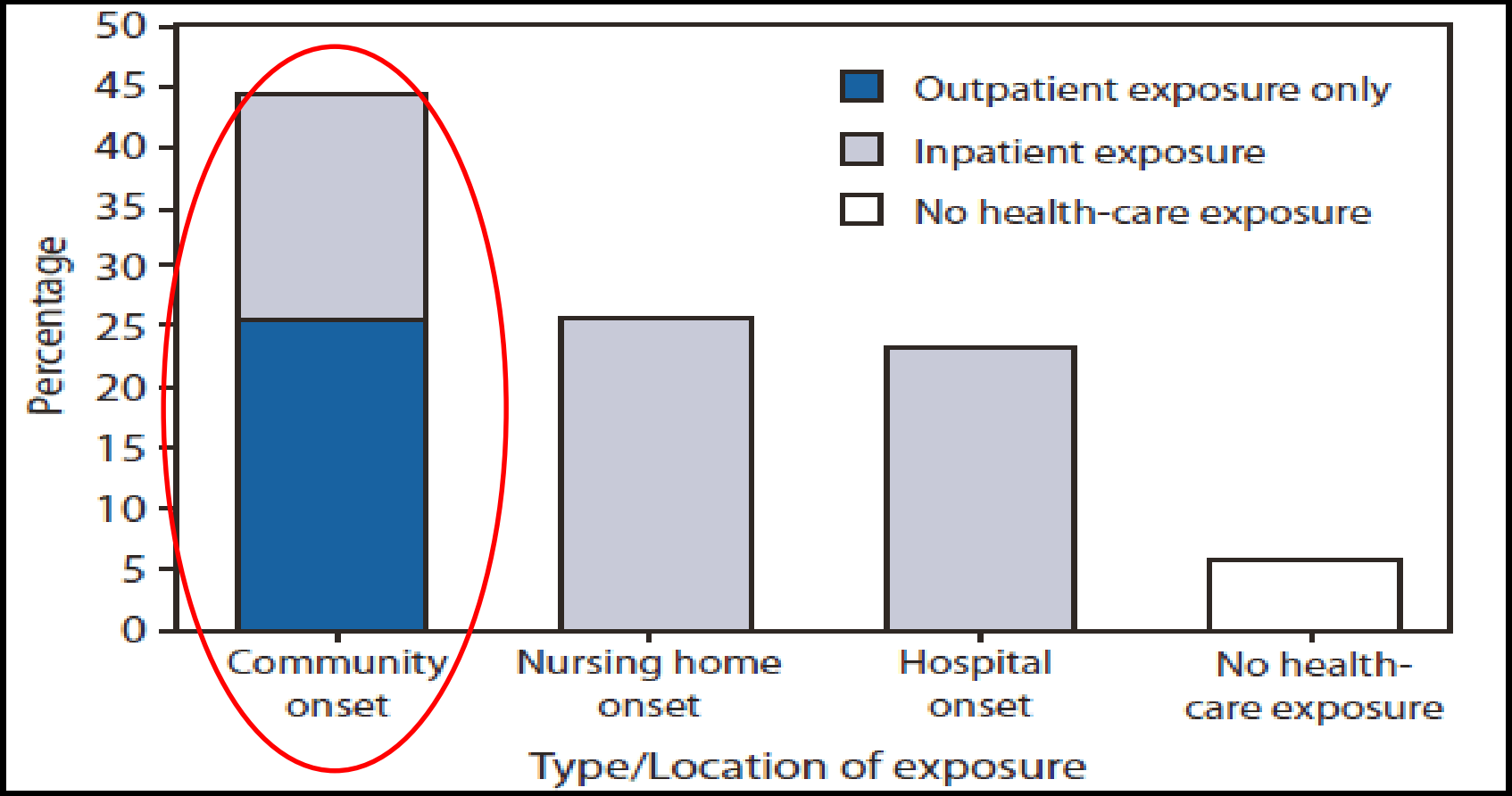
Wilcox et al. *Antimicrob Chemother* 2008;62:388-96.
Kutty et al. *Emerg Infect Dis* 2010;16:197-204
Lambert et al. *Infect Control Hosp Epidemiol* 2009;30:945-51.

Epidemiology of CDI

- Hospital Associated CDI
  - Any hospital or long term care admission within the last 4 weeks
- Community Associated CDI
  - Symptom onset > 12 weeks after last healthcare facility admission

ICHE 28:140; *CID* 25;1543, 2007

Epidemiology of CDI



CDI cases (N = 10,342), by inpatient or outpatient status at time of stool collection and type/location of exposures*

MMWR March 9, 2012

Toxin gene-variant and highly toxigenic strains - NAP1/BI/027

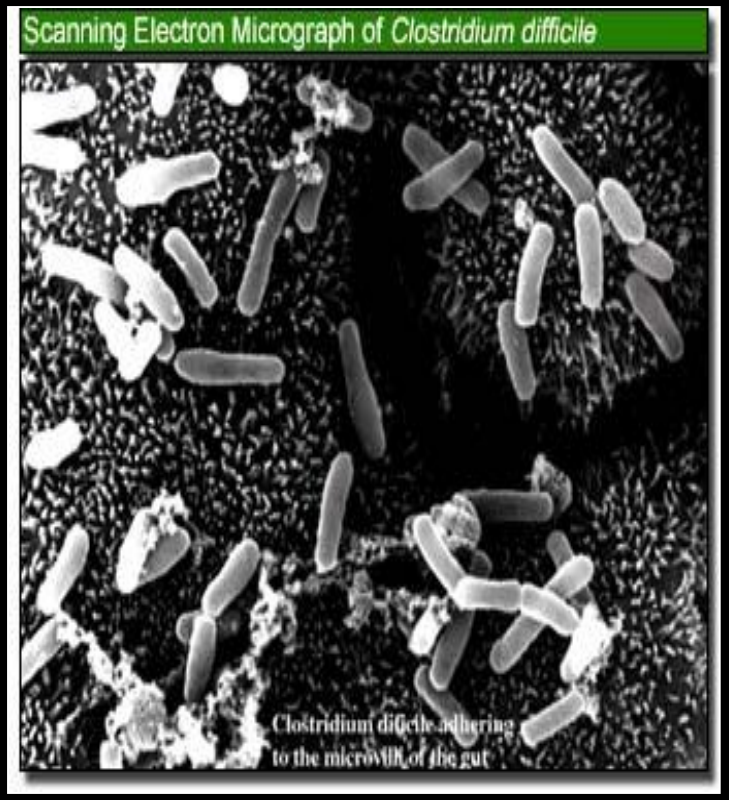
- Highly toxigenic strain of *C. difficile* that produces about 15 to 20 times the amount of toxins A and B
  - Caused nosocomial and community outbreaks in North America, Great Britain, and the Netherlands
    - Toxinotype III
    - North American PFGE type 1 (NAP1)
    - Restriction enzyme analysis type "BI"
    - PCR-ribotype 027

Warny, M et al. *Lancet* 2005; 366:1079.

McDonald, LC, et al. *N Engl J Med* 2005; 353:2433

Toxin gene-variant and highly toxigenic strains - NAP1/BI/027

- Genes
  - *tcd*A Toxin A
    - Causes fluid accumulation in the bowel
  - *tcd*B Toxin B
    - Cell lysis and death
  - *tcd*C porin gene
    - Downregulates production of toxins A and B



Partial deletion in the tcdD gene results in overproduction toxins A and B

C. *difficile* Disease

Antibiotics and CDAD

Highly associated	**Moderately Associated**	**Rarely Associated**
Ampicillin Amoxicillin Cephalosporins Clindamycin	Other Beta-lactam antibiotics Sulfonamides Erythromycin Trimethoprim Quinolones	Parenteral Aminoglycosides Tetracylcines Chloramphenicol Metronidazole Vancomycin

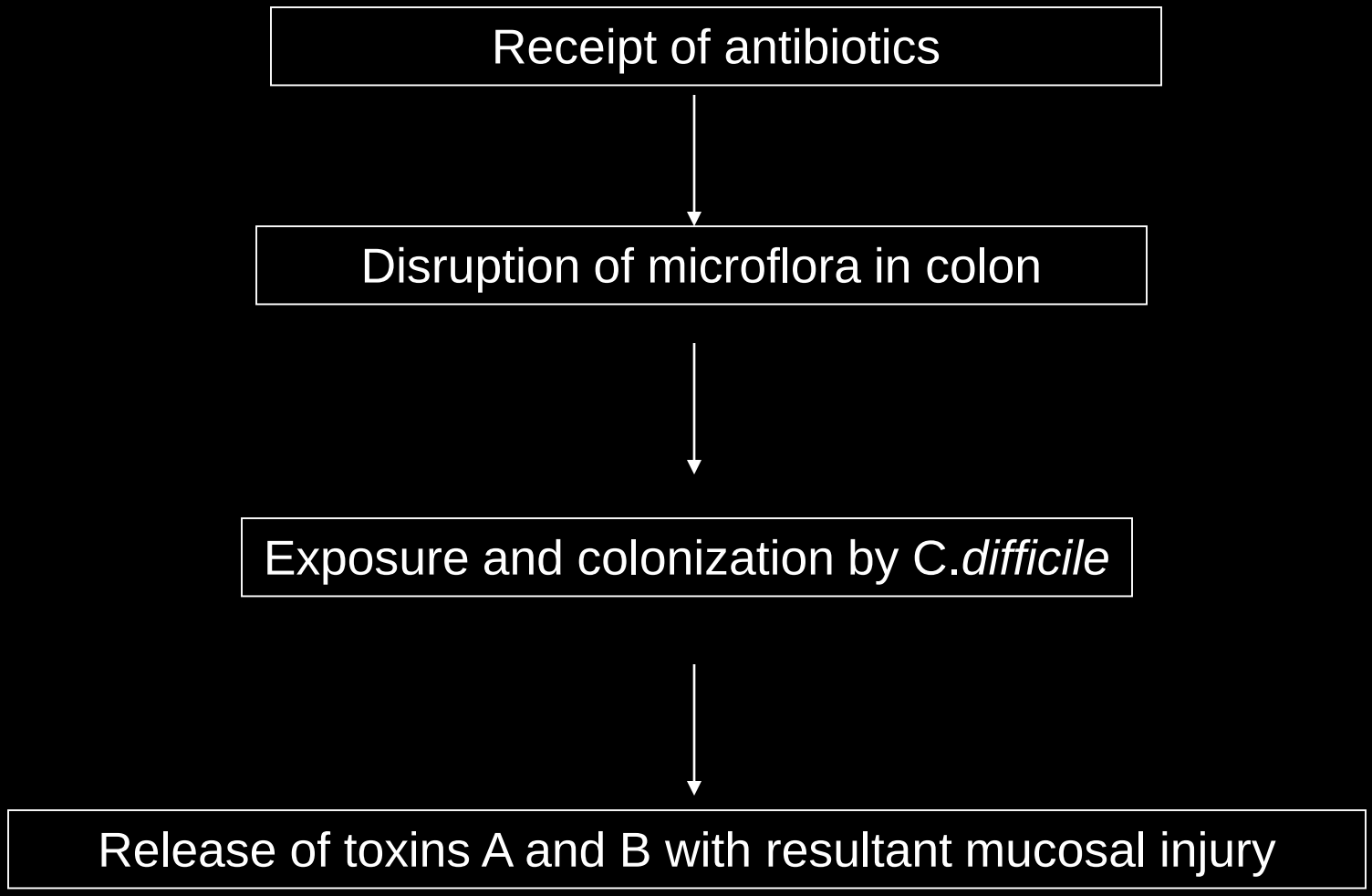
Gurwith MJ et al. *J Infect Dis* 1977; 135 Suppl:S104.

Pepin, et al *Clin Infect Dis* 2005; 41:1254.

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

Muto et al. *Infect Control Hosp Epidemiol* 2005; 26:273.

Risk Factors and Pathophysiology



Carrier State

- Once infected: 2/3 of infected hospitalized patients remain asymptomatic
  - Carriers are reservoirs of toxigenic organisms
- Routine treatment of carriers is not recommended
  - Treatment of carriers may be employed during hospital outbreaks
    - Elimination of the organism from the hospital environment

McFarland, LV et al. *N Engl J Med* 1989; 320:204.

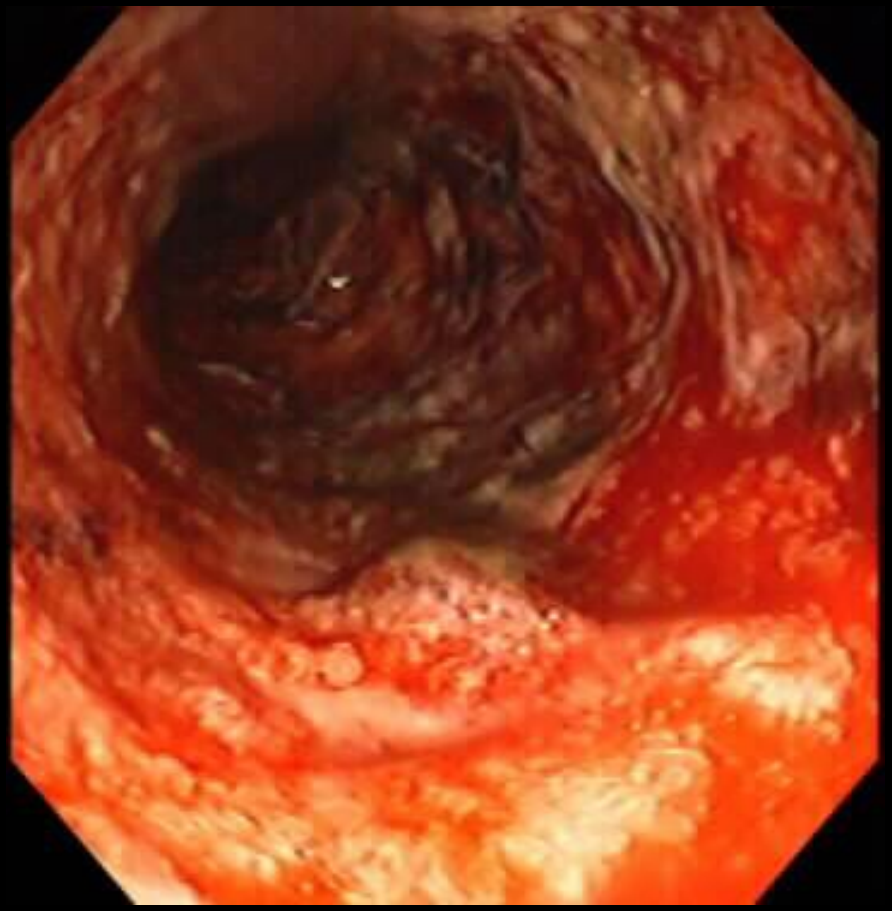
Johnson, S et al. *Ann Intern Med* 1992; 117:297.

Antibiotic Associated Colitis Without Pseudomembrane Formation

- Abdominal pain, nausea, anorexia
- Profuse watery diarrhea
  - 5 to 15 watery bowel movements per day
- Left or right lower quadrant abdominal pain and cramps
- Fever and dehydration
- Sigmoidoscopic examination
  - nonspecific diffuse or patchy erythematous colitis without pseudomembranes

Pseudomembranous Colitis

- Raised yellow or off-white plaques ranging up to 1 cm in diameter scattered over the colorectal mucosa
- Similar clinical symptoms of diarrhea, fever, leukocytosis and abdominal pain



How is Severe C. *difficile* Disease Defined?

Definition of Disease Severity

- Severe disease
  - WBC count >20,000 cells/microL
  - Elevated serum creatinine
- Point (score) assignment system in clinical trial
  - > 2 points = severe disease
    - 1 point assigned each
      - » age >60 years
      - » T>38.3ºC
      - » Albumin <2.5 mg/dL
      - » WBC >15,000 cells/microL
    - 2 points assigned for endoscopic evidence of pseudomembranous colitis or treatment in the ICU

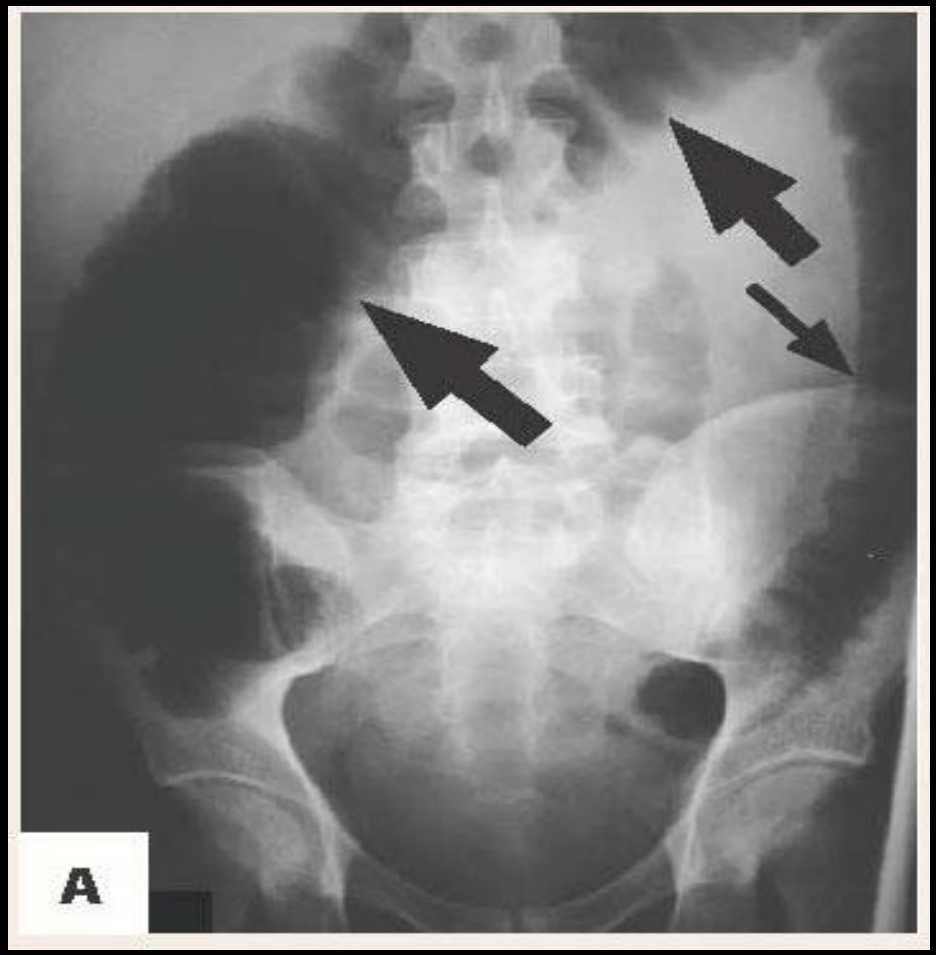
Zar et al. *Clinical Infectious Diseases,* 2007:45: 302-7

Fulminant Colitis and Toxic Megacolon

- 2 or 3 percent of patients
- Marked leukocytosis (>30,000 to 40,000 WBC/microL)
- Fever, chills, dehydration and metabolic (lactic) acidosis
- Diarrhea is prominent
  - However, diarrhea is less prominent in patients with ileus and secondary pooling of secretions in the dilated, adynamic colon

Toxic Megacolon

- Diagnosis based upon the finding of an enlarged dilated colon
  - >7 cm in its greatest diameter
- Accompanied by severe systemic toxicity

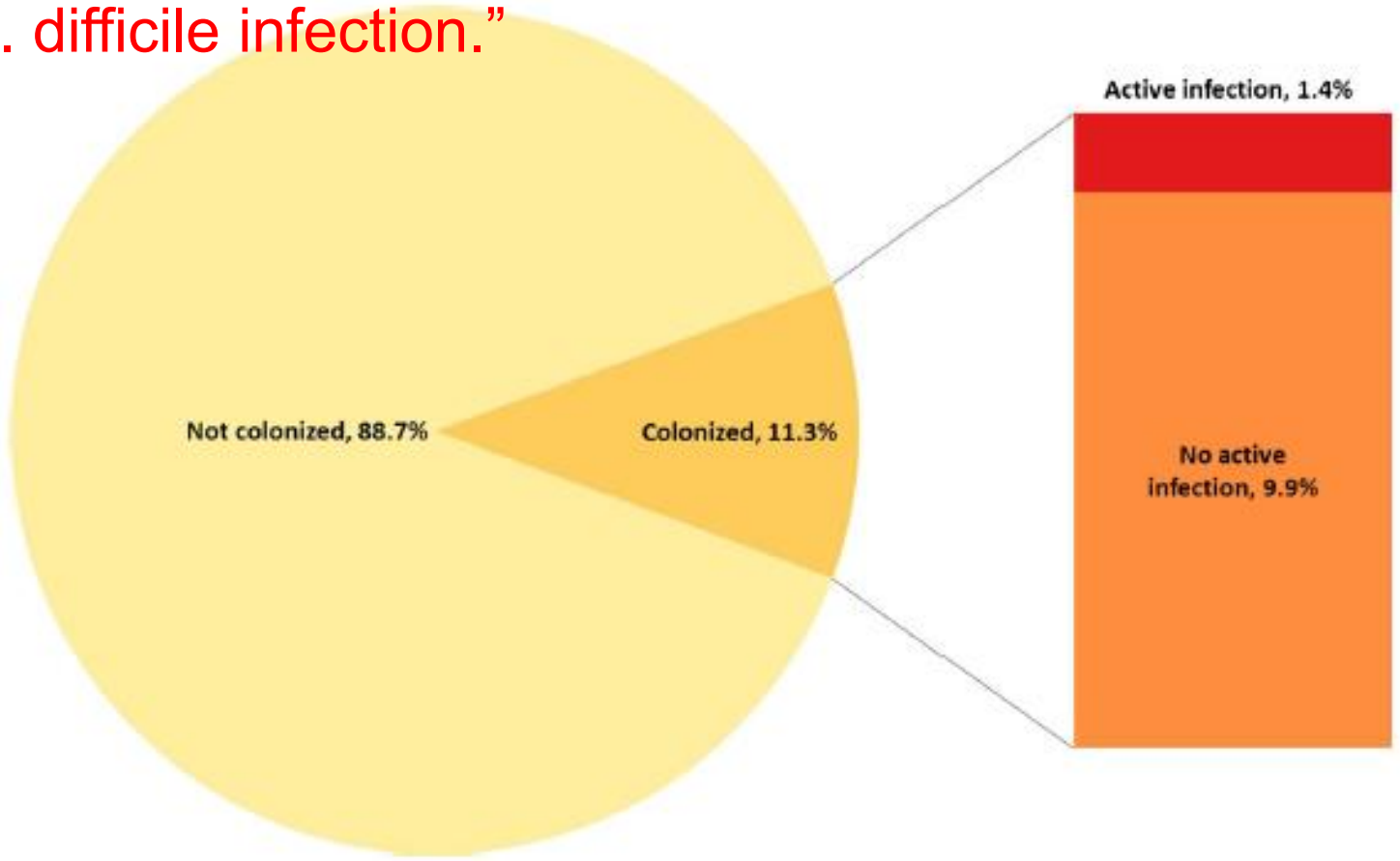


http://www.cfpc.ca/cfp/2004/Nov/_images/Fig0376_104_A.jpg

Diagnosis

C. *difficile* and the problem of Asymptomatic Colonization

"There is no such thing as a test for C. difficile infection."



Wit permission from Morgan DJ, et al. The importance of colonization with Clostridium difficile on infection and transmission. Curr Infect Dis Rep, 2015;17:43.

VCU Health

Caveat-There is No Test of Active Disease (Infection)

***C. difficile* Diagnostic Tests from Highest to Lowest Sensitivity**	
Culture + Toxin confirmation	**Gold standard, labor intensive, not practical**
NAAT/ PCR	**Sensitive, detects gene for toxin production**
EIA for Glutamate Dehydrogenase (GDH)	**Rapid test for the presence of GDH (toxigenic and non-toxigenic *C.difficile*)- must be used in conjunction with a test for toxins and toxin genes**
Endoscopy	**Not a sensitive test**

Adopted from:Gerding DN et al. *Infect Dis Clin Pract (Baltim Md).* 2016 Jan;24(1):3-10.

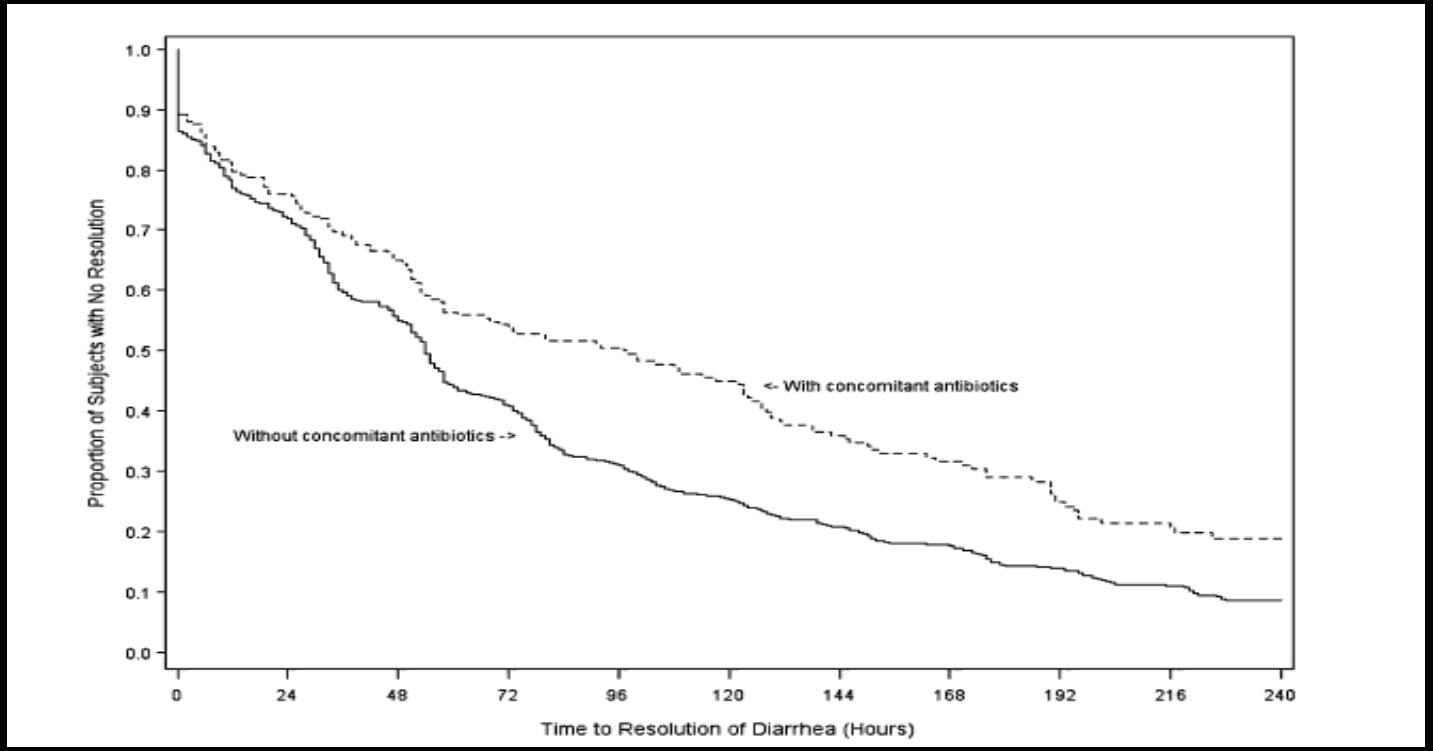
Clinical Practice Guideline: *C.difficile* Diagnostic Testing

- Patient with unexplained, new onset > 3 unformed stools (not on laxatives, tube feeding etc)
- NAAT (PCR) can be used as a stand alone test (+/- GDH EIA)
  - Only on loose/unformed stool
- Do not perform a test of cure

McDonald LC et al. *Clin Infect Dis*. 2018 Mar 19;66(7):987-994.

Treatment

Discontinuation of antibiotics



Delayed resolution of diarrhea if offending antibiotic not discontinued

Mullane KM, et al. Clin Infect Dis. 2011;53:440-447.

Metronidazole

- Oral metronidazole was widely recommended as the drug of choice for most cases of CDAD
  - High in vitro activity against *C.difficile*
  - High concentrations in the stool after both oral and IV administration

Vancomycin

- Poorly absorbed after oral administration
  - Virtually no serum concentration achieved via oral dosing.
    - Sytemic toxicity is minimal
- High fecal concentrations have been documented and are known to be therapeutic
- Use is a significant risk factor for the VRE GI colonization
- More expensive than metronidazole

Prospective Randomised Trial : Metronidazole versus Vancomycin for CDAD

	Treatment		P Value
	Metronidazole N=42	Vancomycin N=52	
Failure (N)	2	0	0.20
Relapses (N)	2	6	0.17

*** Metronidazole and vancomycin have equivalent efficacy and relapse rates and are tolerated to a similar extent by patients with *C-difficile*-related diarrhea and colitis**

Teasly et al. *Lancet* 1983 Nov 5;2(8358):1043-6.

Newer data: Vancomycin vs Metronidazole?

- Randomized, prospective, double blinded placebo controlled trial
- Treatments
  - Oral metronidazole 250mg QID x 10 days
  - Oral vancomycin 125mg QID x 10 days
- Outcomes
  - Clinical cure/ recurrence
    - Stratified by disease severity

Zar et al. *Clinical Infectious Diseases,* 2007:45: 302-7

Vancomycin vs Metronidazole?

Severity	Clinical Cure		
	Metronidazole	Vancomycin	P Value
Mild CDAD N=81	90%	98%	0.36
Severe CDAD N=69	76%	97%	0.02

Disease severity scoring system: one point each was given for age >60 years, temperature >38.3ºC, serum albumin <2.5 mg/dL (25 g/L), or peripheral white blood cell count >15,000 cells/microL within 48 hours of enrollment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit.

Patients with >2 point considered to have severe disease.

Zar et al. *Clinical Infectious Diseases,* 2007:45: 302-7

How to Treat Recurrent Disease?

Relapse- Increasingly More Common

- Relapse of CDAD occurs in 10-50% of patients
  - Likely due to persistence and germination of *C.difficile* spores
    - However, up to 50% of relapses may be due to reinfection with a new strain of *C. difficile*

Mylonakis et al. *Archives of Int Med.* 2001; 161:525-33

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

Barbut et al. *Antimicrob Agents Chemother* 1999;43:2607-11

Musher et al. *Clinical Infectious Diseases* 2005;40:1586–1590

Malnick SDH. *Annals of Pharmacotherapy*. 2002;36:1767-75

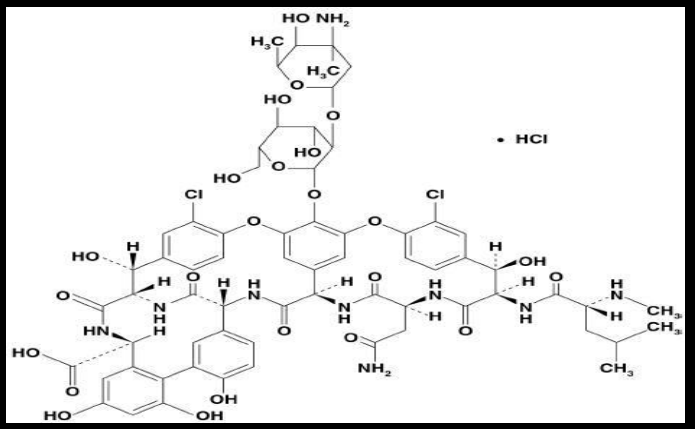
Relapse

- There are is no single best treatment strategy for recurrent *C. difficile* disease

1st Recurrence	**•Repeat Vancomycin therapy** **•Fidaxomicin**
Multiple Recurrences	**•Fidaxomicin** **•Dose titration of vancomycin (pulse taper)** **•Fecal transplantation (FMT)** **•Bezlotuximab**

Vancomycin

- Dose titration with pulse dosing
  - Week 1: 125mg QID
  - Week 2: 125mg BID
  - Week 3: 125 mg QD
  - Week 4: 125mg QOD
  - Weeks 5 and 6: 125 mg every 3 days



•Intermittent administration of antibiotics permits germination of residual spores on the off days.

• With the reintroduction of antibiotics, the organism is consequently destroyed.

Tedesco et al. *Am Journal of Gastroenterol* 1985;80:867-8

Fidaxomicin

- Novel macrocyclic antibiotic -FDA approved for the treatment of *C. difficile*–associated diarrhea
- Fidaxomicin inhibits bacterial protein synthesis
  - noncompetitive inhibition of RNA polymerase
- Fidaxomicin - bactericidal for the treatment of *C. difficile*

Fidaxomicin

Phase III trial	Global Cure (Resolution of diarrhea without recurrence*)		
	Fidaxomicin	Vancomycin	P value
North America Protocol	206/265 (78%)	190/283 (67%)	0.006
International Protocol	172/216 (80%)	154/235 (66%)	<0.001
Combined results	**79%**	**66%**	**P<0.001**

* Reduced recurrence limited to non-027 Cd strains

-Louie TJ et al. N Engl J Med. 2011;364:422–31
-Crook D, et al Presented at the 20th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, April 10–13, 2010
-Miller M et al. Gastroenterology 2009;136:A115
-Hardesty J, Pharmacotherapy 2011;31(9):877–886

Fidaxomicin

- Fidaxomicin - generally well tolerated
  - Adverse effects reported as mild gastrointestinal complaints
- Fidaxomicin -useful for the treatment of severe CDAD and demonstrates decreased rates of recurrence

Comparative Effectiveness of *C.difficile* Treatments

- Systematic review of 11 trials with 1463 participants
- No study comparing 2 antimicrobial agents demonstrated statistically significant superiority on initial cure
  - All studies: low to moderate strength of evidence
- Recurrence is less frequent with fidaxomicin than with vancomycin

Drekonja D et al. *Ann Intern Med* 2011;155:839-47

What About Fecal Microbiota Transplantation?

Fecal Transplantation

- Case series over nine years involving 18 patients with recurrent *C.difficile* colitis treated with donor stool via nasogastric tube
  - 90 days of follow up:
    - 2 patients died of unrelated illnesses.
    - 1 recurrence in 16 patients
    - No adverse effects associated with stool treatment

Aas et al. *Clinical Infectious Diseases* 2003;36:580–585

Intestinal Microbiota Transplantation (Fecal Microbiota Transplantation)

- FMT via suspension of a healthy donor stool into intestine of a patient with CDI
- Meta-analysis: 317 patients
  - 27 case series
    - IMT highly effective with resolution CDI in 92% cases
    - Death and adverse events were uncommon

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

Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD[1], Alexa R. Weingarden[1], Michael J. Sadowsky, PhD[1,3] and Alexander Khoruts, MD[2,3]

- Case series (n=43) of fecal transplantation via colonoscopy with enema
  - Fecal Transplantation Donors
    - 10 patient indentified, individual donors
    - 33 patients received fecal transplantation from volunteer donors
- Descriptive study to overcome barriers in a clinical FMT program

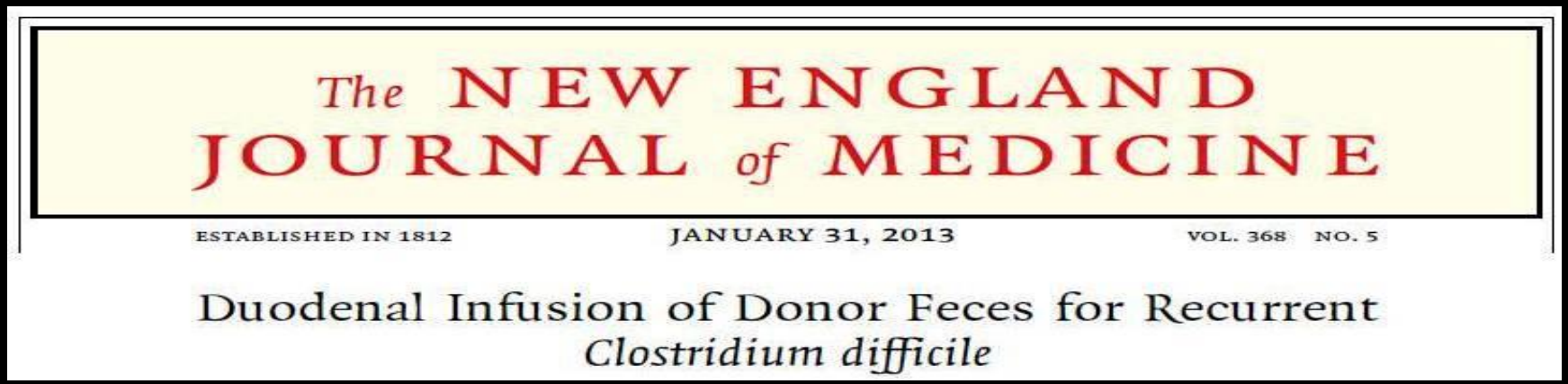
Hamilton MJ et al. *Am J Gastroenterol*. 2012 Jan 31 10.1038/ajg.2011.482.

Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD[1], Alexa R. Weingarden[1], Michael J. Sadowsky, PhD[1,3] and Alexander Khoruts, MD[2,3]

Donor Material	Mean Age	Relapses	Success rate
Individual Donor (n=10)	70	6.2	7/10 (70%)
Standard donor, fresh material (n=12)	83	6.4	11/12 (92%)
Standard donor, frozen material (n=21)	67	5.2	19/21 (90%)
Total experience (n=43)	72	5.9	37/43 (86%)

Hamilton MJ et al. *Am J Gastroenterol*. 2012 Jan 31 10.1038/ajg.2011.482.



- Random assignment of patients to receive one of three therapies:
  - vancomycin (500 mg po TID x 4 days followed by bowel lavage + infusion of a solution of donor feces via NG tube
  - vancomycin 500 mg po TID x 14 days
  - vancomycin 500 mg po TID x 14 days with bowel lavage

Van Nood E et al. *N Engl J Med* 2013 368;5. 407-15

Duodenal Infusion of Donor Feces for Recurrent *Clostridioides difficile*

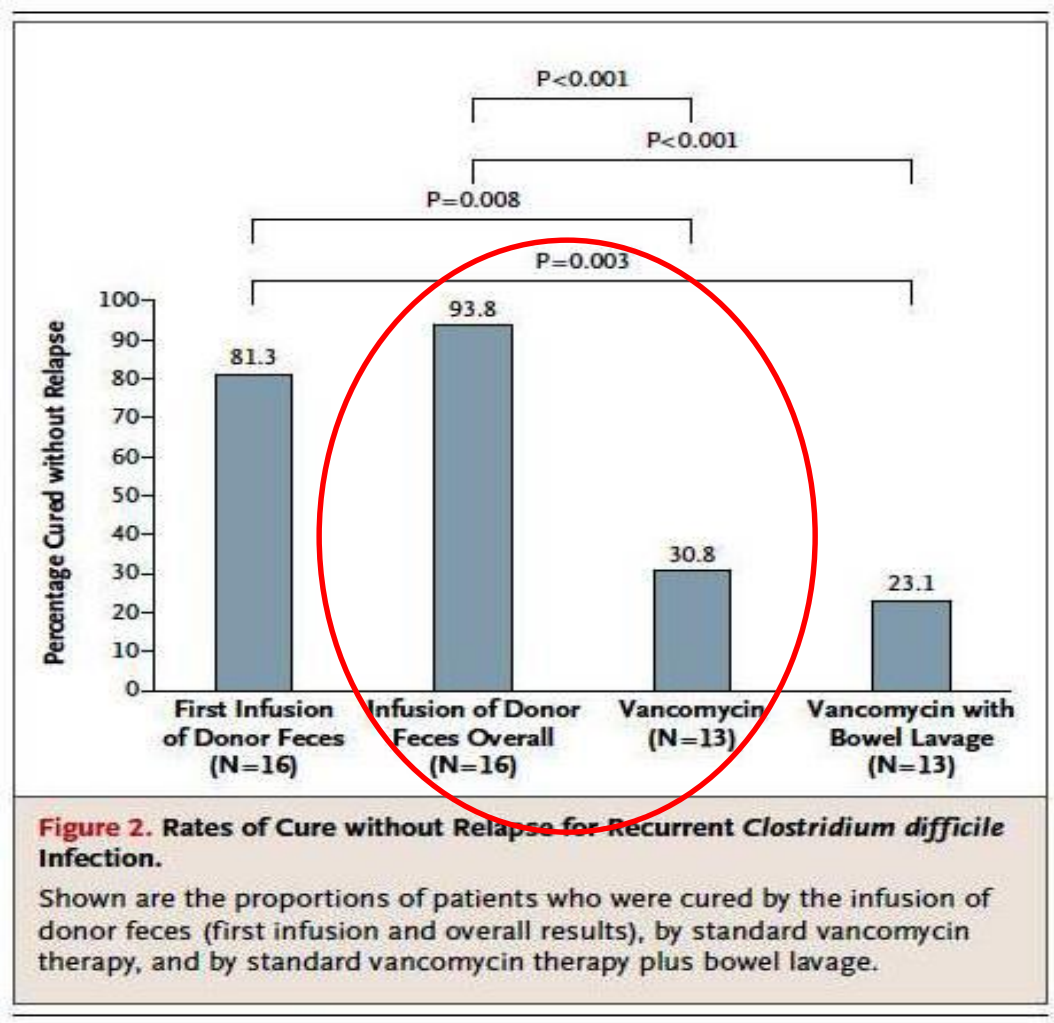


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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

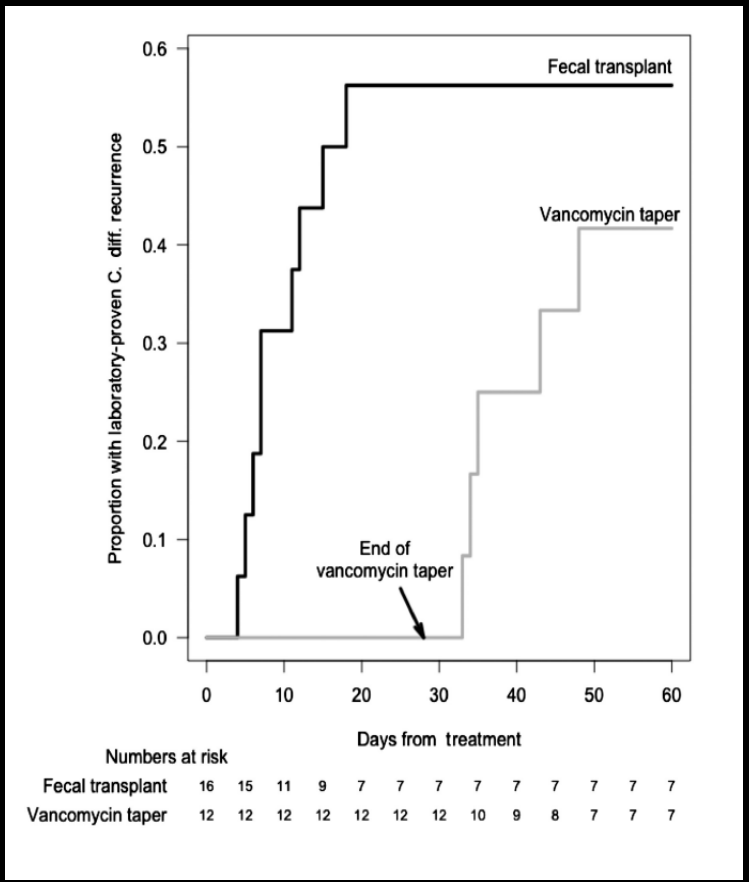
- Study was stopped after an interim analysis
- Fecal donor recipients showed increased fecal bacterial diversity, similar to that in healthy donors

Van Nood E et al. *N Engl J Med* 2013 368;5. 407-15

Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial

Susy S. Hota,[1,2,4] Valerie Sales,[2,3,4] George Tomlinson,[4,5] Mary Jane Salpeter,[1,6] Allison McGeer,[2,7,8] Bryan Coburn,[2,4,9] David S. Guttman,[10,11] Donald E. Low,[2,7,8,a] and Susan M. Poutanen[2,7,8]

- 14 days of oral vancomycin + single FMT by enema vs oral vancomycin taper (standard of care) for recurrent CDI
- Study terminated at interim analysis (30 patients)
- 56% FMT patients vs 42% vancomycin taper with recurrent CDI



Hota SS et al. *Clin Infect Dis*. 2017 Feb 1;64(3):265-271

What About the Use of Monoclonal Antibodies for the Treatment of Recurrent *C. difficile* Infection?

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection

M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, and M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*

- Bezlotoxumab human monoclonal antibodies- against C. difficile toxins A and B
  - After at least 7 days of standard Rx
- Prospective, double blind RCT
  - Patients followed for 12 weeks for CDI recurrence
- Bezlotumimab 17% recurrence vs 27% recurrence for placebo

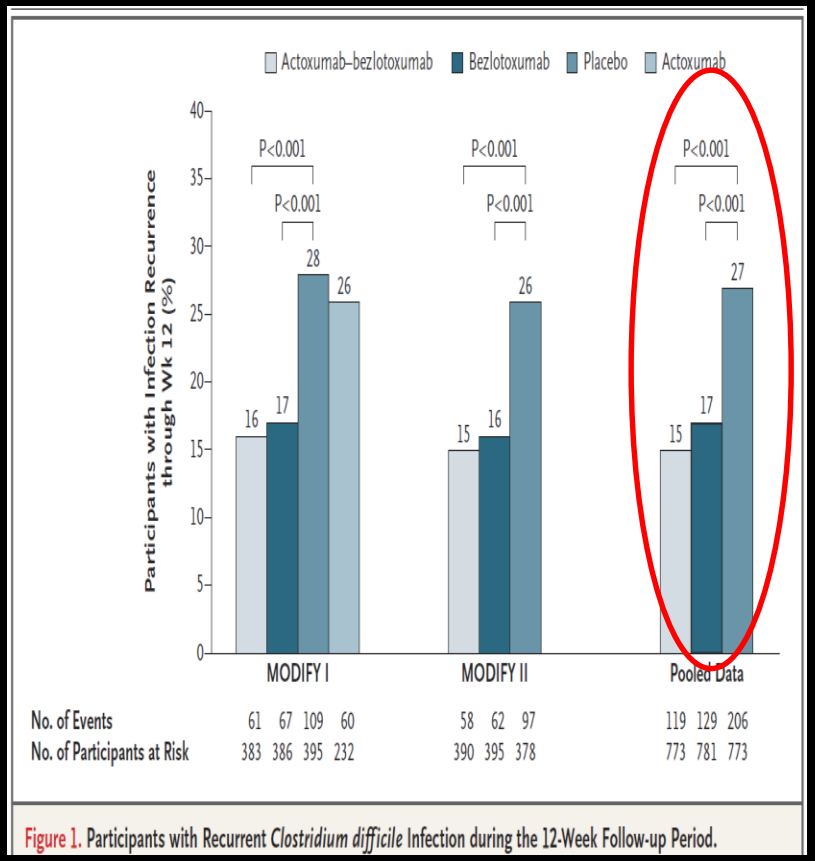


Figure 1. Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.

Wilcox MH et al. *N Engl J Med*. 2017 Jan 26;376(4):305-317

How Does One Prevent Recurrent *C.difficile* in Patients Receiving Systemic Antibiotics?

Efficacy of Oral Vancomycin in Preventing Recurrent *Clostridium difficile* Infection in Patients Treated With Systemic Antimicrobial Agents

Oral Vancomycin Prophylaxis (OVP) 125 mg BID or 250 mg BID during systemic antibiotic therapy up to 1 week after primary Rx completion (Prior history of CDI)

	No OVP N=132	**OVP N=71**	**P value**
Relapse 4 weeks post completion of Rx	26.6%	4.2%	P < .001

Van Hise NW et al. *Clin Infect Dis.* 2016 Sep 1;63(5):651-3

C. difficile Treatment Summary

Non-severe, 1st episode	**•Discontinue offending antibiotic** **•Oral vancomycin or fidaxomicin** **•Metronidoazole if above not available**
Moderate to severe	**•Vancomycin or fidaxomicin**
1st Recurrence	**•Vancomycin or fidaxomicin** **•Vancomycin pulse taper dosing**
Multiple Recurrences	**•Fidaxomicin or vancomycin** **•Dose titration /taper of vancomycin** **•Fecal transplantation** **•Bezlotuximab**
Fulminant disease +/- ileus	**•Vancomycin 500mg QID (PO /NG tube) + IV metronidiazole** **•Rectal vancomycin + IV metronidazole (ileus)** **•Surgical evaluation for complete colectomy**

Adapted from: McDonald LC et al. *Clin Infect Dis*. 2018 Mar 19;66(7):987-994.

Summary

- *C.difficile* is a resurgent pathogen
- CDI is now associated with high rate of relapse and virulence
- Severe disease is preferentially treated with oral vancomycin or fidaxomicin
- Treatment of recurrent CDI includes vancomycin, fidaxomicin, pulse taper vancomycin, monoclonal antibodies (bezlotuximab) and FMT
- OVP limits recurrences of CDI

The End