Treatment of Recurrent *C. difficile* Infections: Anti-infectives vs. Fecal Microbiota Transplant

19th Annual Chicago Infection Control Conference

Navy Pier, Chicago, IL

May 30, 2014

Stuart Johnson, MD
Hines VA Hospital
Loyola University Medical Center

Disclosures

- Consultant: Bio-K+, Summit PLC
- Grants: VA Research Service*
- Only FDA approved CDI Treatment Agents: Vancomycin, Fidaxomicin

**The opinions expressed in this presentation are those of the presenter and do not necessarily represent the views of the Veterans Affairs Health-Care System*

Multistate Point-Prevalence Survey of Health Care-Associated Infections

- One-day survey of randomly selected inpatients from 183 hospitals was performed in 10 geographically diverse states in 2011
- 4.0% (452/11,282) had one or more HA-associated infections
- Most common: Pneumonia (21.8%), SSIs (21.8%), and GI infections (17.1%) – C. difficile was the most common reported pathogen
- Device-associated infections (CA-BSI, CA-UTI, VAP) accounted for 25.6%
- CONCLUSION: As device- and procedure-associated infections decrease, consideration should be given to expanding surveillance and prevention activities to other HAIs

Magill SS et al. N Engl J Med 2014;370:1198-1208.

Multistate Point-Prevalence Survey of Health Care-Associated Infections

Conclusions:
Public health surveillance and prevention activities should continue to address CDI

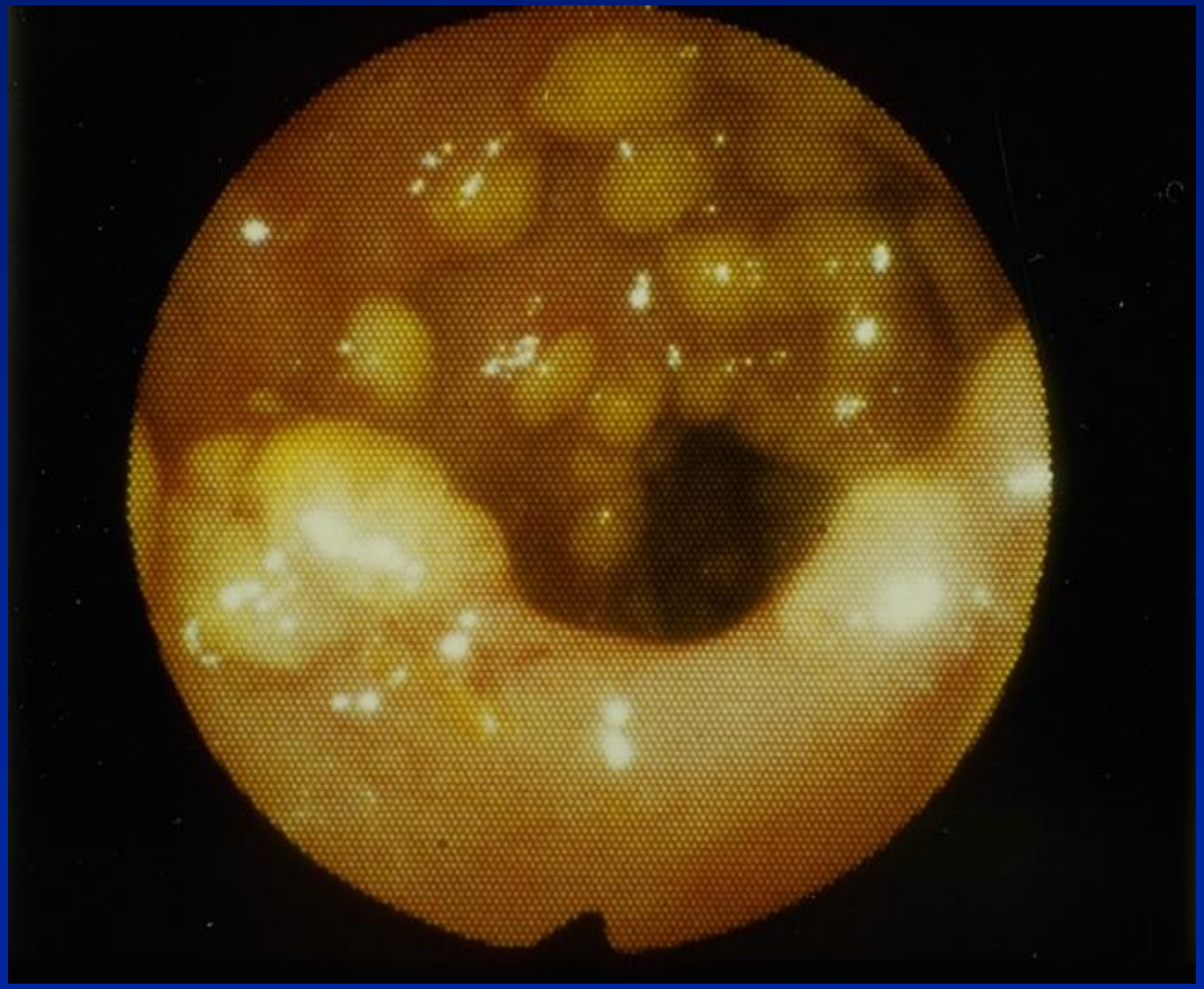
Pathogen	All Health Care–Associated Infections (N=504)†		Pneumonia (N=110)	Surgical-Site Infections (N=110)	GI Infections (N=86)	UTIs (N=65)	Bloodstream Infections (N=50)
	no. (%)	*rank*			*number (percent)*		
Clostridium difficile	61 (12.1)	1	0	0	61 (70.9)	0	0
Staphylococcus aureus	54 (10.7)	2	18 (16.4)	17 (15.5)	1 (1.2)	2 (3.1)	7 (14.0)
Klebsiella pneumoniae or *K. oxytoca*	50 (9.9)	3	13 (11.8)	15 (13.6)	1 (1.2)	15 (23.1)	4 (8.0)
Escherichia coli	47 (9.3)	4	3 (2.7)	14 (12.7)	1 (1.2)	18 (27.7)	5 (10.0)
Enterococcus species‡	44 (8.7)	5	2 (1.8)	16 (14.5)	5 (5.8)	11 (16.9)	6 (12.0)
Pseudomonas aeruginosa	36 (7.1)	6	14 (12.7)	7 (6.4)	1 (1.2)	7 (10.8)	2 (4.0)
Candida species§	32 (6.3)	7	4 (3.6)	3 (2.7)	3 (3.5)	3 (4.6)	11 (22.0)
Streptococcus species¶	25 (5.0)	8	7 (6.4)	8 (7.3)	2 (2.3)	2 (3.1)	2 (4.0)
Coagulase-negative staphylococcus species	24 (4.8)	9	0	7 (6.4)	0	1 (1.5)	9 (18.0)
Enterobacter species	16 (3.2)	10	3 (2.7)	5 (4.5)	0	2 (3.1)	2 (4.0)
Acinetobacter baumannii	8 (1.6)	11, tie	4 (3.6)	2 (1.8)	0	0	0
Proteus mirabilis	8 (1.6)	11, tie	1 (0.9)	5 (4.5)	0	1 (1.5)	0
Yeast, unspecified	8 (1.6)	11, tie	3 (2.7)	0	1 (1.2)	4 (6.2)	0
Stenotrophomonas maltophilia	8 (1.6)	11, tie	6 (5.5)	0	0	2 (3.1)	0
Citrobacter species	6 (1.2)	15, tie	2 (1.8)	1 (0.9)	0	1 (1.5)	0
Serratia species	6 (1.2)	15, tie	2 (1.8)	0	0	2 (3.1)	0
Bacteroides species	6 (1.2)	15, tie	0	5 (4.5)	1 (1.2)	0	0
Haemophilus species	6 (1.2)	15, tie	2 (1.8)	2 (1.8)	0	0	0
Viruses‖	3 (0.6)	19, tie	1 (0.9)	0	0	0	0
Peptostreptococcus species	3 (0.6)	19, tie	0	2 (1.8)	0	0	1 (2.0)
Klebsiella species other than *K. pneumoniae* and *K. oxytoca*	2 (0.4)	21, tie	1 (0.9)	0	0	0	1 (2.0)
Clostridium species other than *C. difficile*	2 (0.4)	21, tie	0	2 (1.8)	0	0	0
Prevotella species	2 (0.4)	21, tie	0	1 (0.9)	0	0	0
Morganella morganii	2 (0.4)	21, tie	0	1 (0.9)	0	1 (1.5)	0
Lactobacillus species	2 (0.4)	21, tie	0	0	1 (1.2)	0	1 (2.0)
Other organisms**	13 (2.6)	—	1 (0.9)	6 (5.5)	0	1 (1.5)	3 (6.0)

Magill SS et al. N Engl J Med 2014;370:1198-1208.

Risk Factors for CDI & Proposed Mechanisms of Risk

Major Epidemiologic Risk Factors	*Proposed Mechanisms:*
• Antibiotics	*Render host susceptible*
• Hospitalization	*Increased chance of exposure to CD*
• Advanced age	*? Waning immunity*

Endoscopic Picture of Pseudomembranous Colitis (PMC)



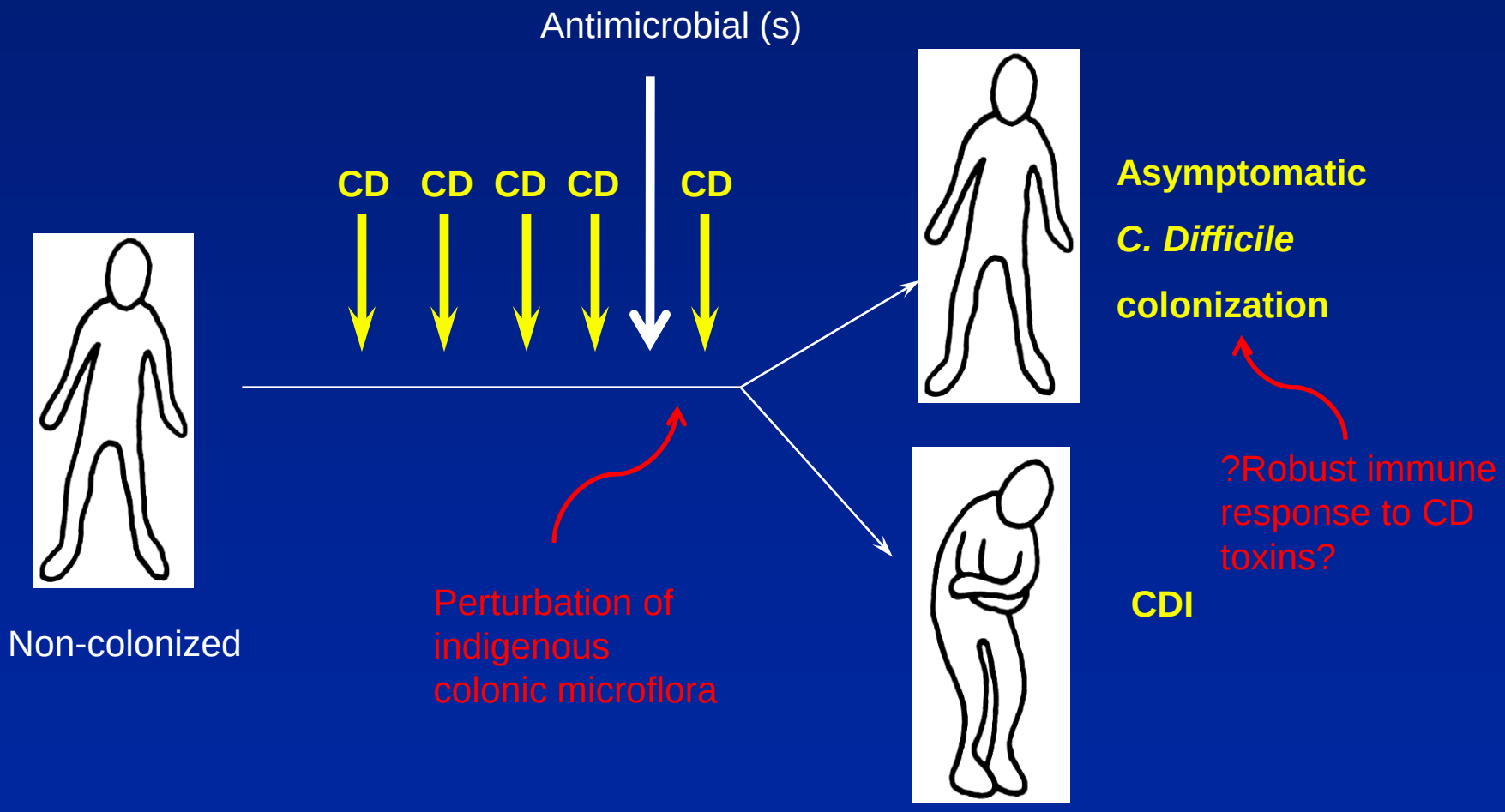
‘Clindamycin Colitis’

- 200 Consecutive clindamyin recipients:
  - 21% diarrhea
  - 10% pseudomembranous colits (PMC)

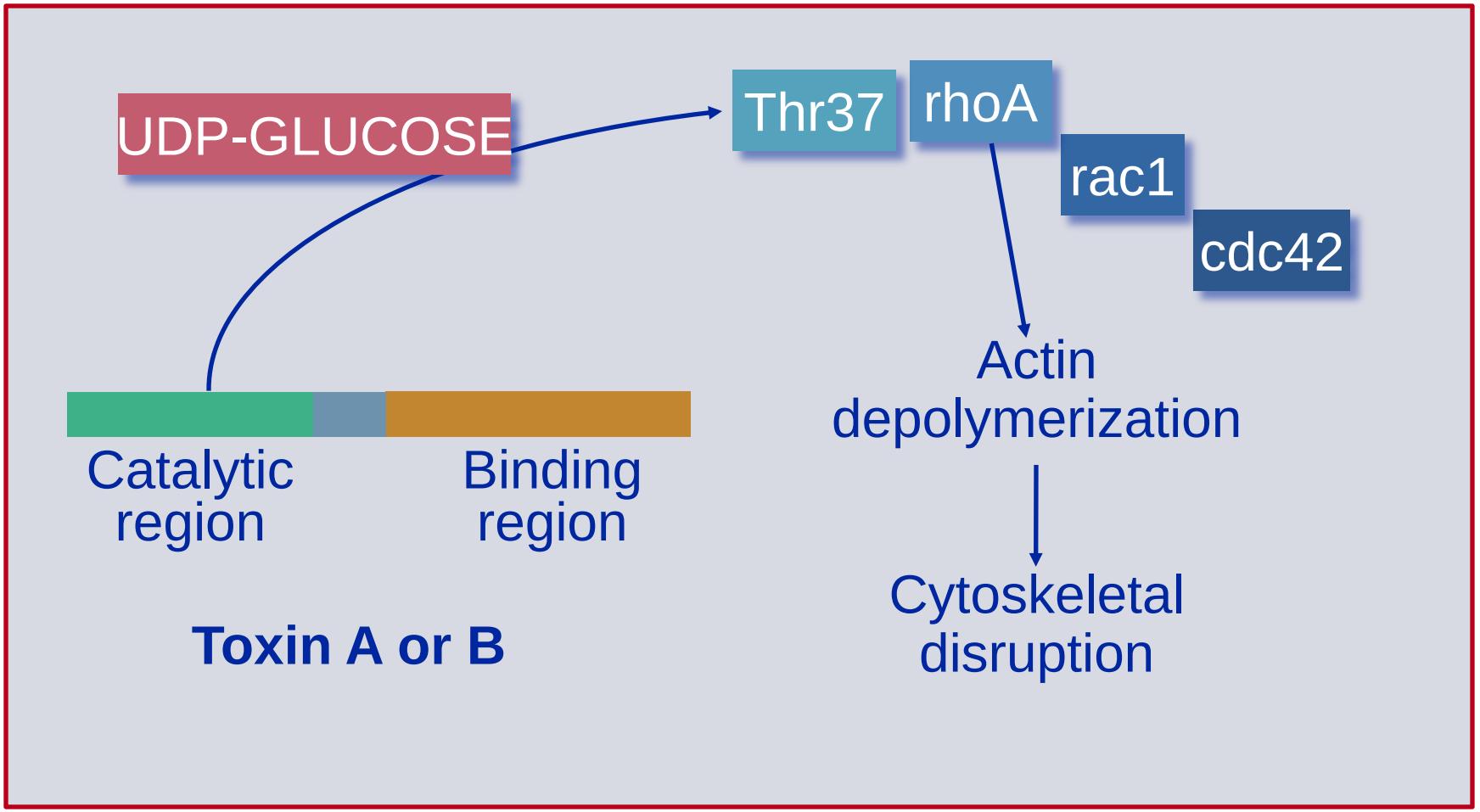
- 16 patients developed diarrhea days to weeks after clindamycin was discontinued

Tedesco FJ, et al. *Ann Intern Med* 1974;81:429

Current Pathogenesis Model for CDI



The Large Clostridial Toxins (A and B) monoglucosylate Rho Proteins



Warny M, Kelly CP. Microbial Pathogenesis 2003:503-524

Human Colonic Microflora

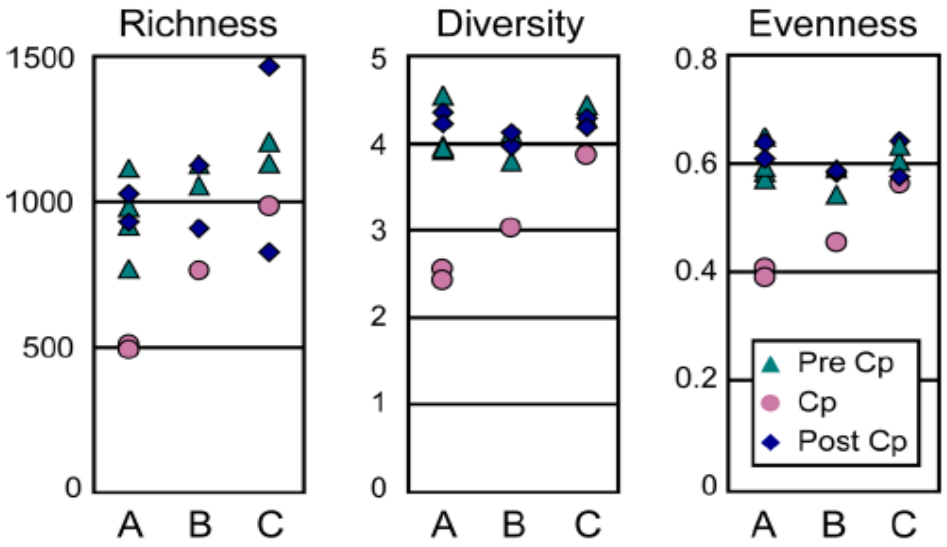
- Colon has dense microbial habitat: 10^{11}-10^{12} cells/ml
- Predominant species are strict anaerobes
- 2 bacterial divisions & 1 archaea division comprise vast majority of colonic microbes:

  Bacteria: Bacteroidetes, Firmicutes

  Archaea: *Methobreviabacter smithii*
- Minority can be cultured
- Cultivation-independent techniques based on amplification of 16S rRNA sequences have defined
  - ~400 phylotypes (operational taxonomic units)
  - > 5,600 taxa by pyrosequencing technology

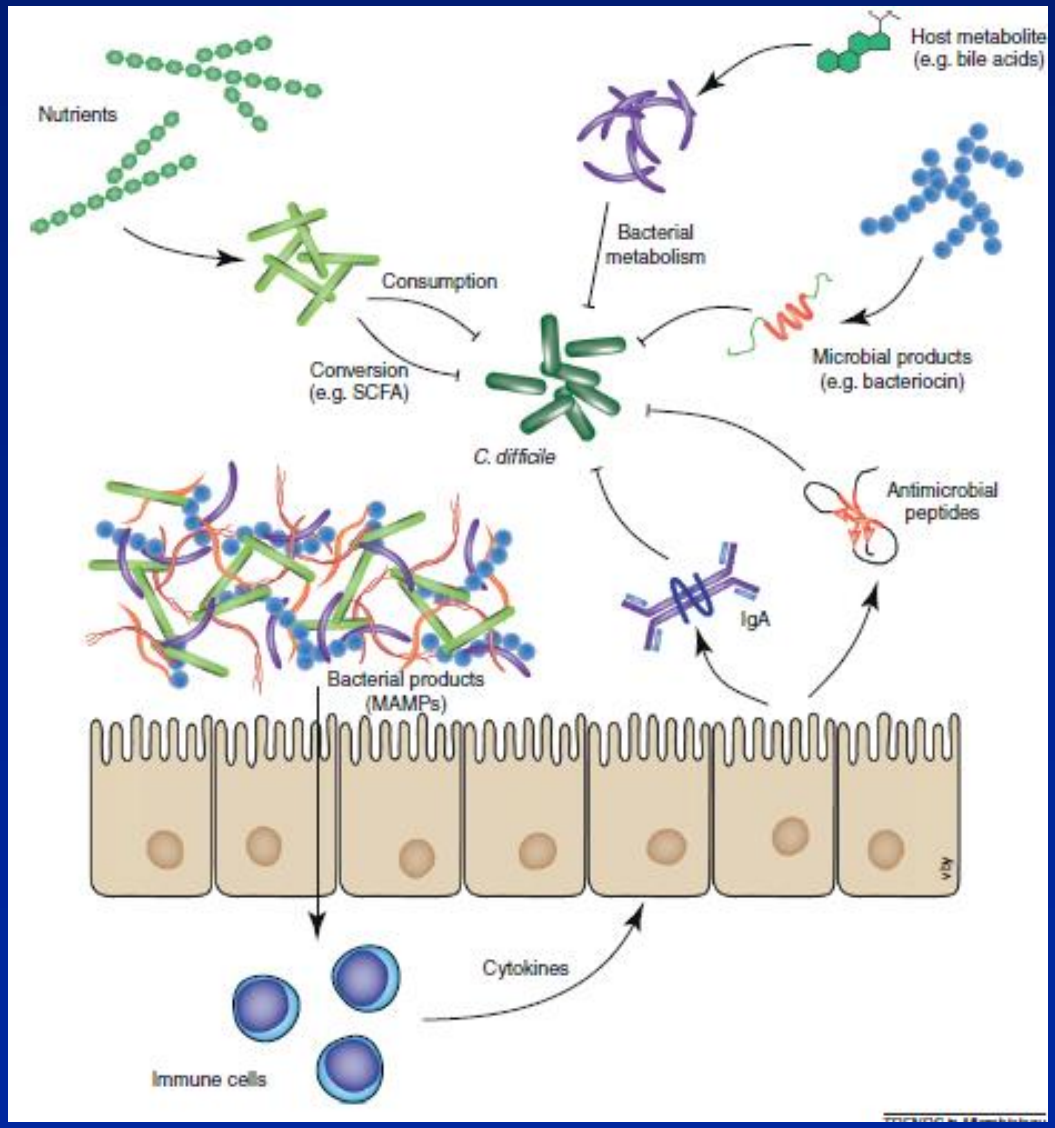
Eckburg PB. Science 2005;308:1635
Ley RE. Cell 2006;124:837
Dethlefsen L. PLOS Biol 2008;6:e280

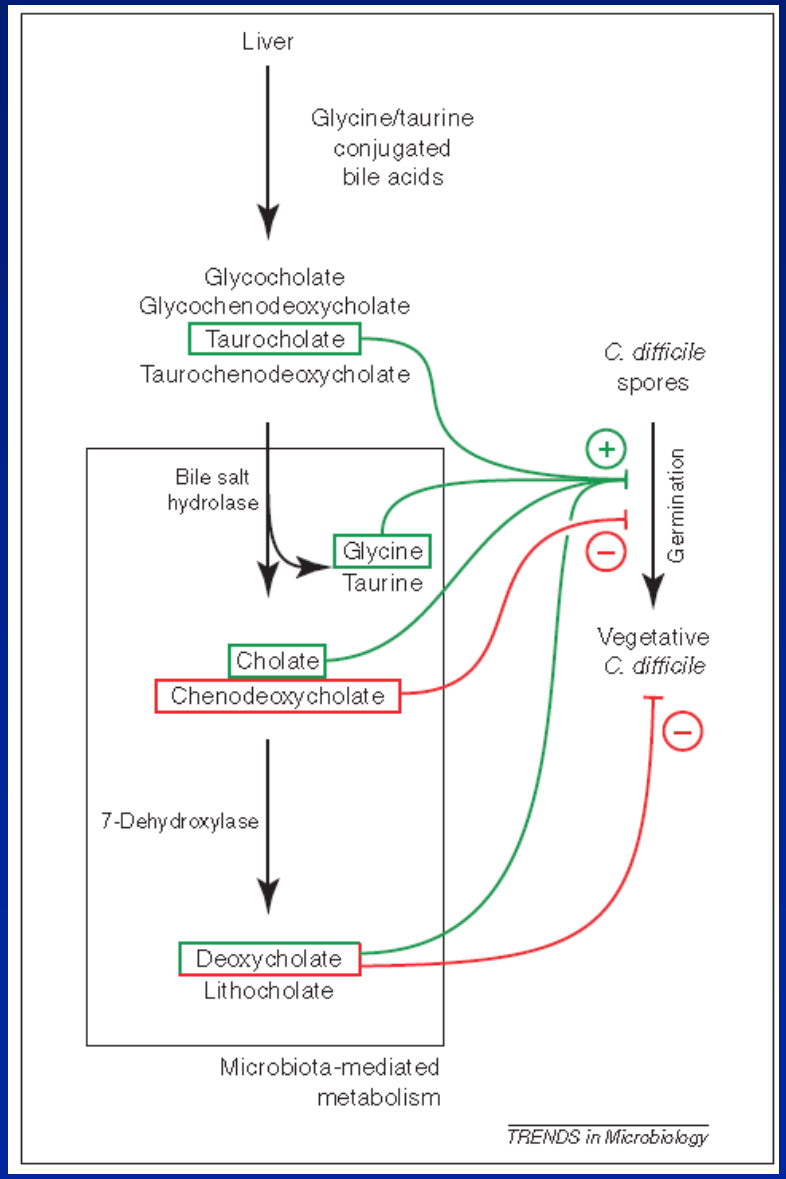
Decreased Taxonomic Richness, Diversity, and Evenness of Intestinal Microbiota in 3 Healthy Humans before & after Treatment with Ciprofloxacin (Cp)



Taxon richness (no. of V3 refOTUs) and Shannon diversity and equitability indices per sample defined by deep 16S rRNA sequencing: *Dethlefsen L PLOS Biol 2008;6:e280*

The Role of Bacteria and Colonization Resistance





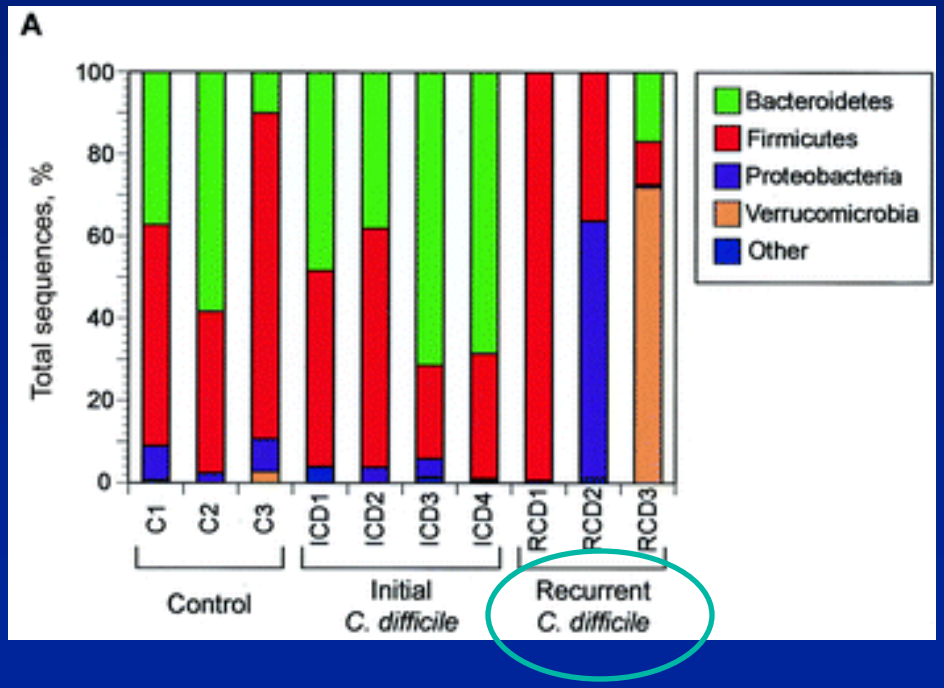
Britton RA. Trends in Microbiology. 20: 313

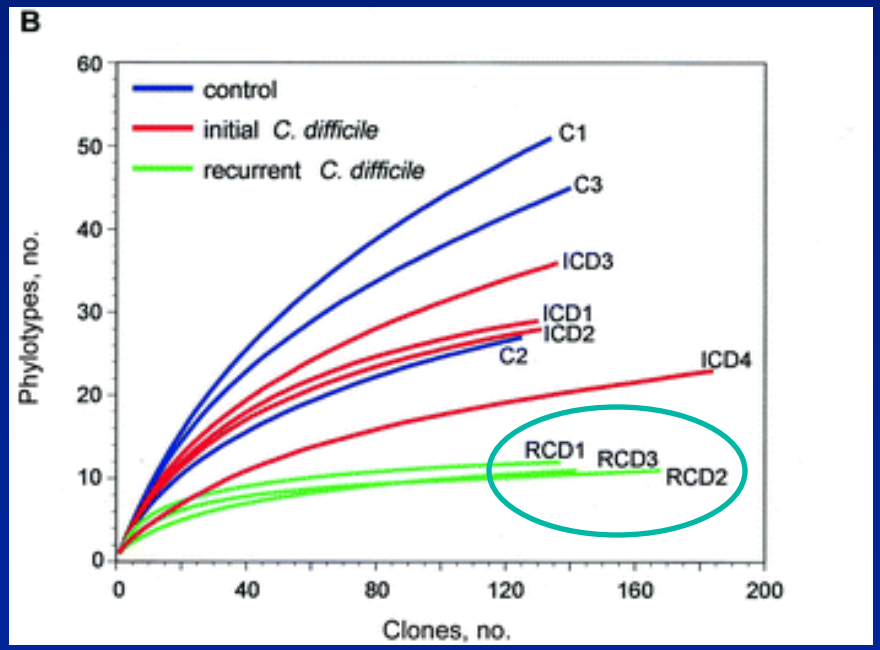
Recurrent CDI

- Occurs ~20% after initial CDI episode
- Risk of subsequent episode in patients who already have had a recurrence: 45%
- Pathophysiology:
  - Reinfection with the original strain or a new strain*
  - Failure to re-establish colonization resistance
  - Failure to mount antibody response
- Antibiotic resistance not a factor in relapse

*Johnson S, et al JID 1989;159:340

Decreased Diversity of Fecal Microbiome in Recurrent CDI





Chang JY. J Infect Dis 2008;197:435

Treatment Recommendations, 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)

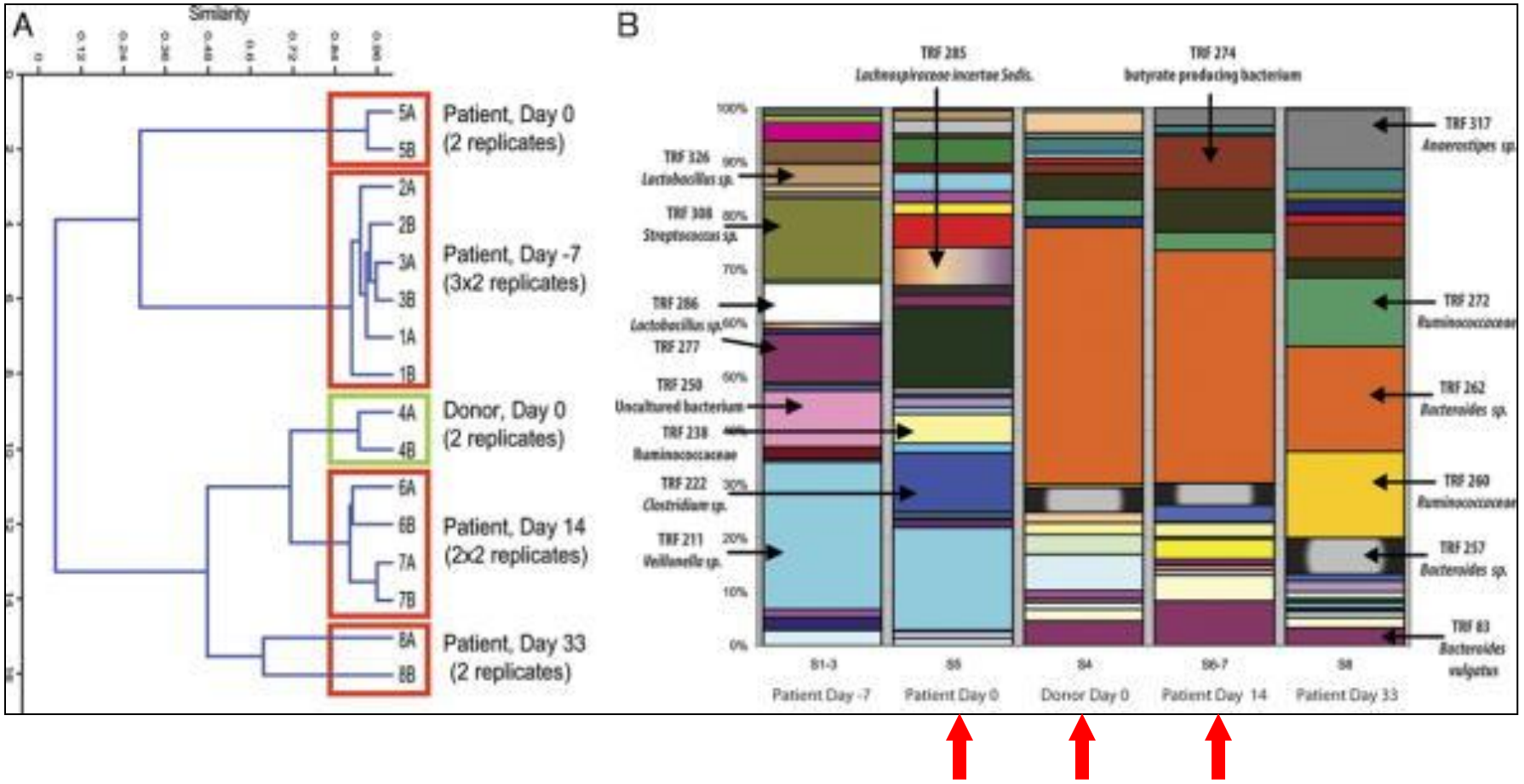
Cohen SH et al. Infect Cont Hosp Epidemiol 2010;31:431-55

Fecal Microbiota Transplantation (FMT) for CDI Recurrences

- 27 case series, 317 patients reviewed in literature. **Overall reported disease resolution was 92%**. FMT administered by enema, nasojejunal tube, gastroscope or colonoscope.
- Effectiveness varied by route of instillation, relationship to stool donor, volume of FMT given, and treatment before infusion.
- Interest in doing FMT is high, but standardization and safety testing of stools have not been established.

Gough, et al. *CID*. 2011;53:994-1002; Bakken JS. *Anaerobe*. 2009;285-289; Bakken, et al. *Clin Gastroenterol Hepatol*. 2011;9:1044-1049.

Changes in the Fecal Microbiome After Bacteriotherapy for Recurrent CDI



Khoruts A, et al J Clin Gastroenterol 2010;44:354-60

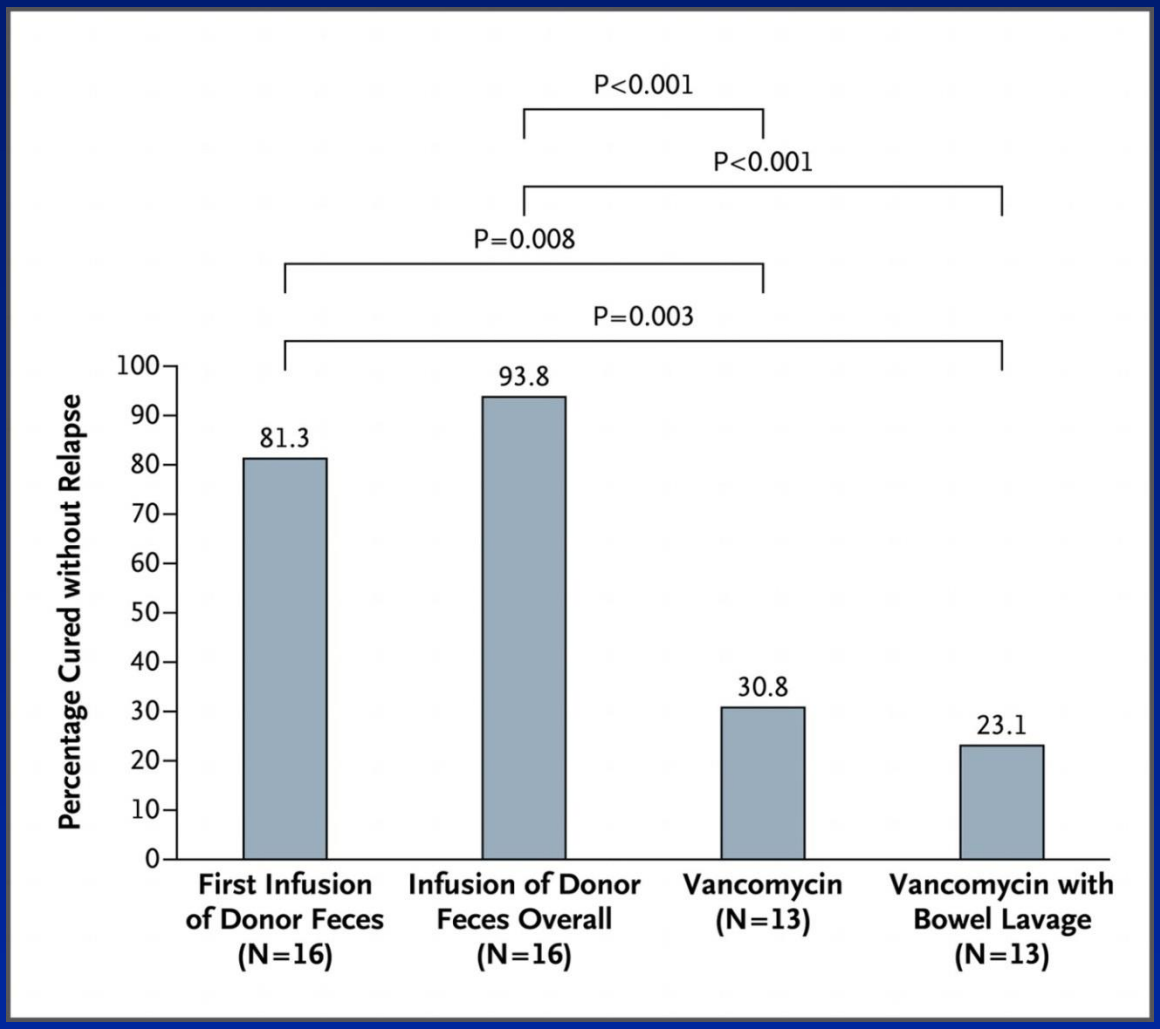
Randomized Trial of Fecal Microbiome Transplant

- Protocol: Feces collected by the donor on the day of infusion and immediately transported to the hospital. Feces diluted with 500 ml of sterile saline (0.9%). This solution was stirred, and the supernatant strained and poured in a sterile bottle. Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube.
- Trial arms:
  - Vancomycin* x 4-5 d, followed by bowel lavage and infusion of donor feces
  - Vancomycin* x 14d followed by bowel lavage
  - Vancomycin* x 14d, alone

  *500 mg PO QID

van Nood et al N Engl J Med. 2013;368:407-15.

Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection



van Nood E et al. N Engl J Med 2013;368:407-415.

The NEW ENGLAND JOURNAL of MEDICINE

Stool Bank of "Super Poopers"

- May 2013 FDA announced regulation of human feces as a "drug"
  - IND application prior to FMT
  - Oversight and standardization
- Stool bank OpenBiome
  - Select donors screened for infectious agents, chronic conditions (metabolic syndrome, autoimmune, digestive problems)
  - Multiple samples collected from single donor (screening $250) and frozen

Smith MB. Nature. 2014. 506:290.

Standardization with RePOOPulate

- Human probiotic/synthetic stool mixture
- Cultured microbial diversity from healthy 41 year female donor
- 33 isolates comprise stool substitute
  - Cultured, formulated in a pre-determined ratio

- Pilot study: 2 patients with multiple RCDI received RePOOPulate with resolution of CDI (up to 32 weeks)
- RCDI due to decreased microbiota diversity is secondary to absence of key organisms

Petrof EO. Microbiome. 2013;1:3

FMT via oral fecal microbial capsules for recurrent CDI

- Related donors, previously screened for transmissible pathogens, provided ~100 grams of freshly passed feces
- The fecal sample was suspended in PBS, centrifuged serially and the sediment of the last centrifugation step was resuspended and micropipetting into gelatin capsules (& over capsulated)
- The recipient stopped vancomycin on the day prior to the procedure and underwent a colonic cleansing (picosalix); 8 hours later the recipient ingested freshly assembled capsules (n=24-34) over 5-15 minutes on an empty stomach
- 27/27 patients with >3 prior CDI episodes responded with one oral procedure
- After FMT numbers of *Bacteroides*, *C.coccoides, C. leptum, Prevotella, Bifidobacteria* and *Desulfovibrio* were significantly increased and *Enterobacteriaceae* and *Veillonella* were significantly decreased

Louie T, et al. ID Week 2013

Doctor Creates Feces Pills To Treat Illness

American Voices• Opinion• ISSUE 49•41• Oct 7, 2013

A Canadian doctor has treated 27 patients suffering from Clostridium difficile infections by giving them each between 24 and 30 handmade pills containing stool from one of their healthy relatives, curing each patient of their illness. What do *you* think?

"I don't need the capsule. Just give me the feces."
Manuel White – Technical Writer

I could see eating 20, maybe 22 feces-filled pills. But 24?... Gross."
Dana Masterson – Systems Analyst

"Did Jerry put you up to this? Because he's been trying to trick me into eating his shit for months."
Lyndell Thirlwell – Drying Oven Tender

Costs of FMT

- **Donors Screening (non standardized donors)**
  - **Donor Stool**
    - **Ova & parasites**
    - **Stool culture**
      - ***Salmonella, Shigella, E. coli*, O157:H7, *Yersenia enterocolitica, Campylobacter***
      - ***C. difficile* toxins A&B**
      - **Cryptosporidium Ag and Giardia Ag**
  - **Donor Serum**
    - **HIV-1 and HIV-2**
    - **Hepatitis A, B, C**
- **Administration**
  - **Colonoscopy**
  - **Nasogastric/nasojejunal administration**
    - **AE: GI bleed, peritonitis, enteritis?**
  - **Enema**
- **Communical disease transmission?**
  - **Case of transmission of Norovirus**
  - **Microbiota associated with obesity, diabetes mellitus**
- **Lack of consistent long term follow-up**
  - **3 weeks to 8 years bewteen studies**

Cost:
$500-$1500
+/-Insurance

Cost:
$2,000- $5,000

Rohlke F. Therap Adv Gastroenterol. 2012; 5: 403
Ridaura VK, et al. Science. 2013;341:1079.
Kassam Z. Am J Gastroenterol. 2013;108:500.

Current Strategies for Managing Multiple Recurrent CDIs

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

Randomized Controlled Trial of Tolevamer (a toxin-binding agent), Vancomycin (VAN) & Metronidazole (MTR) Treatment for CDI

- *First Phase 3 Tolevamer Study*:

	Overall Cure	"Severe CDI" Cure	
Tolevamer	124/266 (47)	35/95 (37)	
VAN	109/134 (81)	28/33 (85)	*p* =0.02
MTR	103/143 (72)	37/57 (65)	

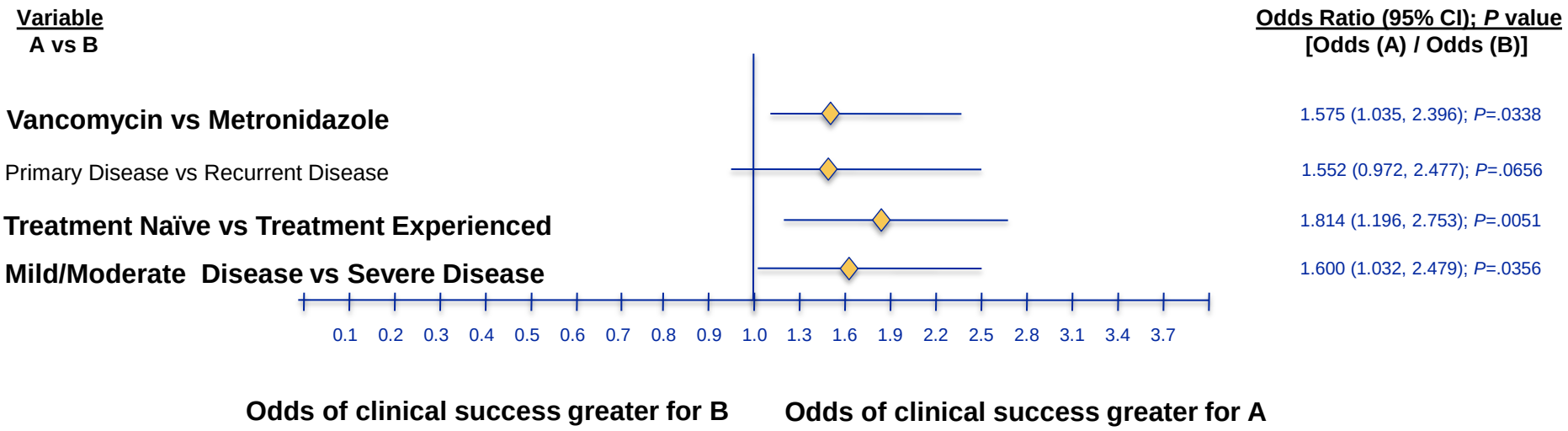
- *Combined Phase 3 Tolevamer Studies*:

	Overall Cure		"Severe CDI" Cure		Recurrence
Tolevamer	236/534 (44)		58/156 (37)		10/222 (5)
VAN	210/259 (81)	*p* =0.02	51/65 (79)	*p* =0.04	43/209 (21)
MTR	202/278 (73)		61/92 (66)		49/213 (23)

Johnson S, et al. Clin Infect Dis 2014:In Press

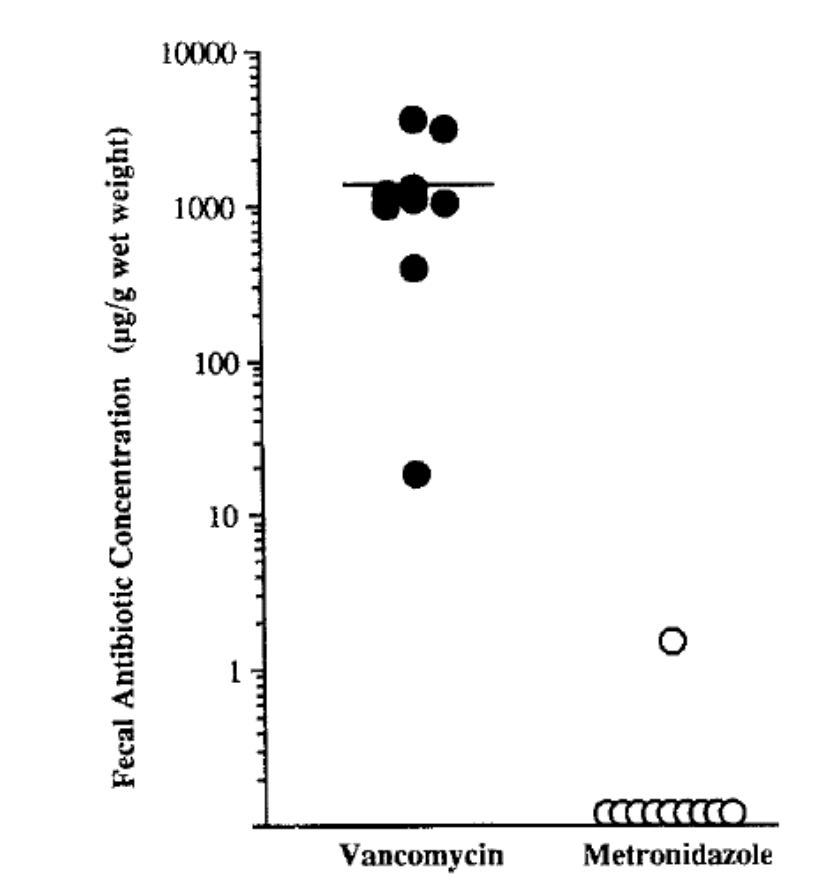
Randomized Controlled Trials of Vancomycin vs Metronidazole vs Tolevamer*

Multivariate logistic regression analysis of factors associated with clinical success



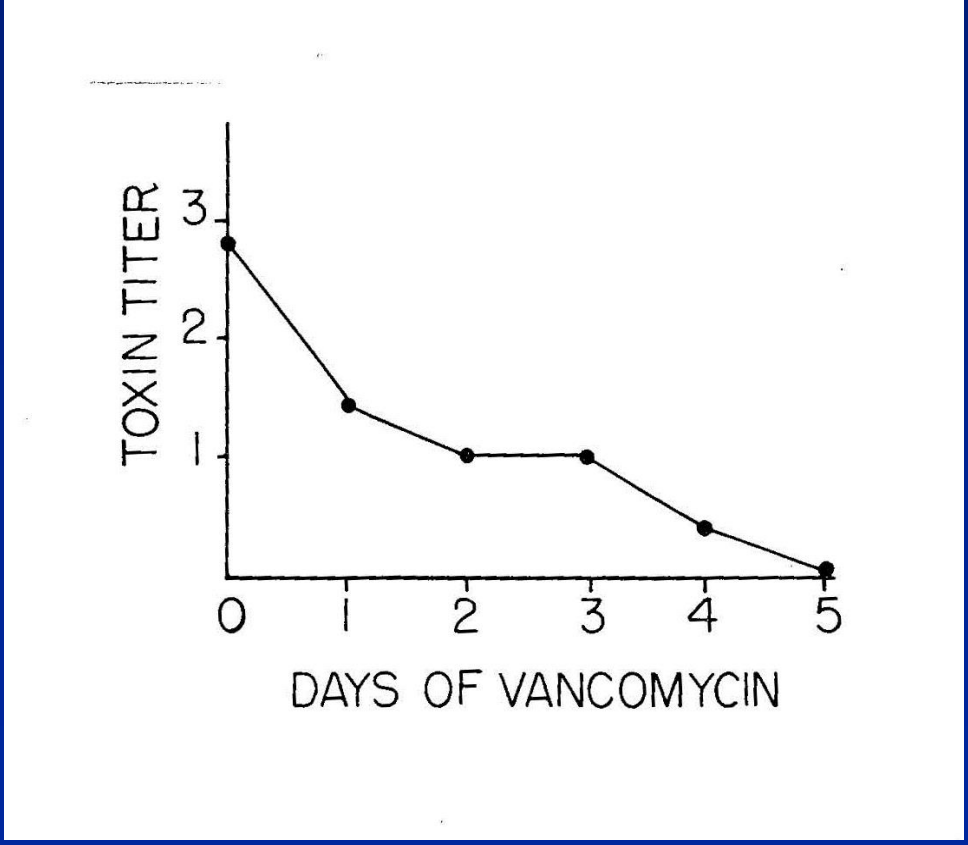
Post hoc analysis of V vs M, pooled data from 2 Phase 3 studies; Johnson S, et al. Clin Infect Dis 2014; In Press

Achievable Fecal Drug Concentrations with Vancomycin 125 mg qid (asymptomatic CD carriers)



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

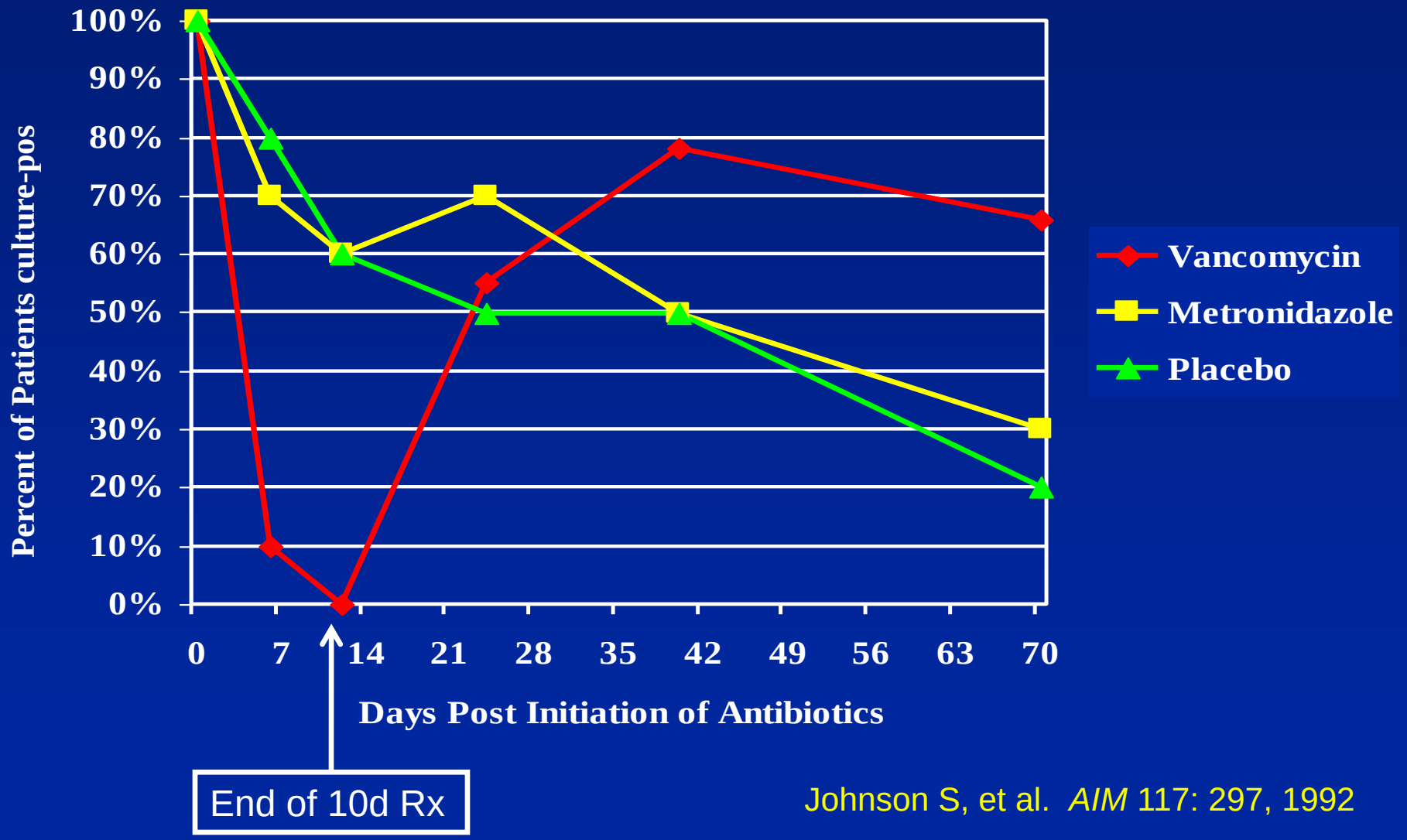
Cytotoxicity titers of Patients with Pseudomembranous Colitis following Treatment with Vancomycin



Bartlett JG et al.Rev Infect Dis 1979;1:370-8

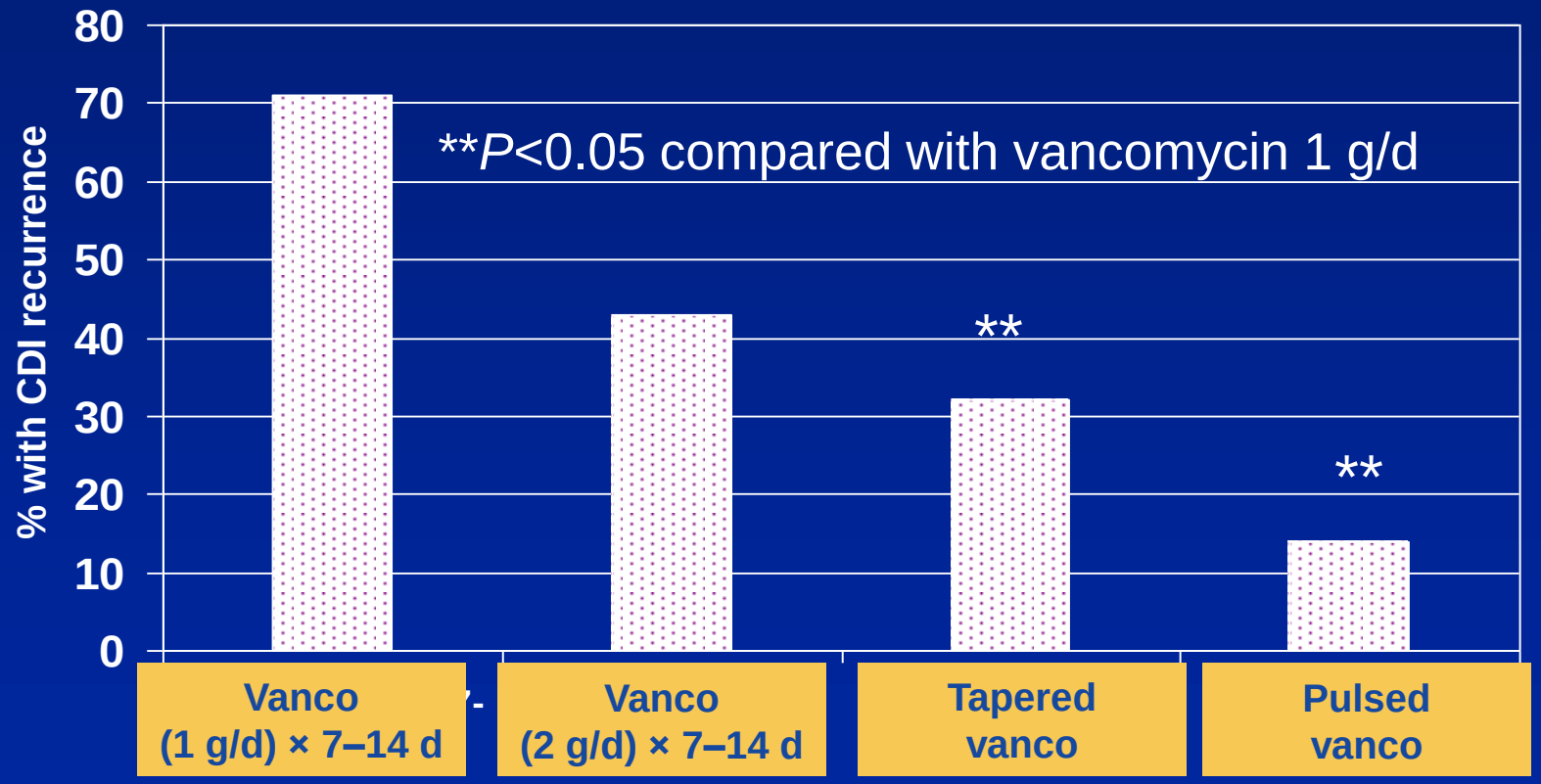
Vancomycin Temporarily Clears *C. difficile* from Feces, but Prolongs Shedding

(Attempted CD Eradication from asymptomatic carriers)



Johnson S, et al. *AIM* 117: 297, 1992

Vancomycin Regimens for rCDI Post-Hoc Analysis From Two Trials (*n*=163)



McFarland LV, et al. *Am J Gastroenterol.* 2002;97:1769-1775.

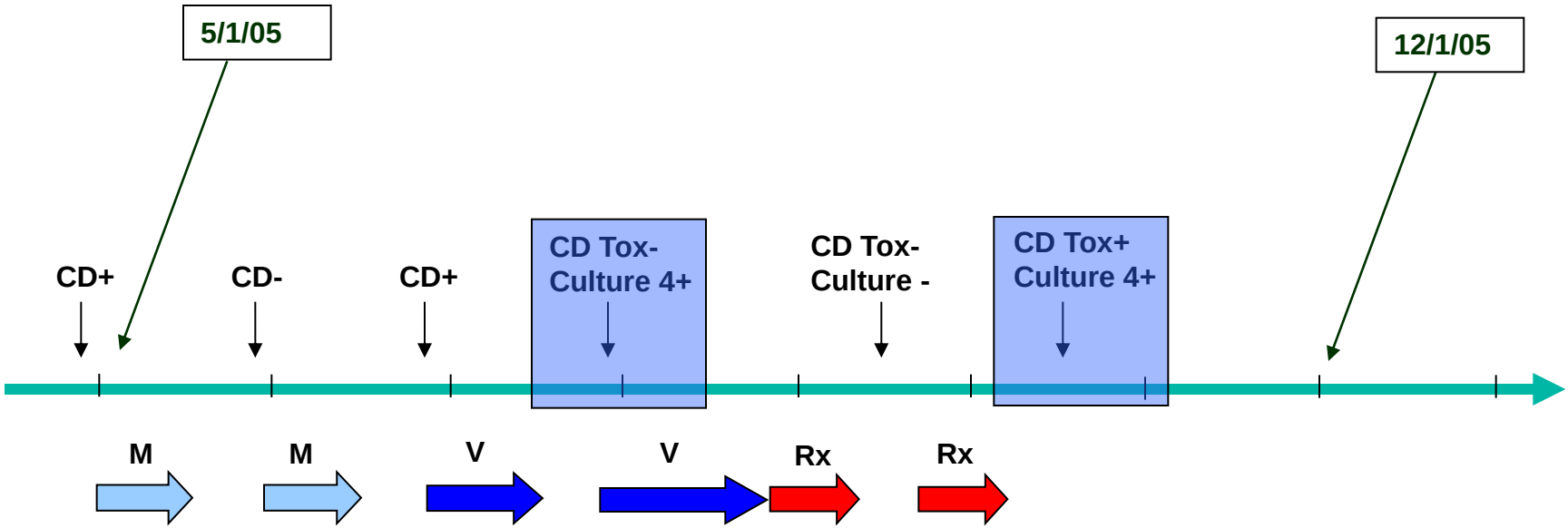
Interruption of Recurrent CDI by Serial Therapy with Vancomycin and Rifaximin* (the "Rifaximin Chaser")

- 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

**Not FDA-approved*

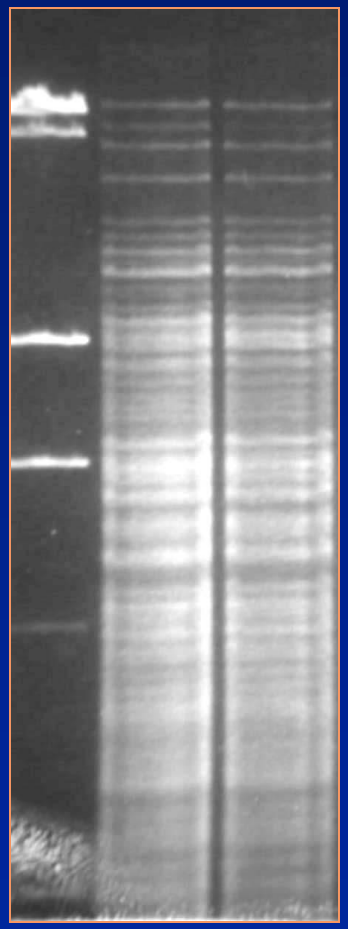
Johnson S, et al. *Clin Infect Dis.* 2007;44:846-8.

Timeline: Patient # 4



Pre-Rifaximin 7/29/05

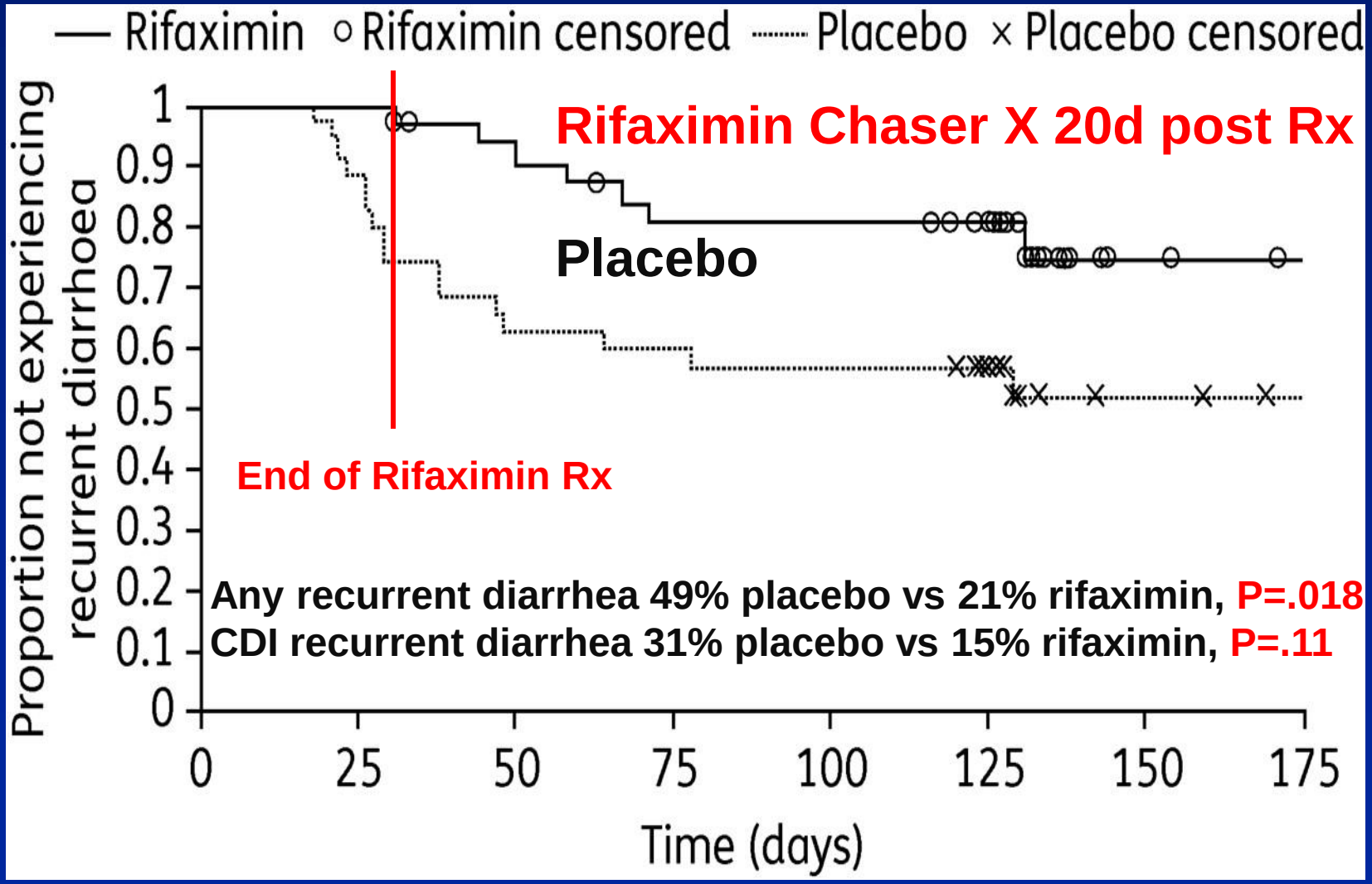
Post-Rifaximin 10/17/05



MIC: 0.0078 µg/mL

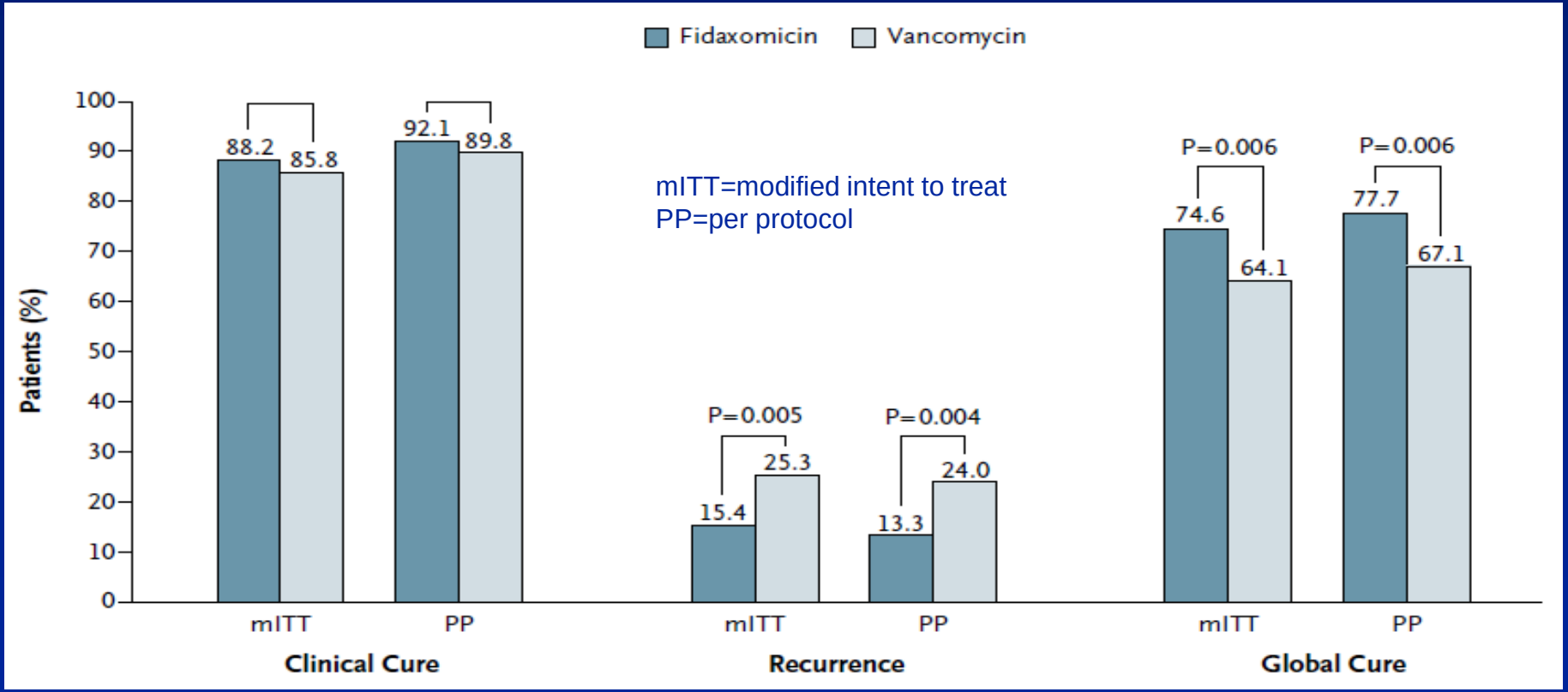
MIC: > 256 µg/mL

Randomized, Placebo-control Pilot Trial of Rifaximin Chaser Strategy



Garey KW, et al. *J Antimicrob Chemother*. 2011;jac.dkr377.

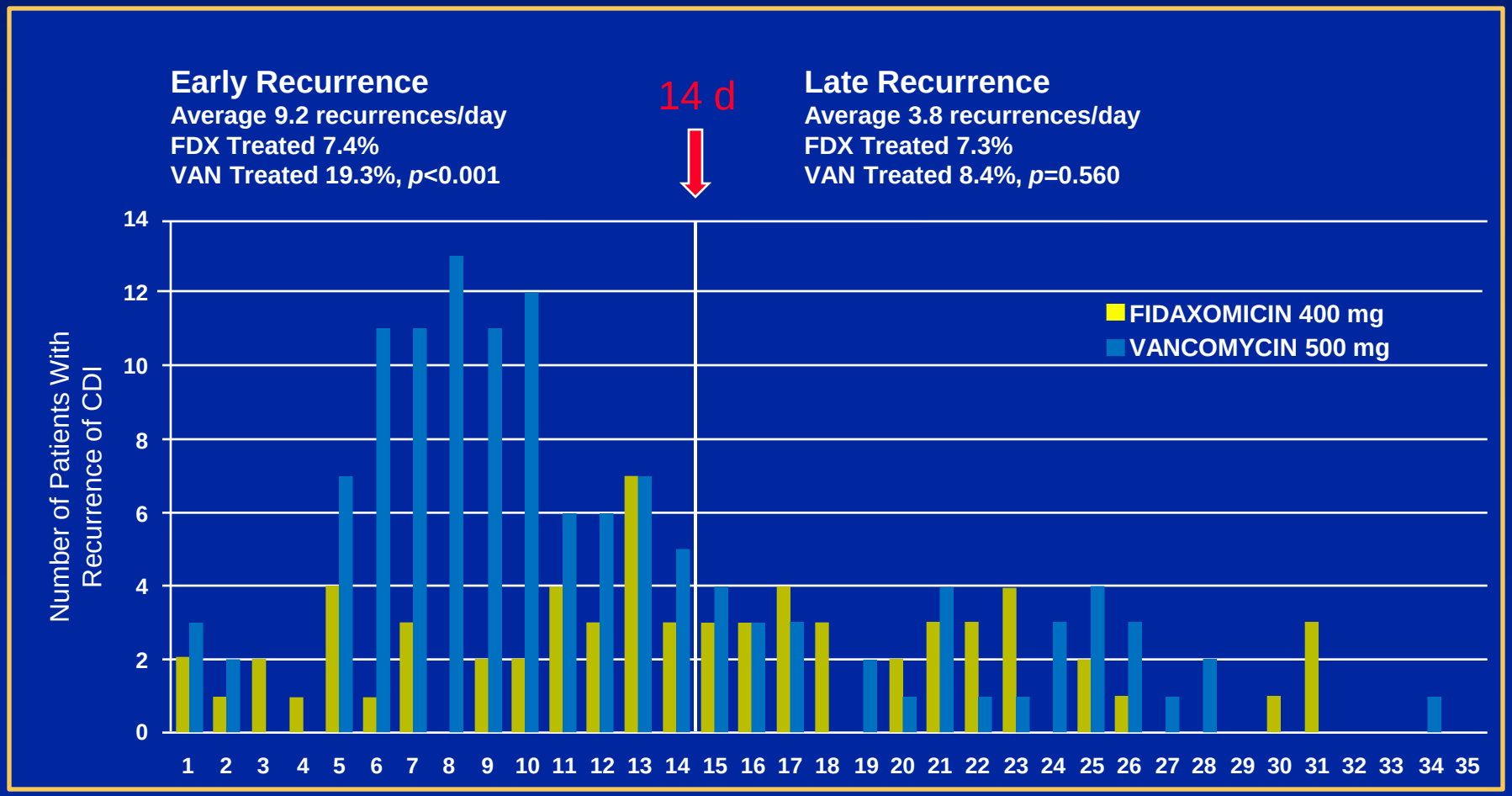
First Phase 3 Trial Results
Fidaxomicin vs. Vancomycin for CDI Rx



Louie TJ, et al. *N Engl J Med*. 2011;364:422-431

Nearly identical results from 2nd phase 3 trial: Cornely OA, et al. Lancet Infect Dis 2012, Feb 8

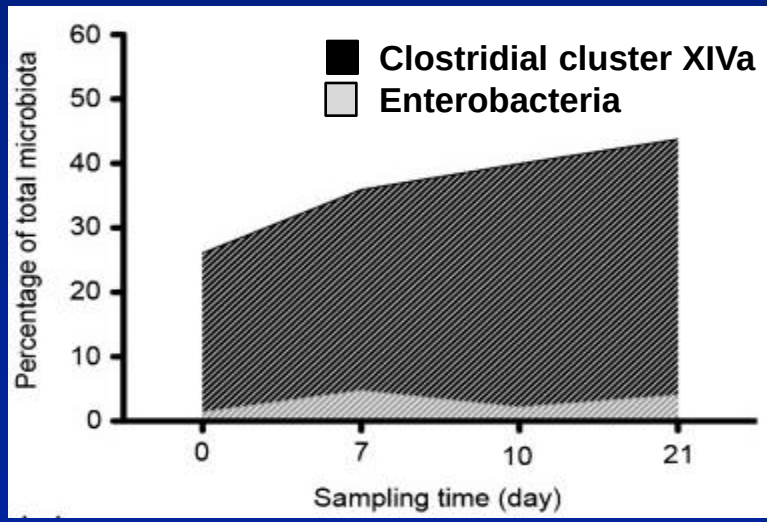
Early vs Late CDI Recurrences and Effectiveness of Fidaxomicin Early



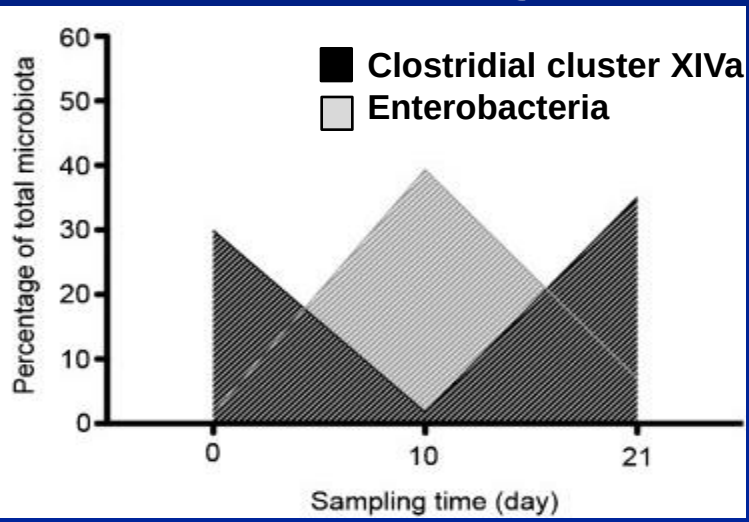
Louie TJ, et al. *New Eng J Med*. 2011;364:422-431.
Cornely OA, et al. *Lancet Infect Dis*. 2012;12:281-289.

Enterobacteria and Clostridial Cluster XIVa Populations During and After 10 Days of Fidaxomicin and Vancomycin Treatment

Fidaxomicin

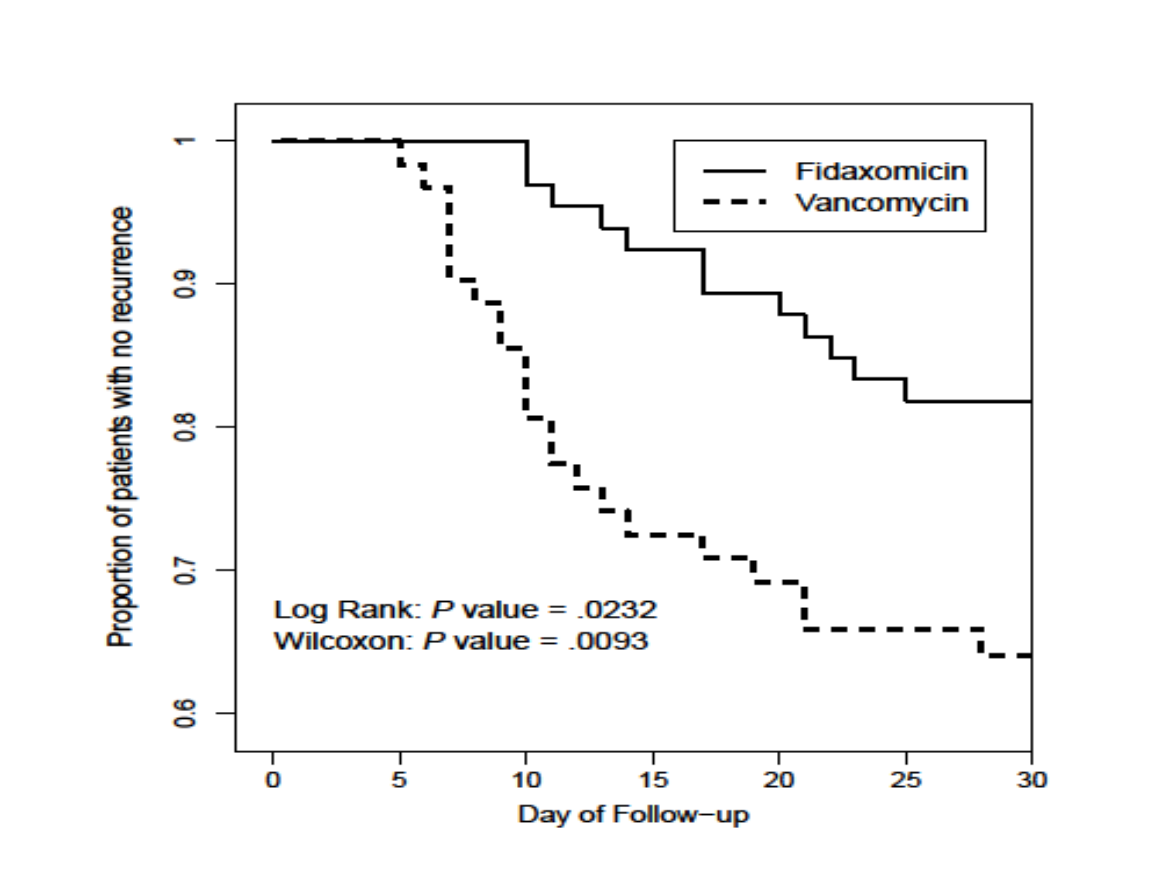


Vancomycin



Tannock GW, et al. *Microbiology*. 2010;156:3354-3359.

Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI: Fidaxomicin vs Vancomycin



Cornely et al, Clin Infect Dis Supplement 2, 2012; 55:S154-61

Caution for this approach in patients with multiple CDI recurrences

- 2 patients with multiple recurrences given treatment doses of fidaxomicin with improvement but followed by symptomatic recurrence
- Prior regimens
  - 62 YOF: M x14d followed by Sb twice, V (many), V tapers (several)
  - 44 YOF: (M x14d twice); V x10d twice, Rifaximin chaser

Orenstein R. *Clin Infect Dis*. 2012; Advanced access June 12.

“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, et al. *Clin Infect Dis.* 2013;56:309-10

.

Evolution of Personal Experience using Fidaxomicin as Salvage Therapy for Recurrent CDI

Fidaxomicin Treatment (FID-TX)

200mg BID x 10 days

1st Rx: 8/25/11

Fidaxomicin Chaser (FID-CH)

CDI Treatment + 200mg BID x 10 days

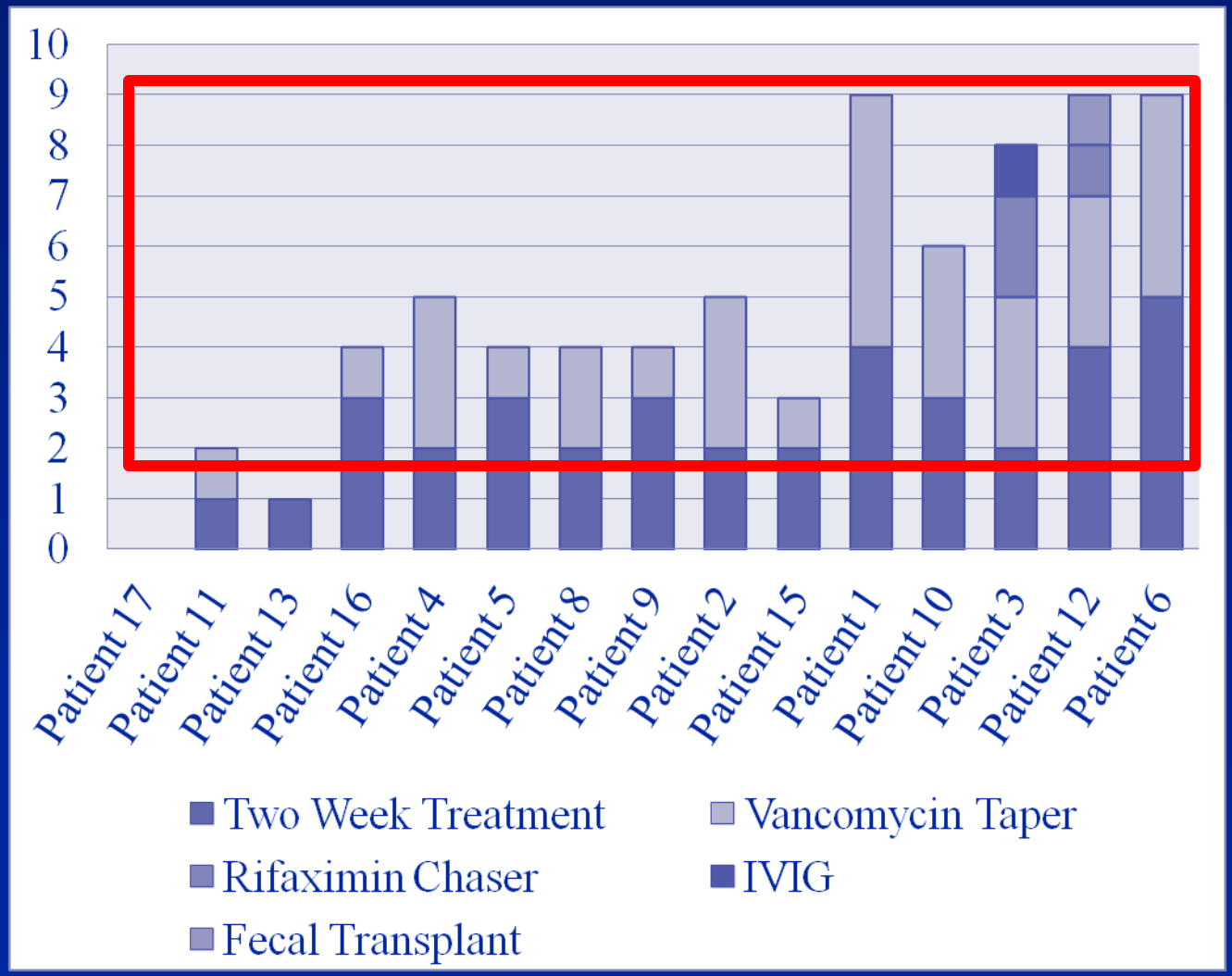
1st Rx: 5/12/12

Fidaxomicin Taper/Pulse (FID-TP/P)

CDI Treatment + 200mg QD x 7 days, QOD x 7-26 days

Soriano M, et al. IDWeek 2013

Previous Antibiotic Courses for Recurrent CDI Episodes Prior to Fidaxomicin



Average number of vancomycin tapers: 2.28 courses

Soriano M, et al. IDWeek 2013

Outcomes for Recurrent CDI Regimens

	Success Rate	Recurrence Rate	SFI
Fidaxomicin Treatment (FID-TX) N=4 (Average length: 10 d)	100%	50%	72 days
Fidaxomicin Chaser (FID-CH) N=8 (Average length: 10d + TX)	100%	50%/33%*	251 days
Fidaxomicin Taper (FID-TP) N=7 (Average length: 14-26d + TX)	100%	17%/0%*	170 days

* Rate when excluding recurrences due to antimicrobial exposure

Soriano M, et al. IDWeek 2013

Summary

- CDI recurrences are common and most occur within 2 weeks of treatment discontinuation
- Management of recurrent CDI, particularly multiple recurrences should involve strategies that address colonic microbiota disruption
- FMT is increasing performed for patients with recurrent CDI, but issues including selection of appropriate patients, standardization of the procedure, cost, and safety still need to be addressed
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be explored (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow up
- Well-designed clinical trials of recurrent CDI are needed

Acknowledgements

- Dale N. Gerding
- Susan P. Sambol
- Farida Siddiqui
- Lorinda Wright
- Adam Cheknis
- Laurica Petrella
- Eric Perdue
- Kayleigh Smith
- Melinda Soriano