CE IN THE MIDDAY

Improving the Lives of Patients with *Clostridium difficile* Infection One Case at a Time

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Supported by an educational grant from Merck

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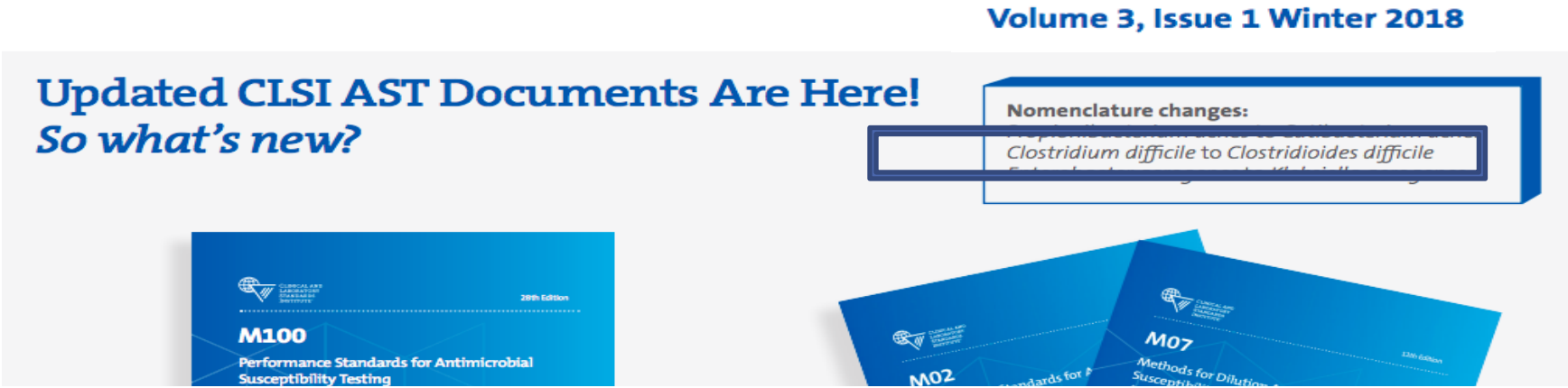
- Kevin Garey
  - Merck, Inc., Summit Therapeutics, and Tetraphase: Research Support
- Krishna Rao
  - Merck, Inc.: Research support (Co-investigator)

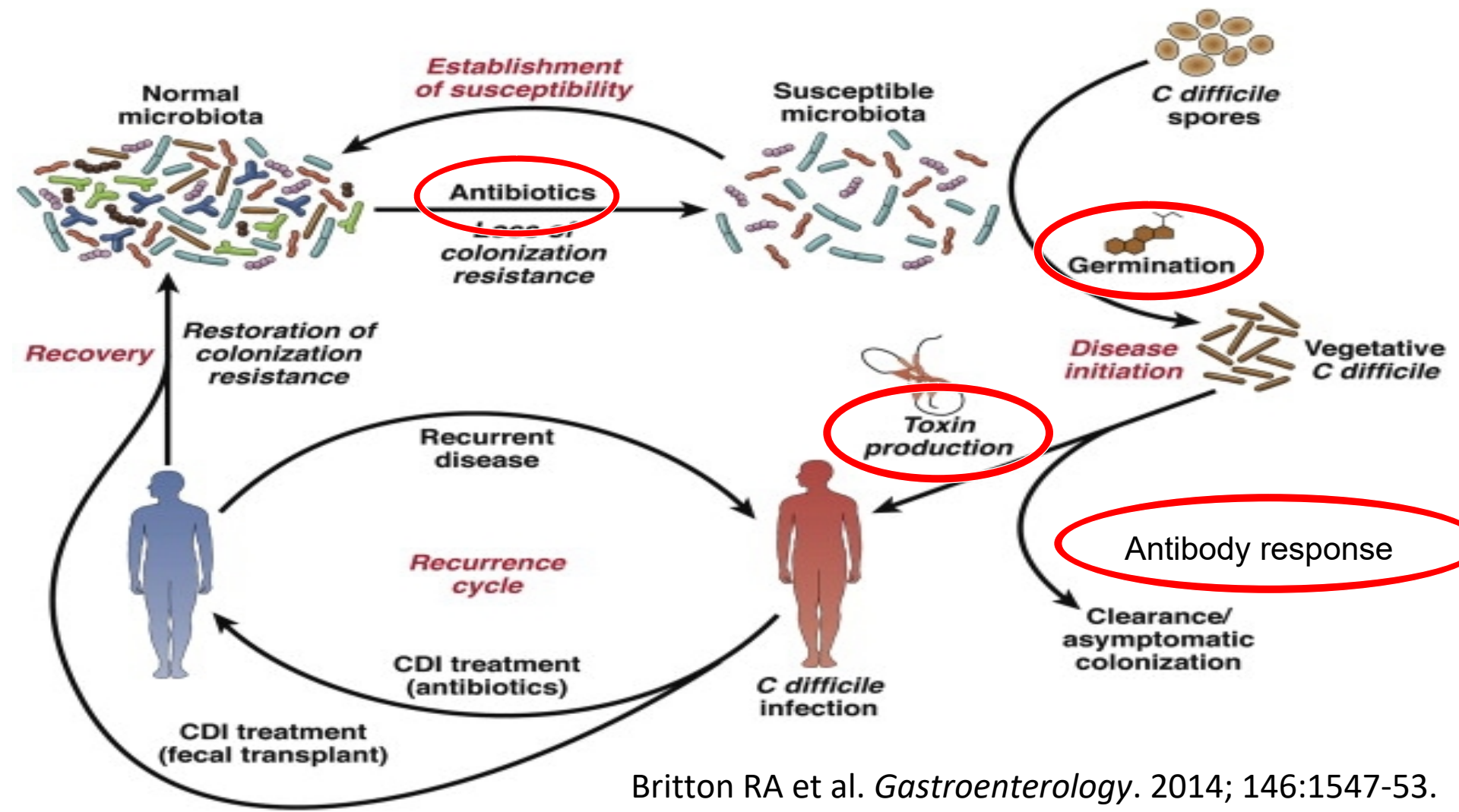
Learning Objectives

- Describe the correlation of *Clostridium difficile* Infection (CDI) and overuse of antibiotics.
- Apply new treatment guidelines to treat patients with CDI.
- Evaluate the use of vancomycin and fidaxomicin for the primary treatment of CDI.
- Discuss the role of newer therapies in the treatment of CDI.

Side note: Nomenclature Change



Clinical & Laboratory Standards Institute Antimicrobial Susceptibility Testing News Update. 2018; 3(1):1-21.



Britton RA et al. *Gastroenterology*. 2014; 146:1547-53.

To start: why do we get CDI in the first place?

Welcome to the wonderful world of the microbiome!

It's your first day on the job as the antimicrobial stewardship pharmacist

You get called into the boss's office:

Why is *C. difficile* the #1 healthcare pathogen in my hospital (and in the U.S.)?

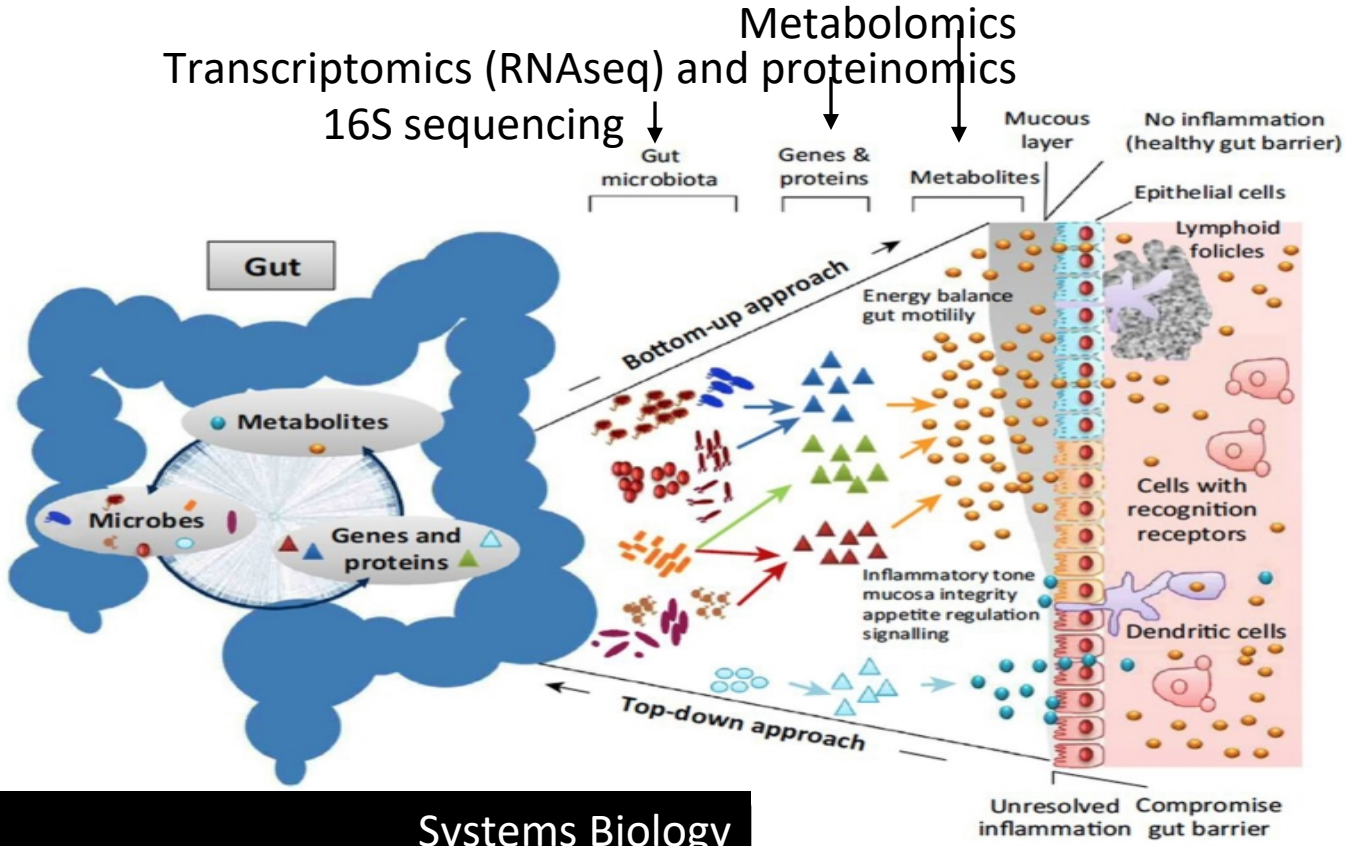
….what are you going to do to decrease the number of infections we see?

Magill SS et al. *N Engl J Med*. 2018; 379:1732-44.

What antibiotic are you going to target to decrease your CDI rates?

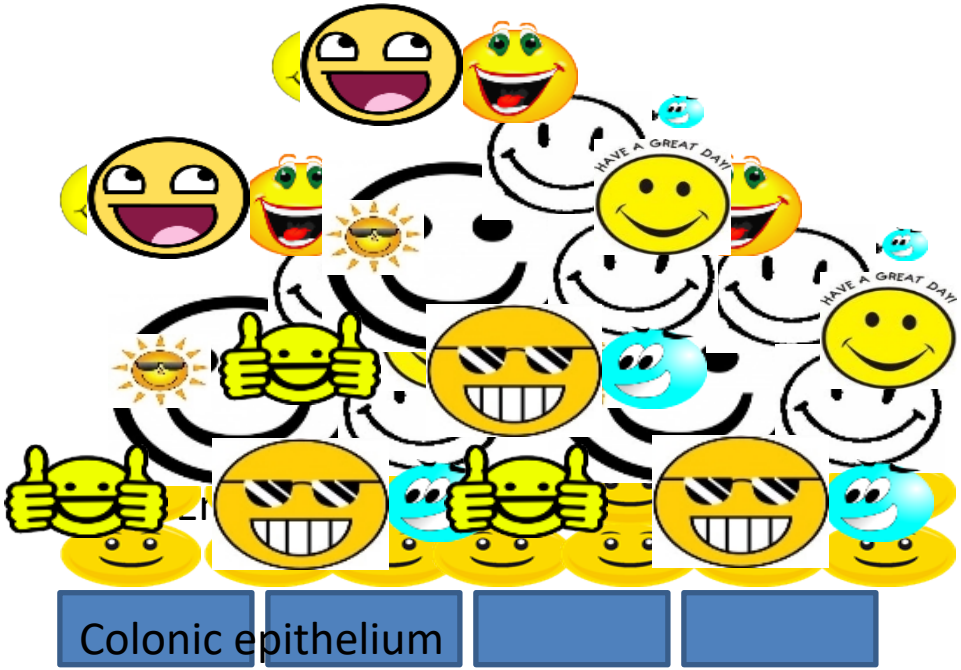
a. Clindamycin
b. Cefepime
c. Meropenem
d. Minocycline
e. Piperacillin-tazobactam

Welcome to a whole new area of science!



Microbiome analysis is all about abundance, diversity, and types of organisms present

Microbiome of non-CDI patients vs. CDI patients

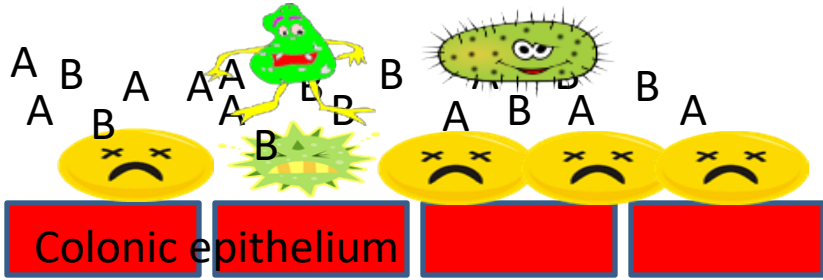


Healthy Microbiome

Total colony forming units (CFU) abundance

Diversity of microbiologic species

Other pathogenic organisms



Recurrent CDI Microbiome

Gut microbiota: 16S RNA sequencing

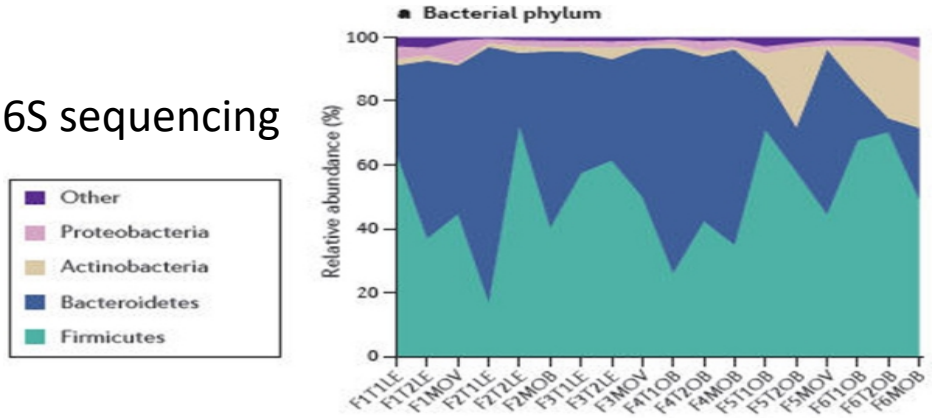
Firmicutes:
Mostly good (*C. diff* is a firmicute)
Mostly spore formers (think: probiotic)
Usually largest component of microbiota

Bacteroidetes
Mostly good (Bacteroides predominates)
Non-spore forming
Usually tied for largest component

Actinobacteria
Mostly good
Not very common, sort of the ugly stepsister of the healthy microbiota

Proteobacteria
Good in small quantities (this is E. coli, Klebsiella, etc)
This is where the 'overgrowth' occurs after antibiotic therapy

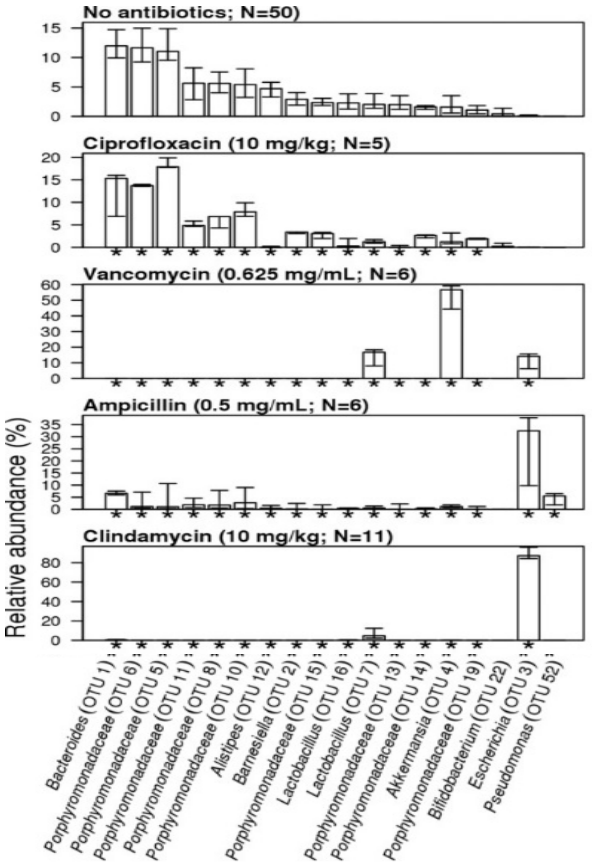
16S sequencing



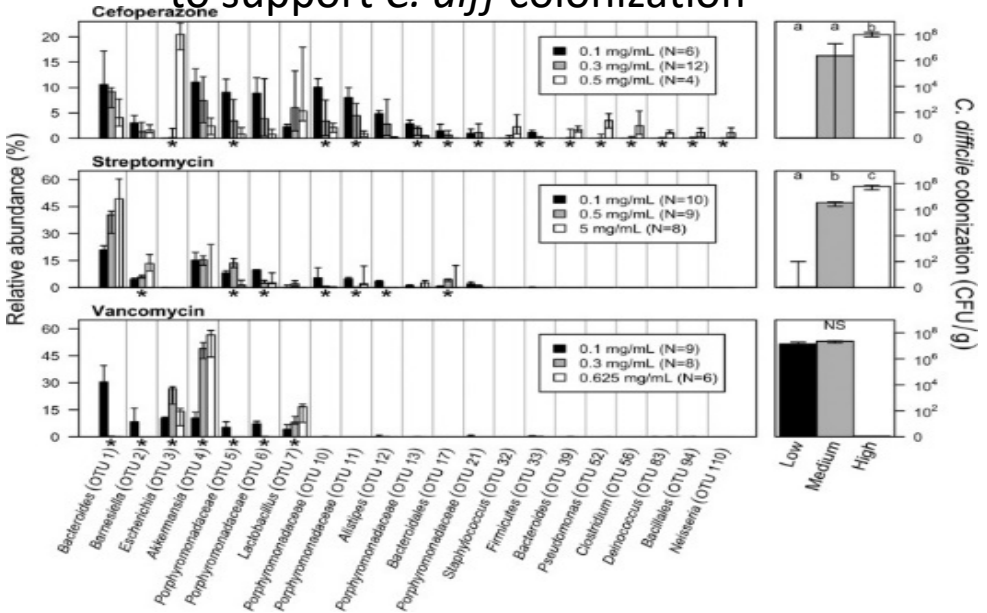
Cho et al. *Nat Rev Genet*. 2012; 13:260-70.

Mice exposed to a variety of antibiotics for 5 days

5 days of antibiotics are more than enough to completely change the microbiota

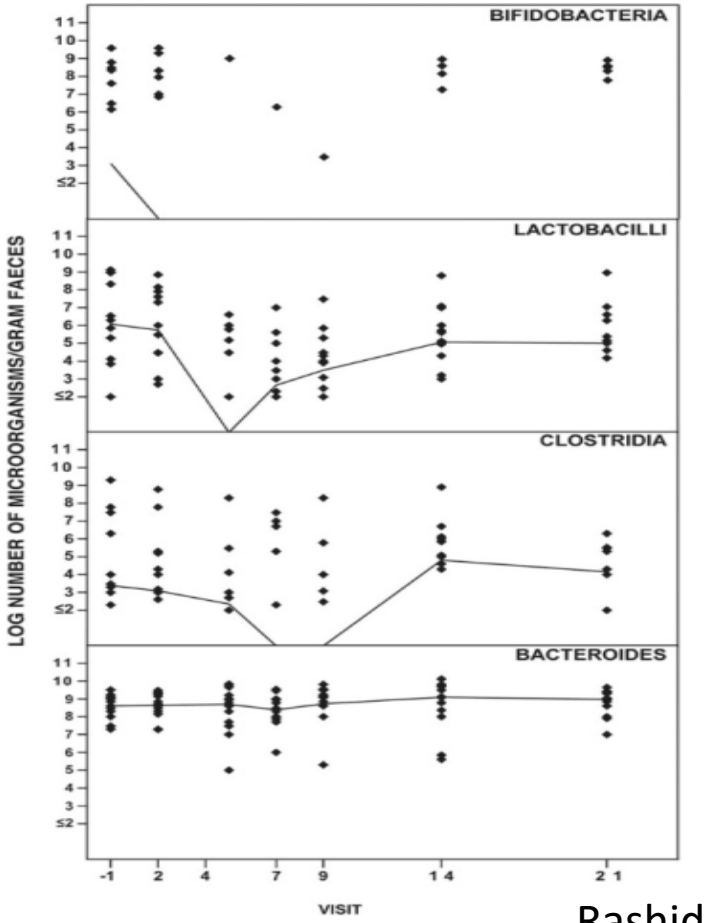


….and this disruption is more than enough to support *C. diff* colonization



Schubert et al. *Mbio*. 2015; 6:e00974.

The effect on the microbiome starts almost immediately



- 14 healthy volunteers given ceftaroline-avibactam X 7 days
- Changes in microbiota assessed over 21 days

Rashid et al. *Antimicrob Agents Chemother.* 2015; 59:4504-9.

We are now able to predict the antibiotics most likely to cause CDI!!

- Any antibiotic that kills firmicutes and/or bacteroides will almost immediately increase CDI risk
- Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI

Antibiotics that increase CDI risk

Drug	Kills firmicutes	Kills bacteroidetes	Commonly used
Ampicillin-sulbactam	Yes	Yes	Medium
Cefepime	Yes	No	Yes
Ceftriaxone	Yes	No	Yes
Carbapenems	Yes	Yes	Yes and increasing
Piperacillin-tazobactam	Yes	Yes	Yes
Clindamycin	Yes	Yes	No
Fluoroquinolones	Yes	Yes	Not as much

30-day risk of CDI among 97,130 hospitalized patients 1,481 of whom developed CDI

Individual Antibiotic	OR (ABX Received (Y/N))	*P*-Value	Antibiotic Use
Ampicillin/Sulbactam	1.640	0.012	1.7%
Cefepime	1.673	< 0.001	16.1%
Ceftriaxone	1.464	< 0.001	21.8%
Ertapenem	1.864	< 0.001	3.6%
Imipenem	2.077	< 0.001	3.2%
Meropenem	1.335	0.020	2.8%
Piperacillin/Tazobactam	1.655	< 0.001	16.6%
Age	1.009	< 0.001	N/A
Proton Pump Inhibitor (Y/N)	1.375	< 0.001	N/A
Charlson Comorbidity Index	1.208	< 0.001	N/A

OR – odds ratio; ABX - antibiotic

Davis M et al. *Clin Microbiol Infect*. 2018; 24:1190-4.

Risk of CDI increased from 0.14% to 6.21% in comorbid patients who received high risk antibiotics and a proton pump inhibitor

Received High Risk Antibiotic?	No						Yes					
Charlson Comorbidity Index	0		1		≥2		0		1		≥2	
Received PPI?	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y
CDI Incidence (%)	0.14	0.58	0.82	0.70	2.31	1.84	0.73	1.33	1.30	2.59	4.04	6.21

- Independent of receipt of high risk antibiotic, more severe Charlson comorbidity index increases CDI risk

Davis M et al. *Clin Microbiol Infect*. 2018; 24:1190-4.

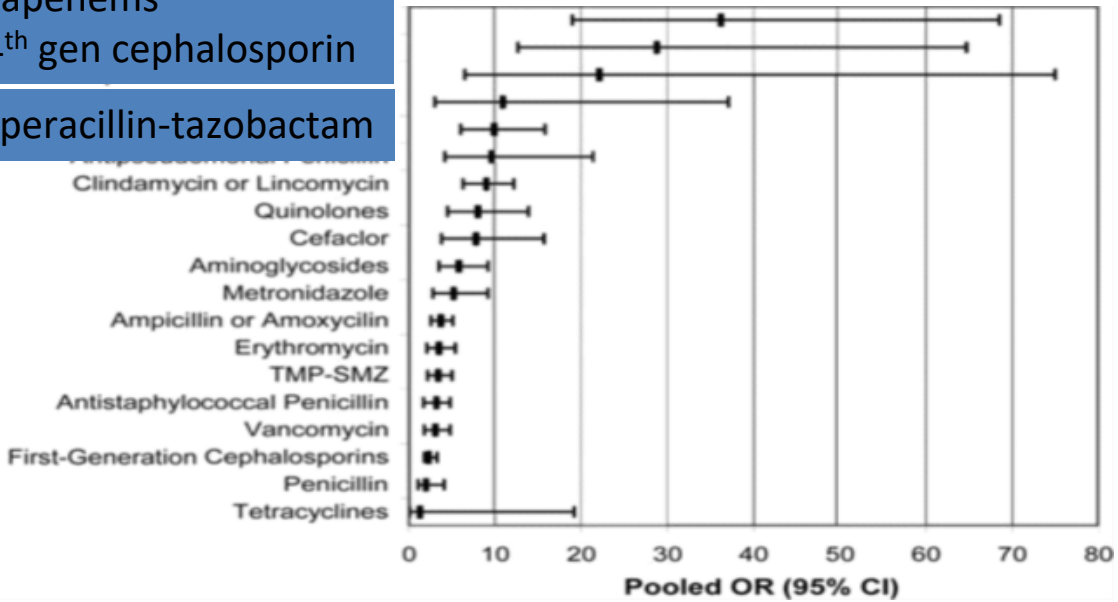
We can now update an old slide with newer antibiotics

1 Carbapenems

2 3rd/4th gen cephalosporin

Piperacillin-tazobactam

3



If I was a betting man, I would guess that carbapenems will be the 'cause' of the next *C. diff* epidemic.

Owens RC Jr et al. *Clin Infect Dis*. 2008; 46(Suppl 1):S19-S31. doi:10.1086/521859.

Despite our best efforts, CDI will be hard to prevent!

71-year-old female with congestive heart failure, gastroesophageal reflux disease, diabetes mellitus, and a history of breast cancer.

Recently discharged after a 2-week hospitalization for bacterial pneumonia.

She now presents to the emergency department with watery diarrhea, leukocytosis (11,000 cells/mL) and elevated serum creatinine (1.1 mg/dL).

Stool is sent to the clinical microbiology lab and tests positive for *C. difficile* toxins.

Betty B

How do you want to treat Betty B?

a. Metronidazole 500 mg orally three times daily
b. Vancomycin 125 mg orally four times daily
c. Vancomycin 250 mg orally four times daily
d. Fidaxomicin 200 mg orally twice daily
e. Vancomycin + metronidazole

*Treat for 10 days (usually)

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

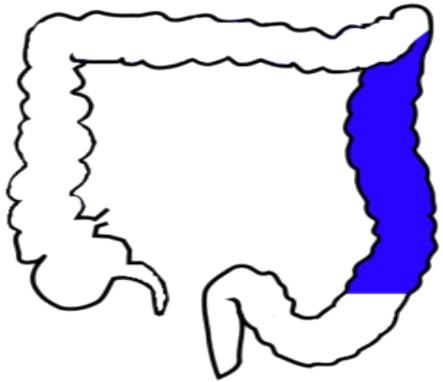
Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

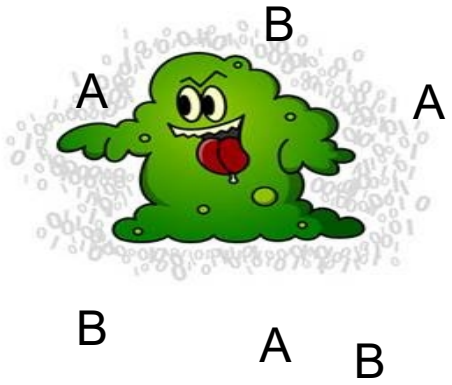
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

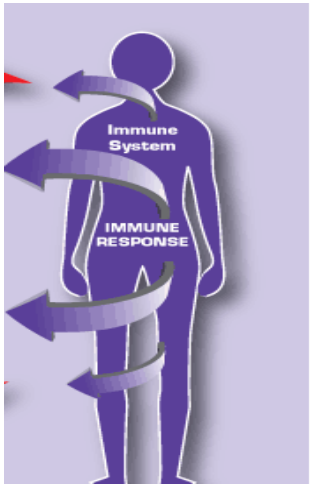
[illegible][1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Car[illegible]yn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

McDonald LC et al. *Clin Infect Dis*. 2018; 66:e1-e48.

There has been an explosion in treatment possibilities for CDI







Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Metronidazole
Vancomycin
Fidaxomicin

IVIG
Monoclonal antibodies vs. *C. diff* toxins

Future: 2nd generation FMT
non-toxigenic *C. diff* M3
Ecobiotics

Ridinilazole

Toxoid vaccines

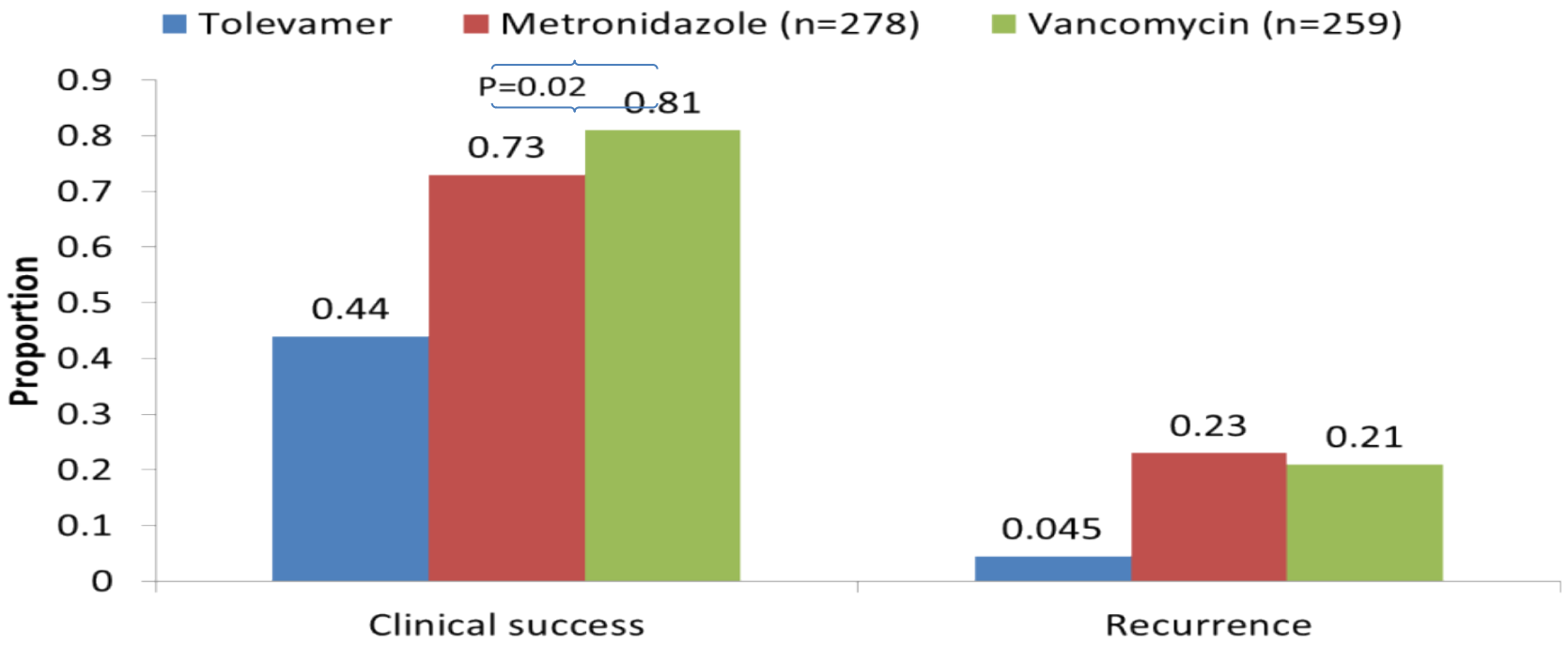
FMT= fecal microbiota transplantation

IDSA/SHEA CDI Guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC < 15,000 and SCr < 1.5 X premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10-14 days	A-I
Initial	WBC ≥ 15, 000 or SCr ≥ 1.5 X premorbid level	Severe	Vancomycin	125 mg PO four times daily 10-14 days	B-I
Initial	Hypotension, shock, ileus, megacolon	Severe, complicated	Vancomycin + metronidazole IV	Vancomycin: 500 mg PO or NG four times daily + Metronidazole: 500 mg IV every 8 hr. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1st recurrence)	----------	----------	Same as initial	Same as initial	A-II
Third (2nd recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed	B-III

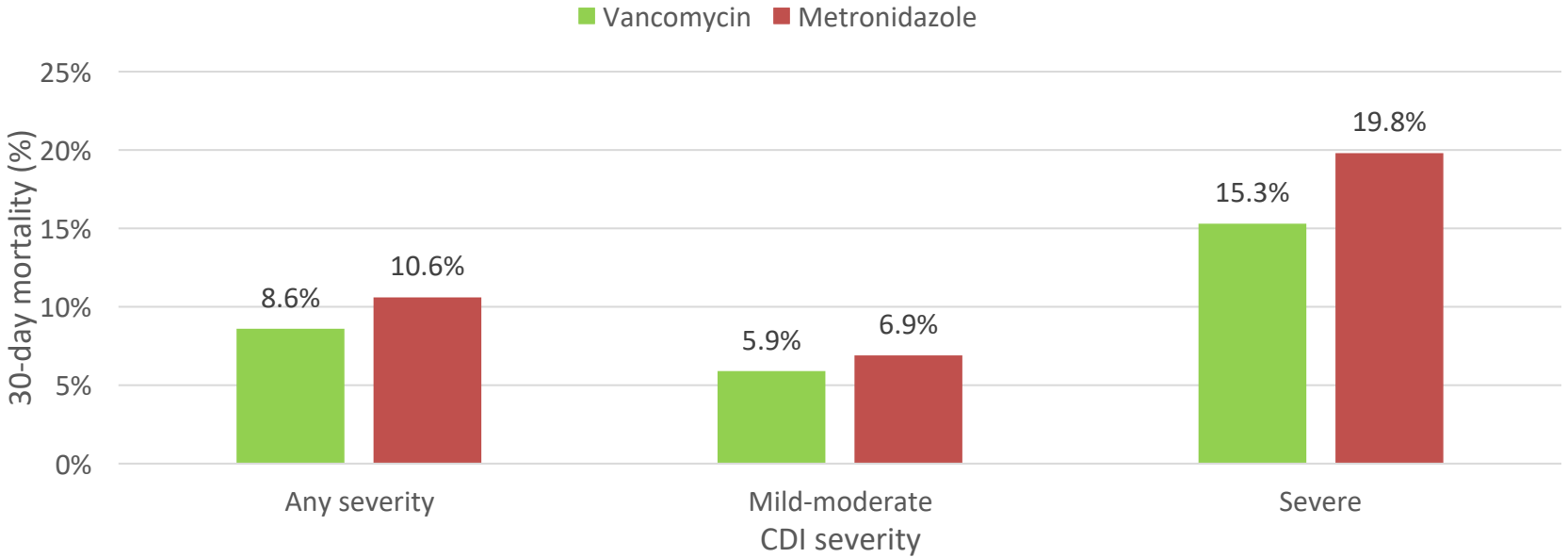
Cohen SH et al. *Infect Control Hosp Epidemiol*. 2010; 31:431-55.

More recently, metronidazole has been shown to be globally inferior to vancomcyin (tolevamer phase III RCT)



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

Increased failure rate of metronidazole also associated with increased 30-day mortality



VA dataset (vancomycin: n=2068; metronidazole: n=8069 propensity matched). Patients given vancomycin had a significantly lower 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3-22.8%).

Stevens VW et al. *JAMA Intern Med*. 2017; 177:546-53.

Summary of metro vs. vanco clinical studies

									Clinical failure		Recurrence	
Study	**Year**	**Location**	**n**	**Single center**	**Blinded**	**Randomized**	**Metro dose**	**Vanco dose**	**metro**	**vanco**	**metro**	**vanco**
Teasley, 1983	82-83	MN	101	yes	no	yes	250 mg QID	500 mg QID	2 of 37 (5.4%)	0 of 45 (0%)	2 of 37 (5.4%)	6 of 45 (13%)
Wenisch, 1996	93-95	Austria	62	yes	no	yes	500 mg TID	500 mg TID	2 of 31 (6%)	2 of 31 (6%)	5 of 31 (16%)	5 of 31 (16%)
Musher, 2006	02-04	USA (Houston)	34	no	yes	yes	250 mg QID	125 mg QID	6 of 34 (17%)	N/A	9 of 28 (32%)	N/A
Zar, 2007	94-02	Chicago	150	Yes	yes	yes	250 mg QID	125 mg QID	13 of 79 (16%)	2 of 71 (3%)	9 of 66 (14%)	5 of 69 (7%)
Johnson, 2013	05-07	World	552	no	yes	yes	375 mg QID	125 mg QID	76 of 278 (27%)	49 of 259 (19%)	48 of 202 (23%)	43 of 210 (21%)

There may have been a MIC creep with metronidazole over the decades

				Metronidazole		
Author	**Location**	**Time period**	**Isolates**	**MIC50**	**MIC90**	**Range**
All strains						
Hecht et al	Various	1983–2004	110	0.125	0.25	0.025–0.5
Edlund et al	Sweden	1998	50	0.125	0.25	0.125–0.25
Betriu et al	Spain	2001	55	0.5	1	≤0.06–1
Citron et al	USA	2003	18	0.5	1	0.25–1
Finegold et al	USA (CA)	2003	72	0.5	1	0.25–2
Karlowsky et al	Canada (Manitoba)	2007	208	0.5	1	0.25–4
Debast et al	Europe	2008	398	0.25	0.5	<0.06-2
Reigadas et al	Spain	2013	100	0.25	0.5	0.06-1
Snydman et al	USA	2011-12	925	1	2	<0.06-4
BI/027/Nap1 strains						
Citron et al	USA	2004–2005		NR	2	0.5–2
Debast et al	Europe	2008		0.5	1	0.5-1
Snydman et al	USA	2011-12		2	2	<0.06-4

MIC=minimum inhibitory concentration

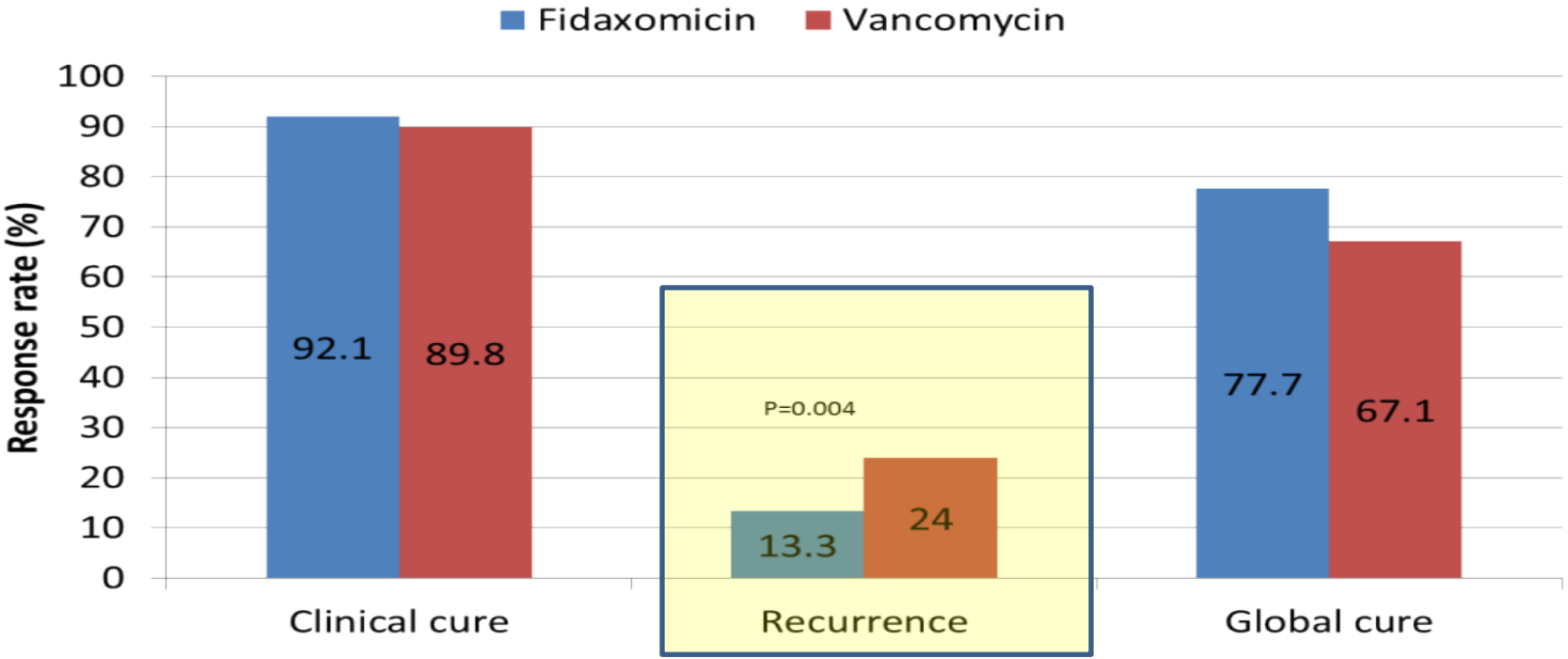
Shah D et al. *Expert Rev Anti Infect Ther*. 2010; 8:555-64.

Bottom line:
This may simply be a PK/PD problem

- Mean concentrations of metronidazole in stool:
  <0.25-9.5 ug/g
- MIC50: 1 ug/mL MIC90: 2 ug/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Bolton RP et al. *Gut*. 1986; 27:1169-72.

Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence



The second phase III study showed similar results (Crook et al. Lancet ID)

Louie et al. *N Engl J Med*. 2011; 364:422-310.

Comparative Treatment Efficacy in CDI

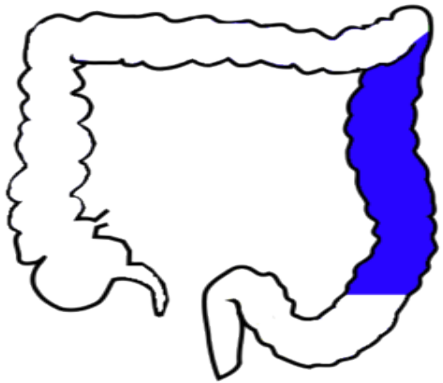
Outcomes	No. of Participants	Resolution, %	*P* Value	Quality of Evidence
Direct comparisons of metronidazole and vancomycin				
Resolution at end (10 days) of treatment	843 (5 studies)	**87 (VAN)** 78 (MTR)	0.0008	High
Resolution of diarrhea at end of treatment without recurrence*	843 (5 studies)	**73 (VAN)** 63 (MTR)	0.003	High
Direct comparisons of fidaxomicin and vancomycin				
Resolution at end (10 days) of treatment	1105 (2 studies)	88 (FDX) 86 (VAN)	0.36	High
Resolution of diarrhea at end of treatment without recurrence**	1105 (2 studies)	**71 (FDX)** 57 (VAN)	<0.0001	High

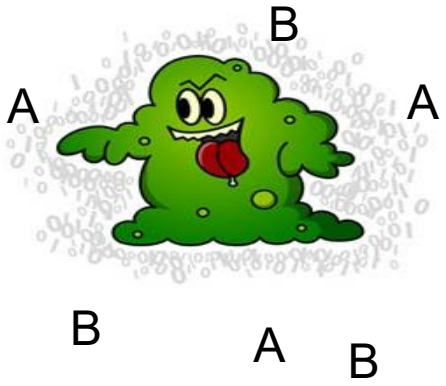
*1 month after treatment; **56 days after treatment

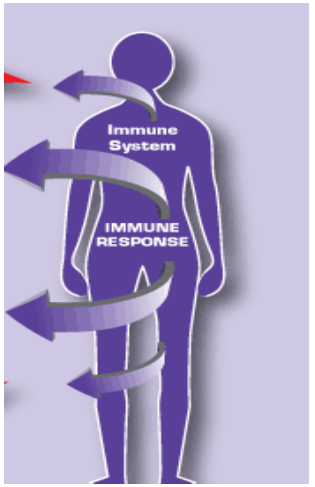
VAN = vancomycin, MTR = metronidazole, FDX = fidaxomicin

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

Explosion in Treatment Possibilities for CDI Minus 1







Current: Probiotics
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Use narrow-spectrum antibiotics

Vancomycin
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IVIG
Monoclonal antibodies vs. *C. diff* toxins

Future: 2nd generation FMT
non-toxigenic *C. diff* M3
Ecobiotics

Ridinilazole

Toxoid vaccines

Recommendation for initial treatment of CDI in adults

Clinical definition	Supportive clinical data	Recommended treatment
Initial episode, non-severe	WBC < 15,000 cells/mL and serum creatinine < 1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days Alternate if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days
Initial episode, severe	WBC ≥ 15,000 cells/mL or a serum creatinine > 1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hr if ileus present

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

McDonald LC et al. *Clin Infect Dis.* 2018; 66:987-94.

Recommendation for recurrence of CDI in adults

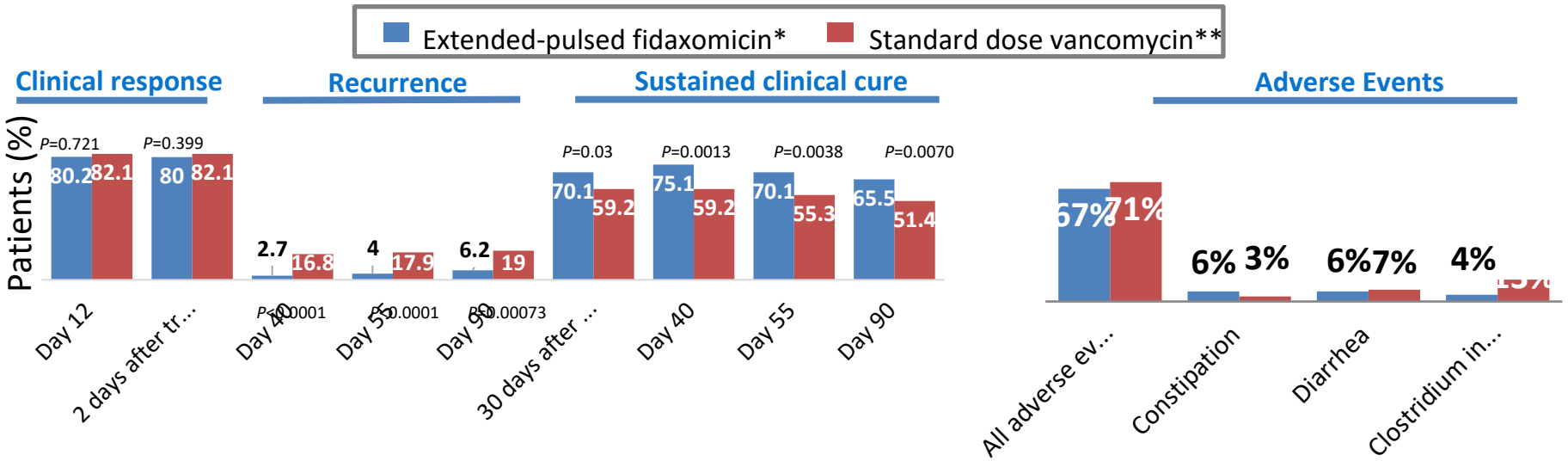
Clinical definition	Supportive clinical data	Recommended treatment
First recurrence		• VAN SD if metronidazole was used for the first episode OR • Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR • FDX SD if VAN was used for the initial episode
Second or subsequent recurrences		• VAN in a tapered or pulsed regimen OR • VAN SD followed by rifaximin 400 mg three times daily for 20 days OR • FDX SD OR • Fecal microbiota transplantation

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

McDonald LC et al. *Clin Infect Dis.* 2018; 66:987-94.

Extended-Pulsed Fidaxomicin vs. Standard Dose Vancomycin in Patients >60 years of age

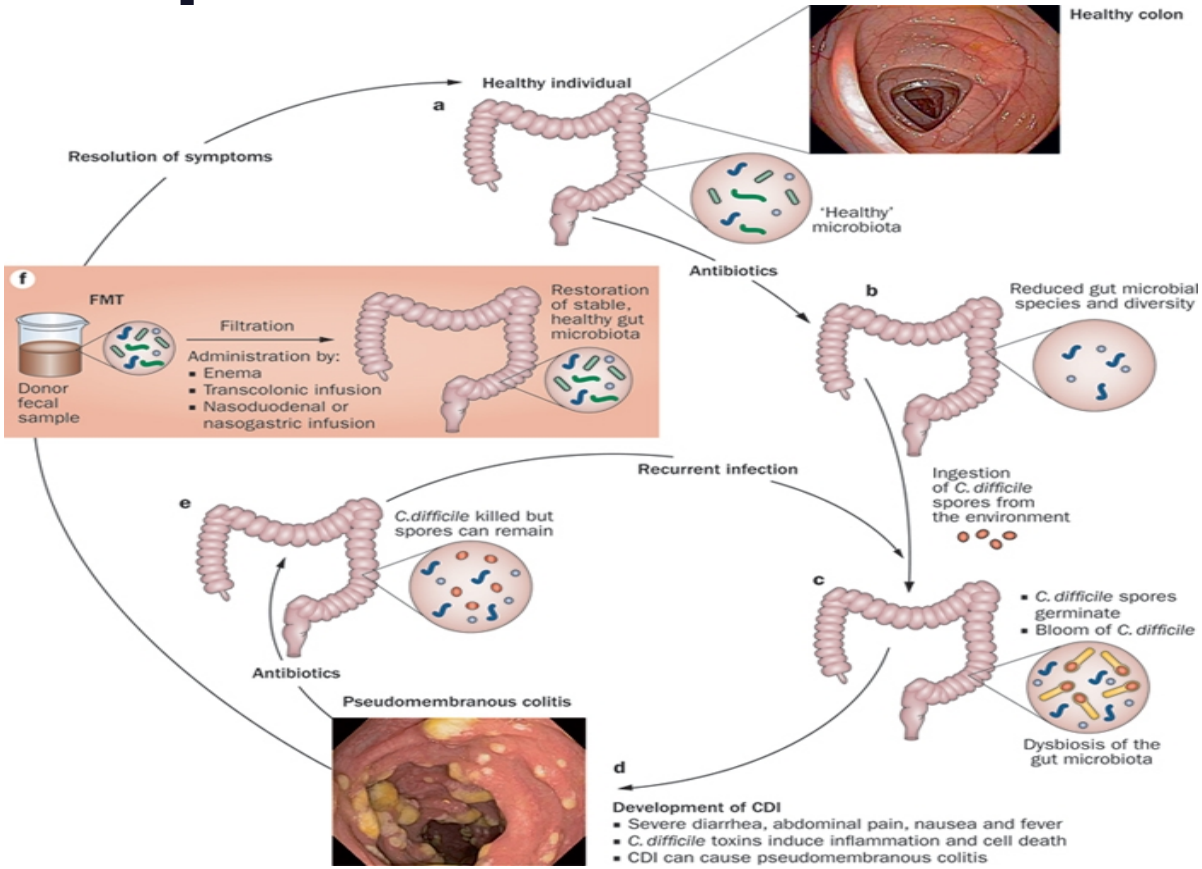
EXTEND: randomized, controlled, open-label, phase 3b/4 trial in 181 patients
≥60 years old with initial or recurrent CDI confirmed by presence of toxin A or B in stool sample



*Fidaxomicin: 200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25
**Vancomycin: 125 mg oral capsules, four times daily on days 1–10

Guery B et al. *Lancet Infect Dis*. 2017; 18:296-307.

FMT for patients with recalcitrant CDI



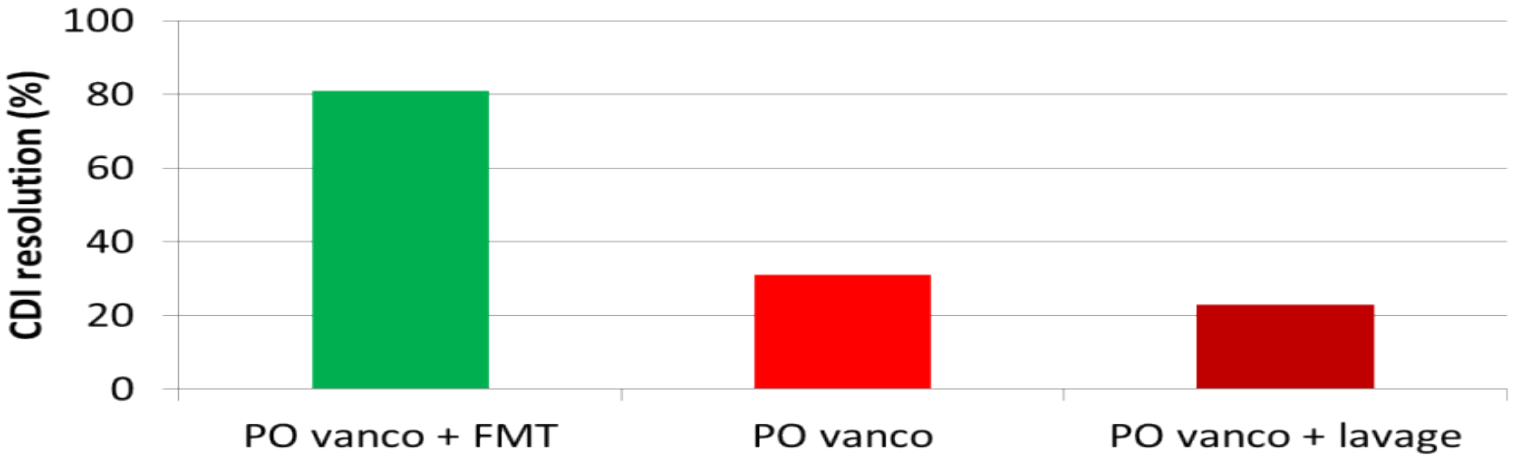
Recurrent *C. difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube

	Before stool transplant	After stool transplant
Deaths	N/A	2 (unrelated)
# of Recurrence	64 (2-7)	1

Aas J et al. *Clin Infect Dis*. 2003; 36:580-5.

Duodenal infusion of donor feces for recurrent *C. difficile* infection

RCT of PO vanco + FMT (n=16), PO vanco alone (n=13), or PO vanco + bowel lavage (n=13). Study stopped prematurely due to superiority of FMT



Resolution: no diarrhea without relapse after 10 weeks

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

Protocol utilizing a staggered and tapered antibiotic regimen for the treatment of recurrent *Clostridium difficile* infection that has failed to respond to standard antibiotic therapy.

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

Antibiotic Time Course	Metronidazole Dose/Frequency		Vancomycin Dose/Frequency		Kefir
Weeks 1-2	250 mg Q 6h		125 mg Q 6h		150 mL TID
Weeks 3-4	750 mg Q 72h		375 mg Q 72h		150 mL TID
Weeks 5-6	500 mg Q 72h	**OR**	250 mg Q 72h	**PLUS**	150 mL TID
Weeks 7-8	250 mg Q 72h		125 mg Q 72h		150 mL TID
Weeks 9-15					150 mL TID

Bakken JS. *Clin Infect Dis*. 2014; 59:858-61.

Alternative Therapies for *Clostridium difficile* Infection:

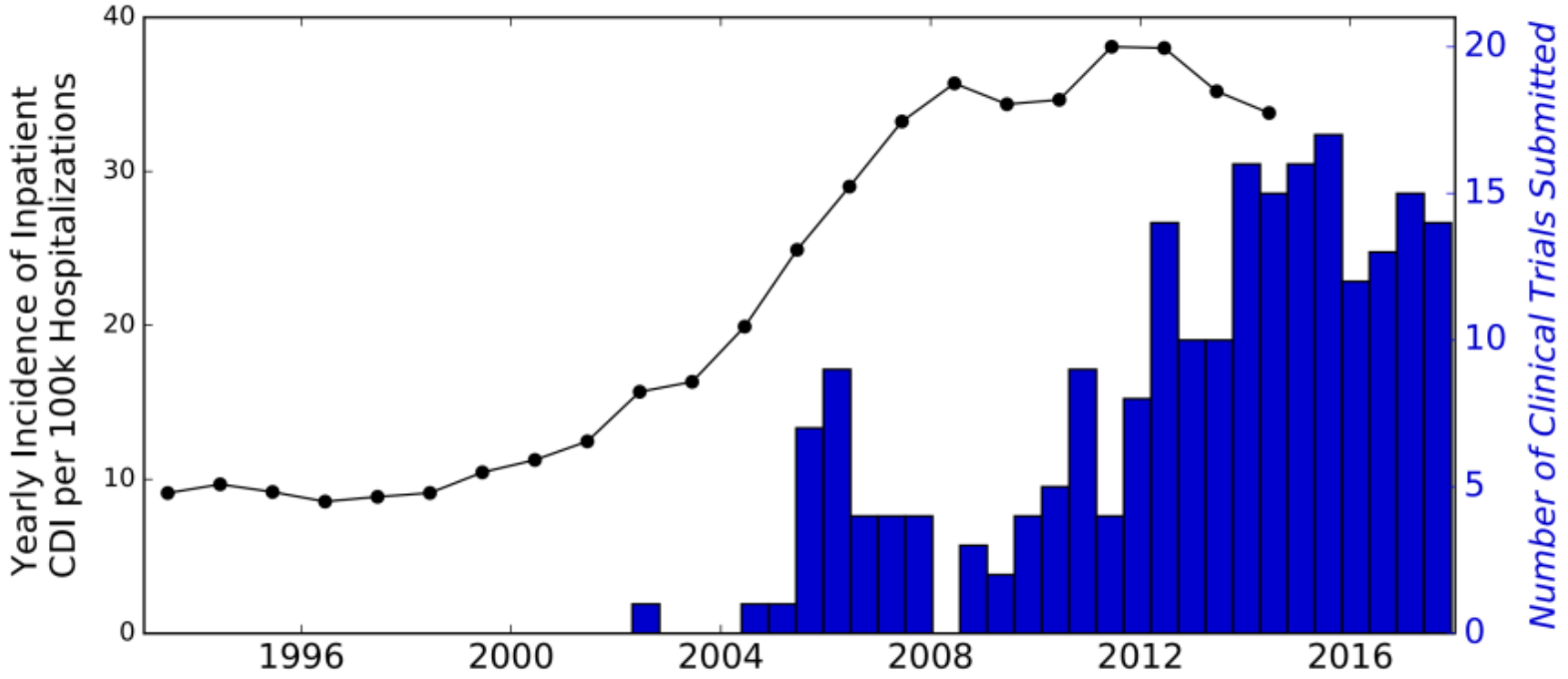
Antibiotics, Immune Therapy, and Beyond

A. Krishna Rao, M.D., M.S.
Assistant Professor of Internal Medicine
University of Michigan

Outline

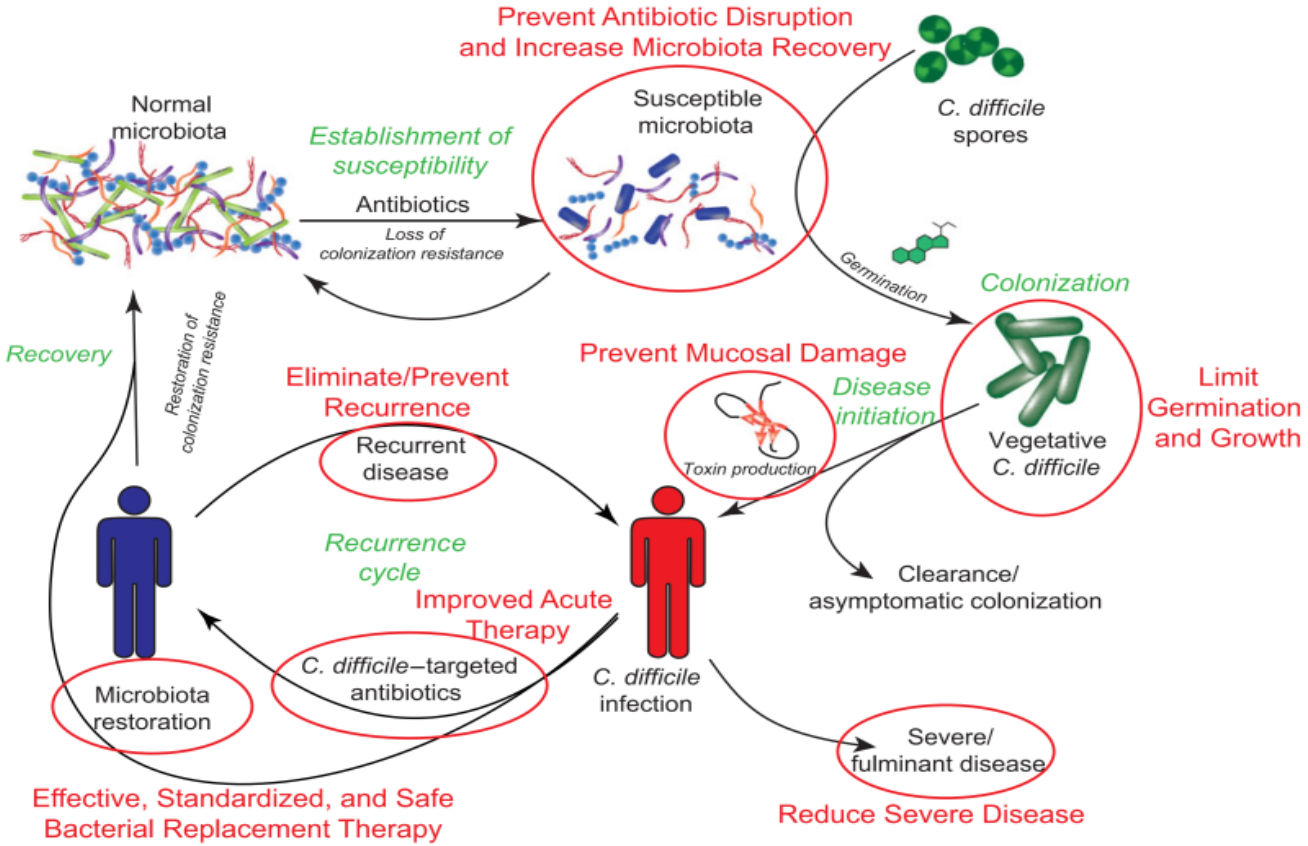
- Overview of new CDI treatment landscape
- **Why** we need alternative treatments for CDI
- Borrowing **old antibiotics** for new uses in CDI
- New **antimicrobial** approaches to CDI treatment
- Novel **non-antibiotic** approaches to CDI treatment

CDI incidence vs. Clinical Trial Registries



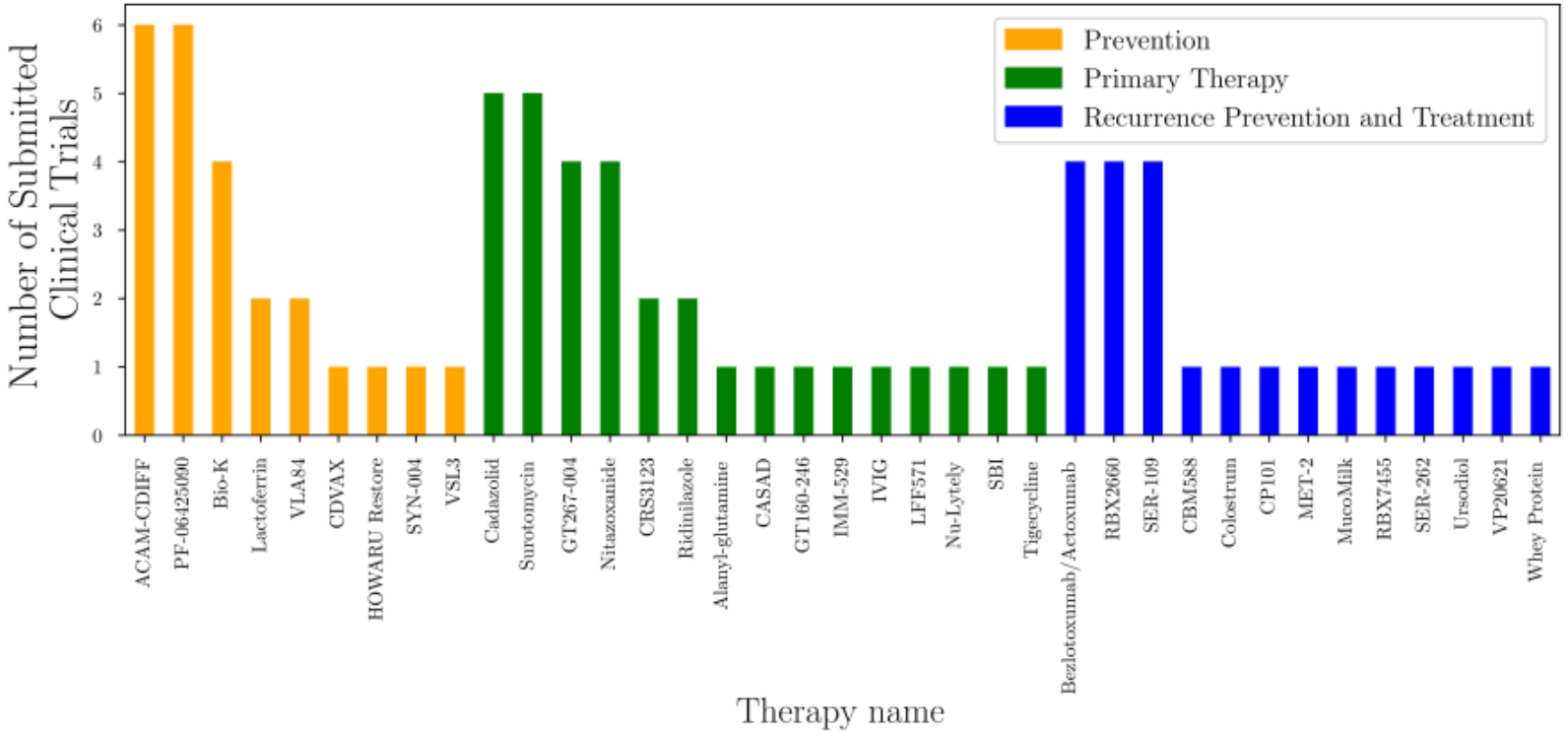
Dieterle MG et al. *Ann N Y Acad Sci*. 2018. doi: 10.1111/nyas. 13958 [Epub ahead of print].

Targets for alternative CDI treatments?



Britton RA, Young VB. *Gastroenterology.* 2014; 146:1547-53.

CDI clinical trials vs. treatment goal



Dieterle MG et al. *Ann NY Acad Sci*. 2018. DOI: https://doi.org/10.1111/nyas.13958.

So…why do we need alternative treatments?

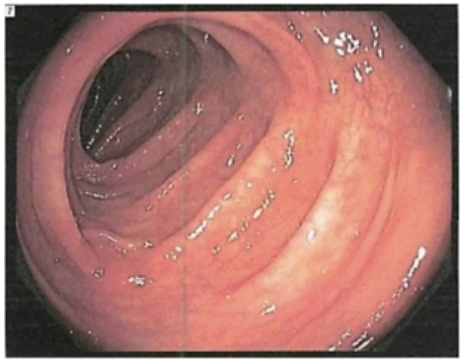
- Clinical failure / persistent symptoms
- Severe and complicated disease
- Recurrence

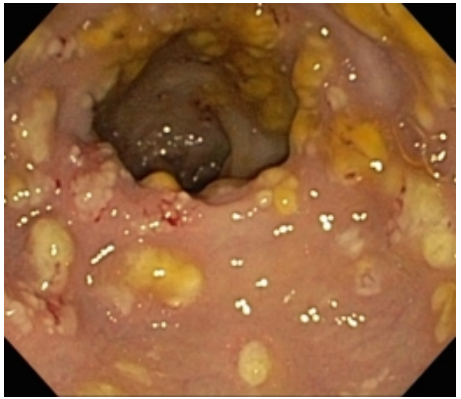
Clinical failure

- Continued or worsening symptoms by day 5 of therapy
- Initial resolution but early (<2 weeks) relapse of symptoms
- Failure to achieve 2 consecutive days with absence of symptoms
- Common: up to 1/3 in some studies
- **Can clinical failure be reduced by alternative treatments?**

Severe CDI

- Age >65 yr
- WBC >15,000 cells/mL
- Albumin <2.5 mg/dL
- Fever
- Colonic thickening / Severe abdominal pain
- Acute kidney injury (Cr >1.5 x premorbid level)
- Pseudomembranous colitis (rare in IBD)
- **Can severe CDI be prevented with alternative approaches?**

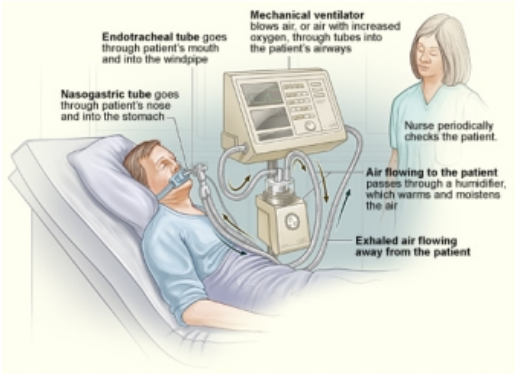




Source: Samir, Wikipedia 2009

Complicated CDI

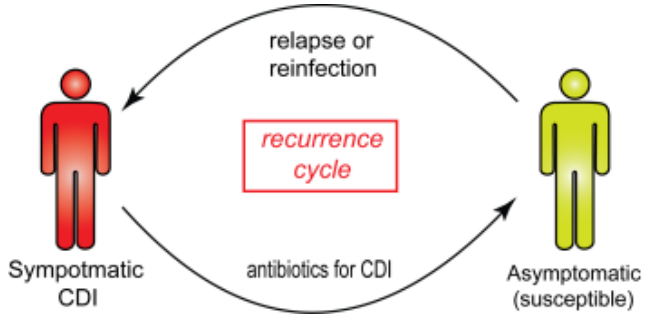
Source: NIH 2011



- Hypotension / shock / sepsis
- Ileus / megacolon
- Peritonitis
- Bowel perforation
- **Can complicated CDI be prevented with new approaches?**

Recurrent CDI

- 2nd Recurrence: 30-45% of 1st
- 3rd Recurrence: 45-60% of 2nd
- ≤5% of all patients → chronic, recurrent pattern
- No universal treatment algorithm



Can recurrent CDI be prevented with new approaches?

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

Borrowing old antibiotics for new uses in CDI

Metronidazole and reduced clinical success?

Direct comparisons of metronidazole and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	RCTs prior to 2000: 156 (2)	95 (MTR) 98 (VAN)	RR, 0.97 (.91–1.03)	.4		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	75 (MTR) 85 (VAN)	RR, 0.89 (.82–.96)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	78 (MTR) 87 (VAN)	RR, 0.89 (.85–.96)	.0008	⊕⊕⊕⊕ High	
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	RCTs prior to 2000: 156 (2)	85 (MTR) 84 (VAN)	RR, 1.0 (.90–1.2)	1.0		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	59 (MTR) 70 (VAN)	RR, 0.84 (.74–.94)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	63 (MTR) 73 (VAN)	RR, 0.87 (.79–.96)	.003	⊕⊕⊕⊕ High	

- Metronidazole inferior to vancomycin for clinical success
- Some high-risk populations may benefit from vancomycin up front
- Guidelines now advise against metronidazole

McDonald LC et al. *Clin Infect Dis*. 2018; 66:987-94.

Rifaximin

- Non-absorbable rifamycin antibiotic
- Approved for traveler's diarrhea
- Excellent in-vitro activity against *C. difficile*, but resistance develops rapidly
- Guidelines for ≥2nd recurrence:

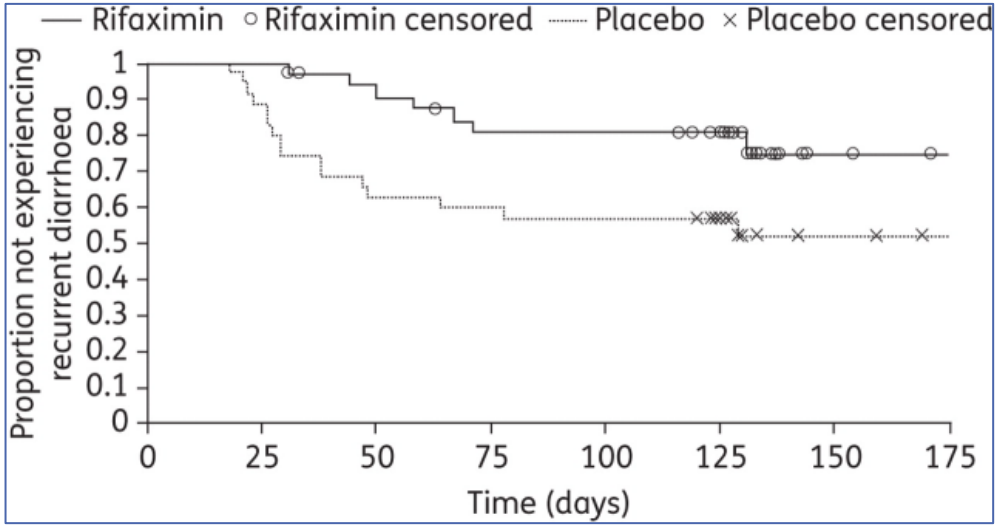
  - VAN in a tapered and pulsed regimen, OR
  - VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR
  - FDX 200 mg given twice daily for 10 days, OR
  - Fecal microbiota transplantation[c]

- Recent RCT testing "chaser" following vancomycin[1]
  - Rifaximin 400 mg three times a day for 2 weeks, reduced to 200 mg three times a day for a further 2 weeks
  - 12-week recurrence 29.5% (18/61) placebo vs. 15.9% (11/69) rifaximin: RR 0.54 (0.28-1.05, P=0.07)

[1] Gut. 2018 Sep 25. pii: gutjnl-2018-316794.

Rifaximin

- Garey et al. 2011
  - Double-blind, placebo-controlled, RCT 68 patients
  - 20 days of 400 mg TID following standard therapy
  - Less recurrent diarrhea (21% vs. 49%, *P* = 0.002)
  - Trend to less CDI recurrence (15% vs. 31%, *P* =0.11)



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

Toxin binders

Cholestyramine & colestipol

- Non-absorbable anionic polymers
- No efficacy demonstrated
- WARNING: may actually bind vancomycin! Do not co-administer!

Tolevamer

- Johnson et al. 2014: Inferior to metronidazole / vancomycin (cure 44.2% vs. 72.7% and 81.1%, *P* = 0.02)

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

Linezolid

HAS IN VITRO ACTIVITY AGAINST CDI

CASE REPORTS PUBLISHED WITH SUCCESS

FAILURES ALSO PUBLISHED, INCLUDING A FATALITY WHERE LINEZOLID WAS IMPLICATED

AT THIS TIME: **NOT RECOMMENDED**

Valerio M et al. *Int J Antimicrob Agents*. 2012; 39(5):414-9.

Tigecycline

- Good in-vitro activity
- High fecal concentrations
- Low risk for development of CDI
- Systematic review: Larson et al. 2011:
  - Six case reports
  - All but one refractory to metronidazole and/or vancomycin
  - Success with tigecycline in all 6 cases
  - No recurrence
- Four retrospective cohort studies[1] in past 3 years differ, but possible benefit in severe CDI as adjunctive treatment
- Conclusion: shows promise; in need of better data

[1]Gergely Szabo B et al. *Clin Microbiol Infect*. 2016; 22(12):990-95; LaSalvia MT et al. *Open Forum Infect Dis*. 2017; 4(1):ofw264; Manea E et al. *Clin Microbiol Infect*. 2018; 24:180-4; Bishop EJ et al. *Intern Med J*. 2018; 48:651-60.

Nitazoxanide

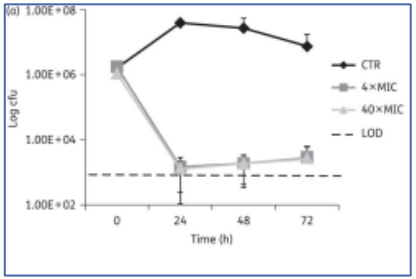
- Used to treat intestinal parasites (*Cryptosporidium parvum*)
- Blocks anaerobic metabolism
- Inhibits *C. difficile* in vitro at low concentrations, including metronidazole-resistant strains
- Similar efficacy to metronidazole and vancomycin in two RCTs (Musher et al., 2006 and 2009)
- Jury is out on recommending for clinical use

Musher DM et al. *Clin Infect Dis*. 2006; 43:421-7.
Musher DM et al. *Clin Infect Dis*. 2009; 48:e41-6.

New Antimicrobial Approaches to CDI Treatment

Ridinilazole

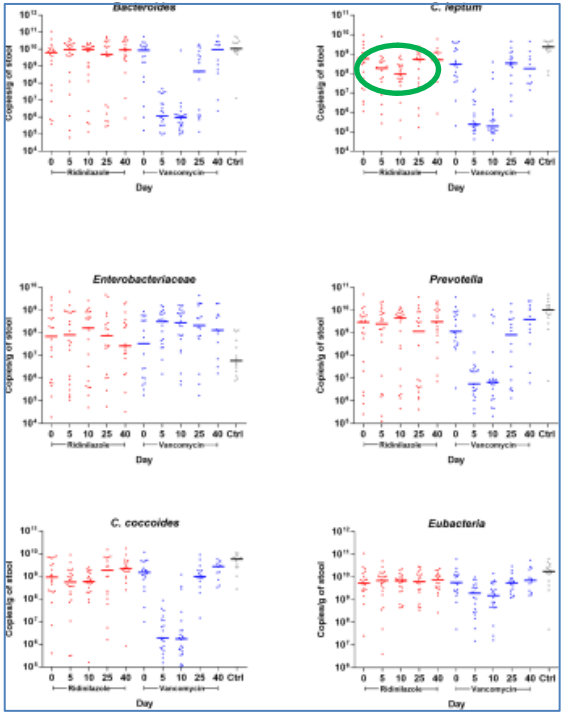
- Narrow spectrum, non-absorbable antibiotic
- Potent anti-*C. difficile* activity
- Decreased inflammation (calprotectin/lactoferrin)
- CoDIFy Phase 2 trial (Vickers et al. Lancet. 2017):
  - Multicenter, double-blind RCT
  - 1° endpoint: sustained clinical response
  - Noninferiority to vancomycin design
  - Superiority demonstrated: 66.7% vs. 42.4% (difference in treatment proportions 21.1%; 90% CI 3.1, 39.1)
  - 50% reduction in recurrence

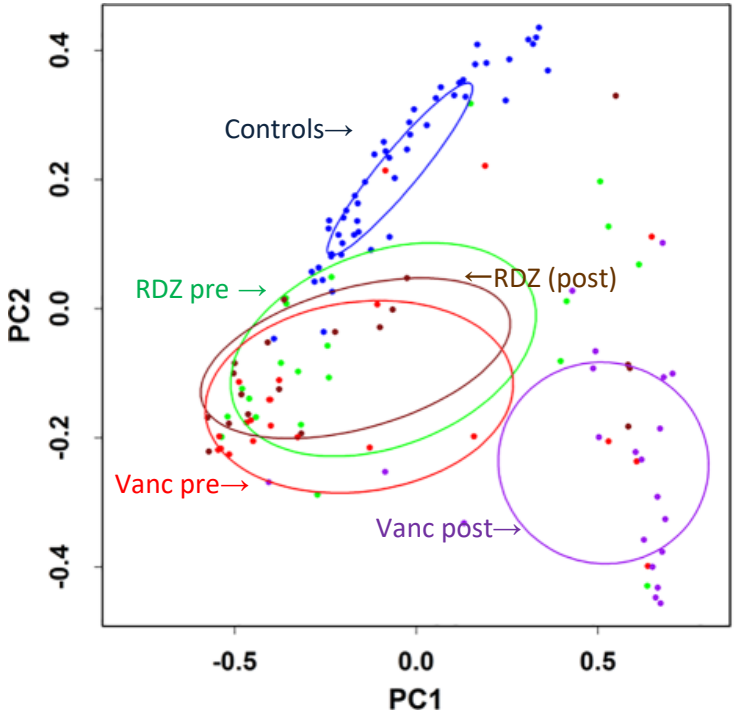


Bassères et al. 2016

Vickers RJ et al. *Lancet Infect Dis.* 2017; 17:735-44.

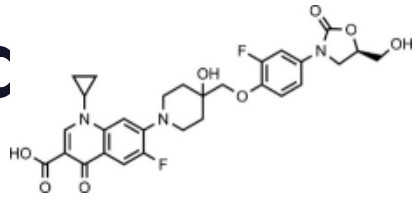
Ridinilazole (RDZ) effects on microbiome?



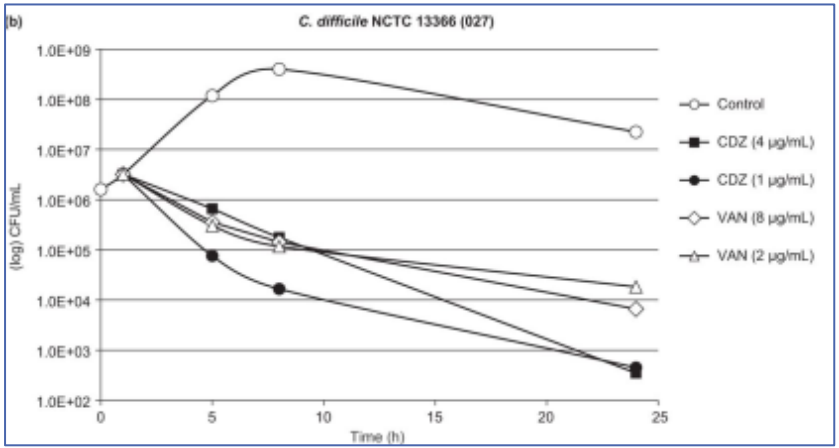


PLoS One. 2018;13:e0199810.

Cadazolic



- Non-absorbable, narrow-spectrum protein synthesis inhibitor
- Potent, but similar to vancomycin



Locher HH et al. *Antimicrob Agents Chemother*. 2015; 58(2):892-900.

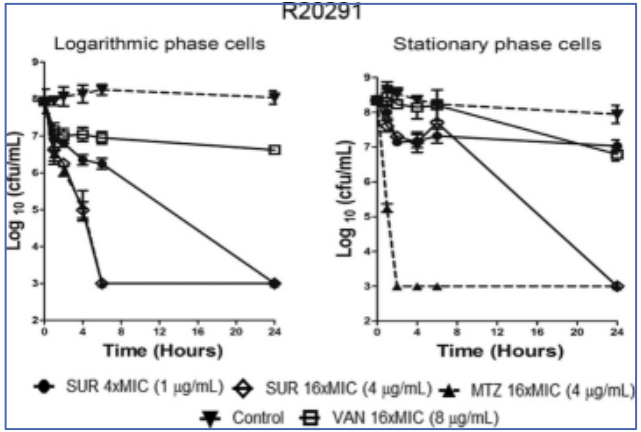
- Phase 2 results promising

Parameter	Value			
	Cadazolid			Vancomycin (125 mg QID)
	250 mg BID	500 mg BID	1,000 mg BID	
Clinical cure rate [*n* (%)]	13 (76.5)	16 (80.0)	13 (68.4)	15 (68.2)
80% CI	58.4, 89.3	63.9, 91.0	51.1, 82.5	52.3, 81.3
Treatment group *P* value (right sided)[b]	0.57	0.41	0.83	
n	17	20	19	22
Recurrence rate [*n* (%)]	2 (18.2)	3 (25.0)	2 (22.2)	7 (50.0)
80% CI	4.9, 41.5	9.6, 47.5	6.1, 49.0	30.5, 69.5
n	11	12	9	14
Sustained clinical response rate [*n* (%)]	9 (60.0)	9 (56.3)	7 (46.7)	8 (33.3)
80% CI	40.4, 77.4	37.5, 73.7	28.2, 65.8	19.6, 49.7
n	15	16	15	21
Median time to resolution of diarrhea (h)	141.2	173.6	135.5	133.7
80% CI	107.3, 180.7	86.7, 212.1	110.8, 286.3	90.7, 190.9
n	17	20	19	22

Louie LT et al. *Antimicrob Agents Chemother.* 2015; 59(10):6266-73.

Surotomycin

- Potent in vitro activity
- Louie et al. (ASM Microbe 2016)
  - Phase 3, double-blind RCT
  - Clinical response compared to vancomycin
  - Noninferiority design
  - Cure 83.4% vs. 82.1% (*P* = .281)
  - Sustained clinical response no different (63.3% vs. 59%)
  - **Recurrence 27.9% for surotomycin 125 mg twice daily, 17.2% for surotomycin 250 mg twice daily and 35.6% for vancomycin (*P* =.035).**
  - Minimal disruption of *B. fragilis* and *Bacteroides/Prevotella* groups and decreased VRE counts compared with vancomycin (Chesnel et al., ASM Microbe 2016)



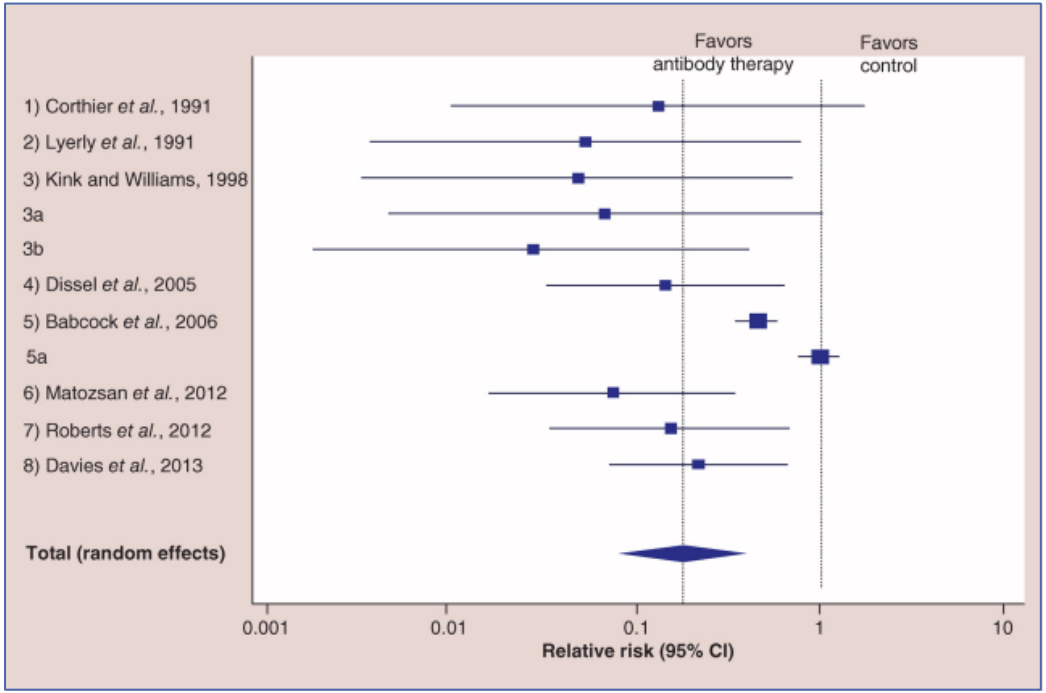
Alam MZ et al. *Antimicrob Agents Chemother*. 2015; 59:5165-70.

Novel non-antibiotic approaches to CDI treatment

immune therapy

Immunoglobulins: animal data

- RR 0.18



Diraviyam T et al. *Immunotherapy*. 2016; 8:649-63.

Immunoglobulins: human data

- Most case series and studies show a benefit
- 17 studies included, but only three met criteria for meta-analysis

Table 6. Effect of passive immunotherapy against *Clostridium difficile* infection in human subjects.

Study (Year)	No. cases with diarrhea/No. in group (%)		Relative risk	95% Confidence interval
	Intervention	Control		
Juang *et al.* (2007)	6/18	5/18	1.200	0.446 to 3.232
Mattila *et al.* (2008)	8/18	9/20	0.988	0.486 to 2.005
Lowy *et al.* (2010)	7/101	24/99	0.286	0.129 to 0.633

Severe CDI

Symptoms

Recurrent CDI

Diraviyam T et al. *Immunotherapy*. 2016; 8:649-63.

Monoclonal antibodies

- Two candidates: actoxumab (ACT) and bezlotoxumab (BEZ)
- Two phase 3 RCTs: MODIFY I and MODIFY II
  - ACT study arm stopped early: lack of efficacy
  - Pooled analysis of 2327 patients who received either ACT + BEZ or BEZ alone
  - rCDI in 15.4% and 16.5%, respectively, versus 26.6% in the placebo arm (P <.001)
  - Held across subgroups: age ≥65 years, history of CDI, ribotype 027 infection, and severity

Wilcox MH et al. *N Engl J Med*. 2017; 376:305-17.

Vaccines: In development for 20 years—many candidates

Vla84: *C. difficile* vaccine candidate (Bezay et al., Vaccine. 2016)

- Targets cell-binding domains of TcdA and TcdB
- Phase 2 single-blind, placebo-controlled RCT
- Seroconversion 60–83% against both toxins
- Seroconversion 92–97% against TcdA
- The antibodies were toxin neutralizing
- Safe and well-tolerated

PF-06425090: phase III

- Genetically modified *C. difficile* toxins A and B
- Given IM induces antitoxin antibody production.

Bezay N et al. *Vaccine.* 2016; 34:2585-92.

Novel non-antibiotic approaches to CDI treatment

bacteriotherapy* and beta-lactamases

***excluding fecal transplant**

Nontoxigenic *C. difficile* spores

- Gerding et al. 2015, phase 2 trial
  - Strain M3 (VP20621; NTCD-M3)
  - Double-blind, placebo-controlled RCT
  - Secondary outcome: 6-week recurrence

Table 4. CDI Recurrence Within 6 Weeks as Defined by Diarrhea Criteria and by Investigator Decision to Re-treat for Recurrent CDI

		NTCD-M3 Dosage			
Events in Intention-to-Treat Safety Population	Placebo (n = 43)	10^4 Spores/d for 7 d (n = 41)	10^7 Spores/d for 7 d (n = 43)	10^7 Spores/d for 14 d (n = 41)	All (n = 125)
CDI recurrence, No. (%)	13 (30)	6 (15)	2 (5)	6 (15)	14 (11)
Unadjusted comparison with placebo, *P* value[a]		.09	.002	.09	.003
Adjusted comparison with placebo[b]					
Odds ratio (95% CI)		0.4 (0.1-1.2)	0.1 (0.0-0.6)	0.4 (0.1-1.2)	0.28 (0.11-0.69)
P value		.11	.01	.10	.006
Use of antibacterial treatment for CDI, No. (%)	14 (33)	6 (15)	4 (9)	7 (17)	17 (14)
Unadjusted comparison with placebo, *P* value[a]		.05	.008	.10	.006
Adjusted comparison with placebo[b]					
Odds ratio (95% CI)		0.3 (0.1-1.1)	0.2 (0.1-0.8)	0.4 (0.1-1.3)	0.32 (0.14-0.75)
P value		.07	.02	.14	.009
CDI recurrence based on NTCD colonization, No./total (%)[c]					
Colonized with NTCD	0/4 (0)	1/26 (4)	1/31 (3)	0/29 (0)	2/86 (2)[d]
Not colonized with NTCD	13/39 (33)	5/15 (33)	1/12 (8)	6/12 (50)	12/39 (31)[d]
CDI recurrence based on presence of toxin-positive *C difficile* on day 1, No./total (%)					
Day 1 toxin-positive *C difficile*	1/6 (17)	3/12 (25)	2/9 (22)	3/9 (33)	8/30 (27)
No day 1 toxin-positive *C difficile*	12/37 (32)	3/29 (10)	0/34 (0)	3/32 (9)	6/95 (6)

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

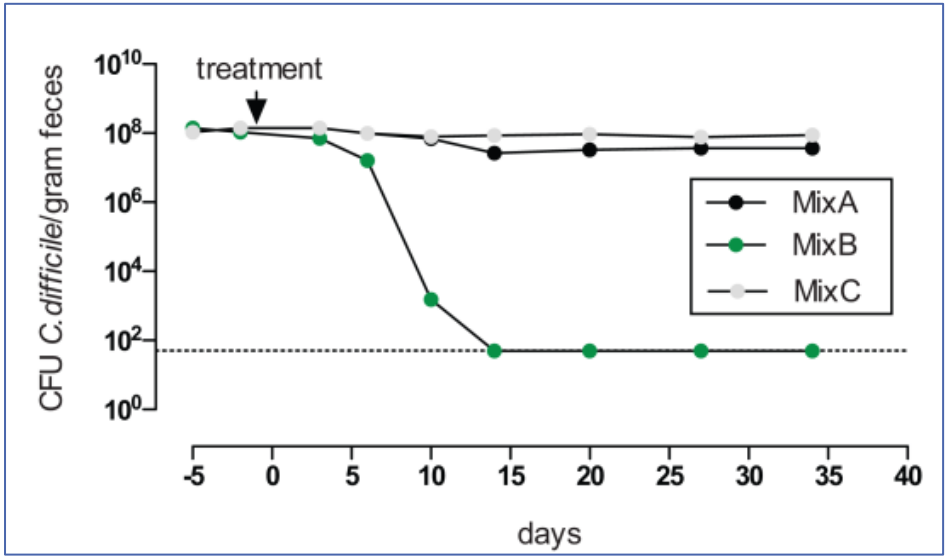
Defined microbial communities

- Lawley et al. 2012
  - Mice with CDI treated with FMT had resolution of symptoms
  - Studied community structure of healthy feces
  - Rational, stepwise approach to develop a product
  - Developed many combinations of the bacterial phyla and tested them in lieu of standard FMT
  - Most of these mixtures did not work….

Lawley et al. PLoS Pathog. 2012; 8:e1002995.

Defined microbial communities

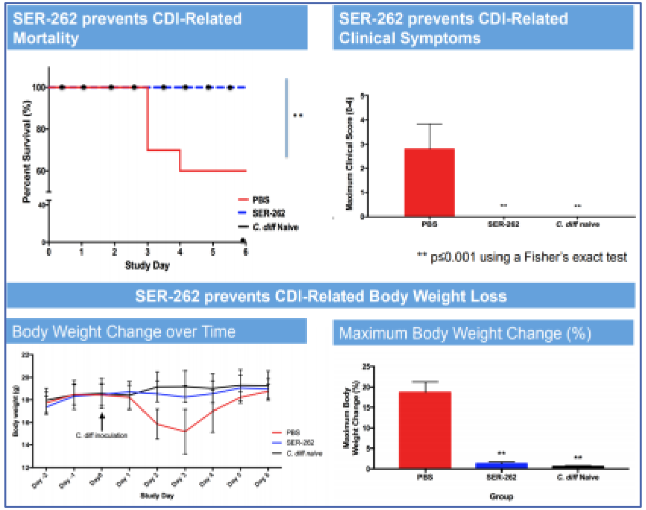
- Mixture B:
  - *Bacteroidetes* novel species
  - *Lactobacillus reuteri*
  - *Enterococcus hirae*
  - *Anaerostipes* novel species
  - *Staphylococcus warneri*
  - *Enterorhabdus* novel species

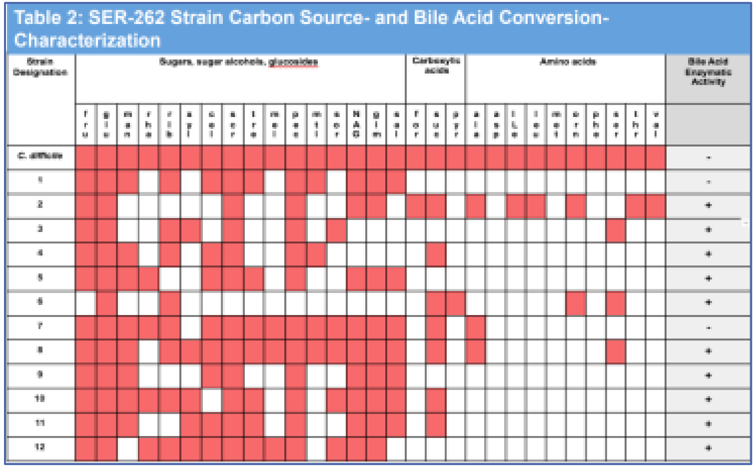


Lawley TD et al. *PLoS Pathog*. 2012: 8(10):e1002995.

Ser-262: defined microbial community

- Spores of anaerobic, indigenous microbes
- Produced by in-vitro fermentation
- Phase I testing underway for rCDI (NCT02830542)

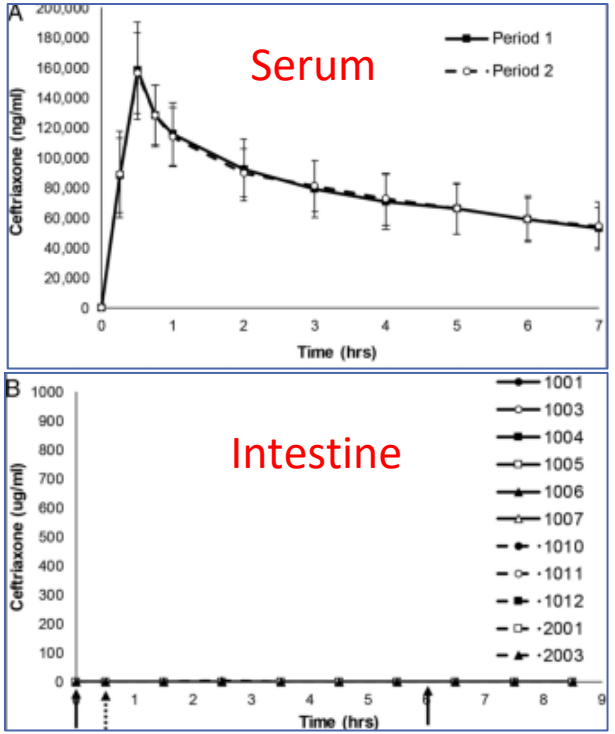




Wortman JR et al. Design and Evaluation of SER-262: A Fermentation-Derived Microbiome Therapeutic for the Prevention of Recurrence in Patients with Primary *Clostridium difficile* Infection; poster at ASM Microbe 2016.

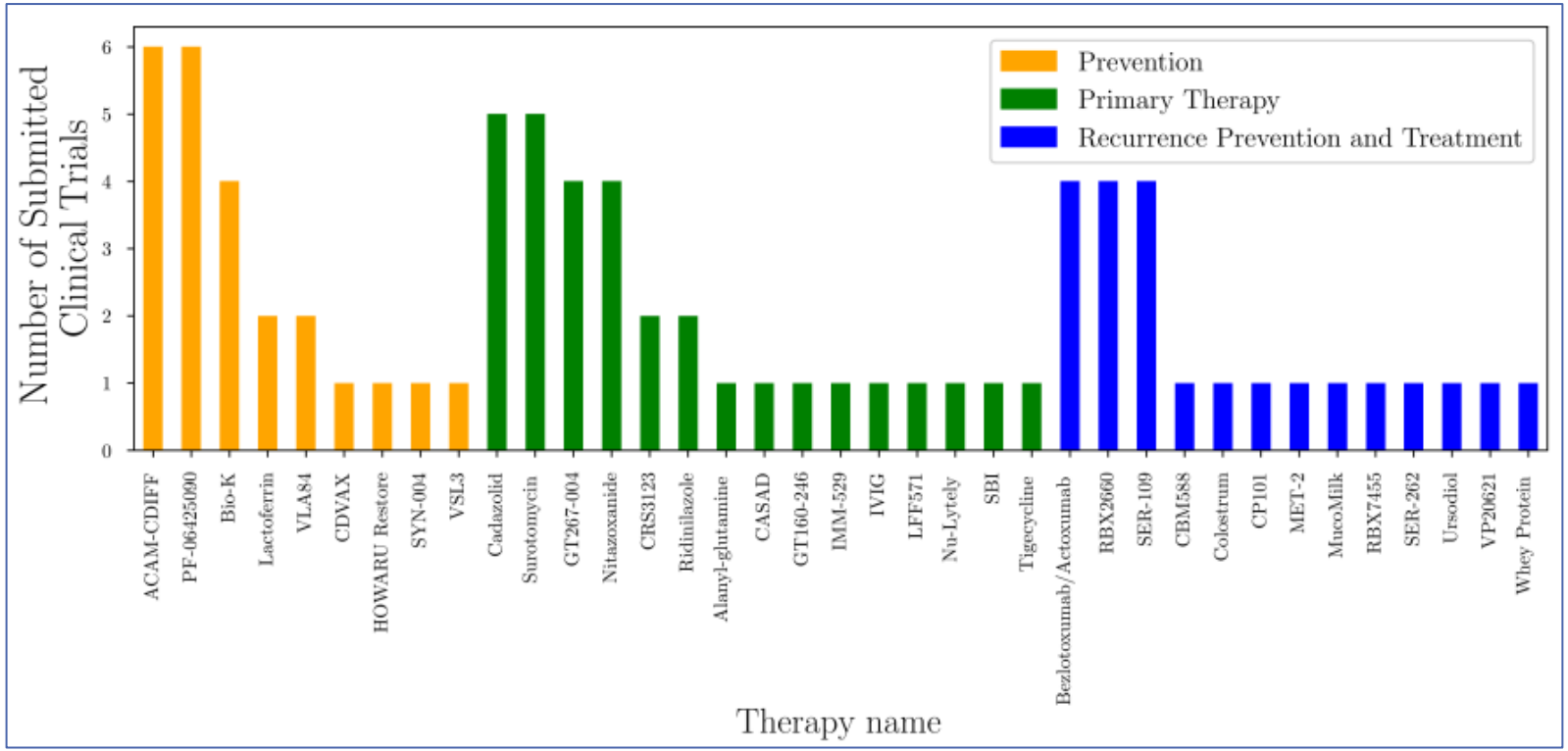
Ribaxamase: an oral β-Lactamase to Prevent *Clostridium difficile*

- Ribaxamase(Syn-004), a novel, oral, recombinant β-lactamase
- Given during treatment with IV β-lactam antibiotics
- Phase 2a trials in patients with ileostomy for sampling of intestinal chyme
- In vivo, syn-004 degrades ceftriaxone excreted in the human intestine
- No systemic absorption and no change in systemic ceftriaxone levels
- Proton pump inhibitor administration did not change the effect



Antimicrob Agents Chemother. 2017 Feb 23;61(3). pii: e02197-16.

And many more…



Dieterle MG ett al. *Ann NY Acad Sci*. 2018. DOI: https://doi.org/10.1111/nyas.13958.

Future of CDI treatment?

- Substantial near-term impact: narrow-spectrum, non-absorbable antibiotics
- Long-term: pharmaceutical grade, FDA-approved filtered stool products and defined communities
- Better risk-stratification models to assign expensive or experimental treatments

PART 2: THE BIG QUESTION!

- Should fidaxomicin or vancomycin be considered the front-line antibiotic for CDI
- PRO-CON Debate time!

Who do you want to present each side of the debate?

a. Option 1

   Vanco PRO: Kevin Garey, Pharm.D.

   Fidaxo PRO: Krishna Rao, M.D.

b. Option 2:

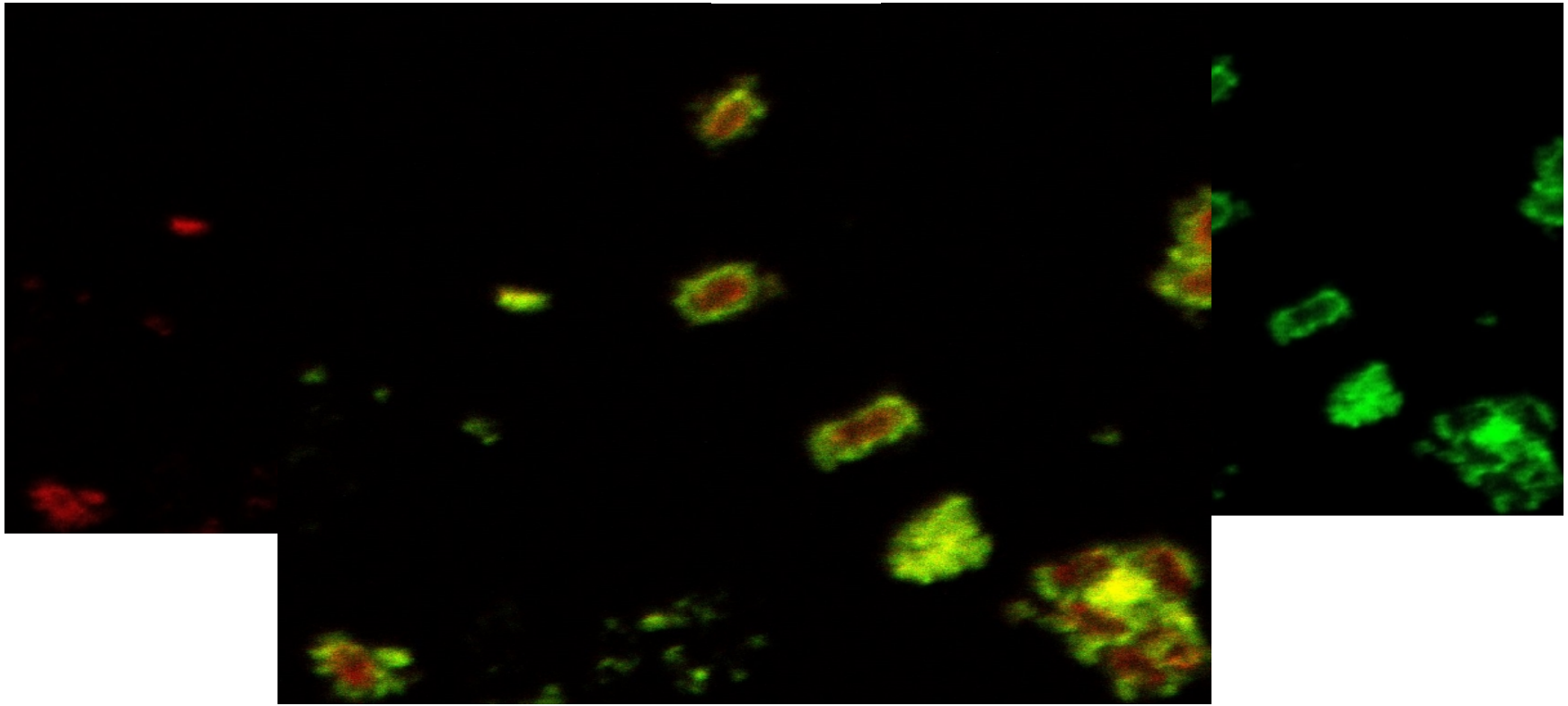
   Fidaxo PRO: Kevin Garey, Pharm.D.

   Vanco PRO: Krishna Rao, M.D.

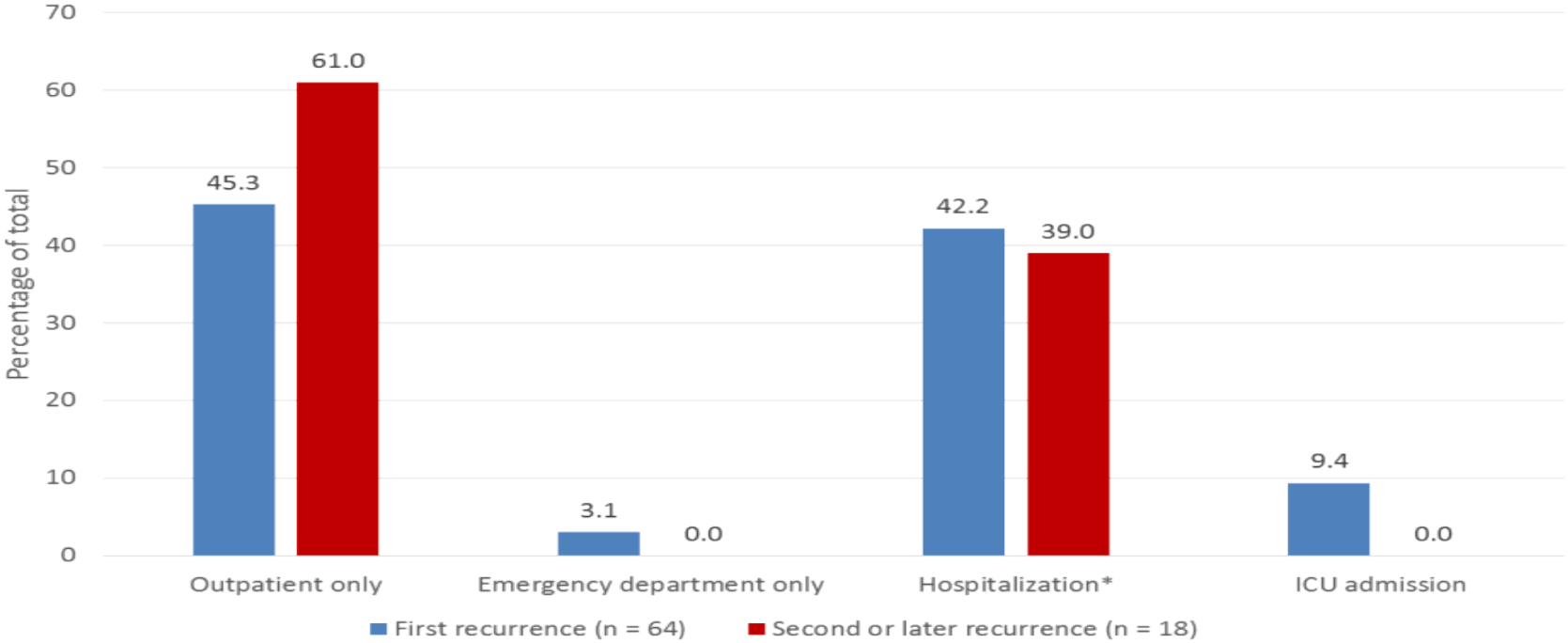
KEVIN GAREY PRO – CON debate

- PRO Fidaxomicin

Fidaxomicin has some really cool anti-recurrence properties



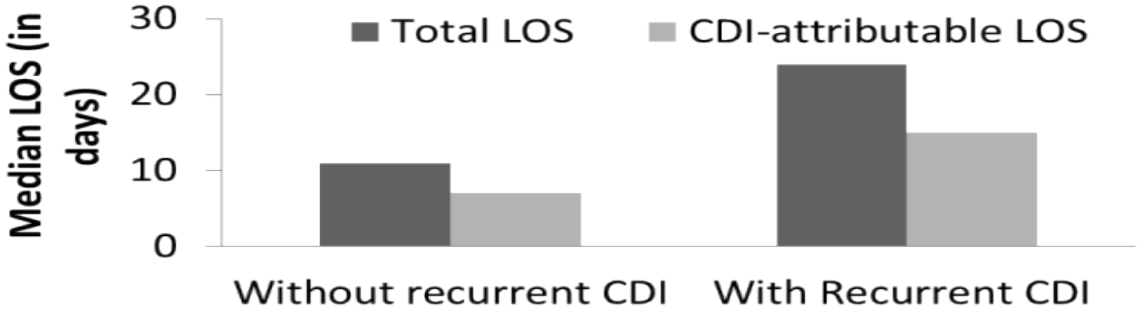
Recurrent CDI is costly: Healthcare utilization for recurrent CDI



* Of disease-attributable readmission, 85% returned to the initial hospital for care

Aitken SL et al. *PLoS One*. 2014; 9:e102848.

Increased healthcare utilization = increased healthcare costs



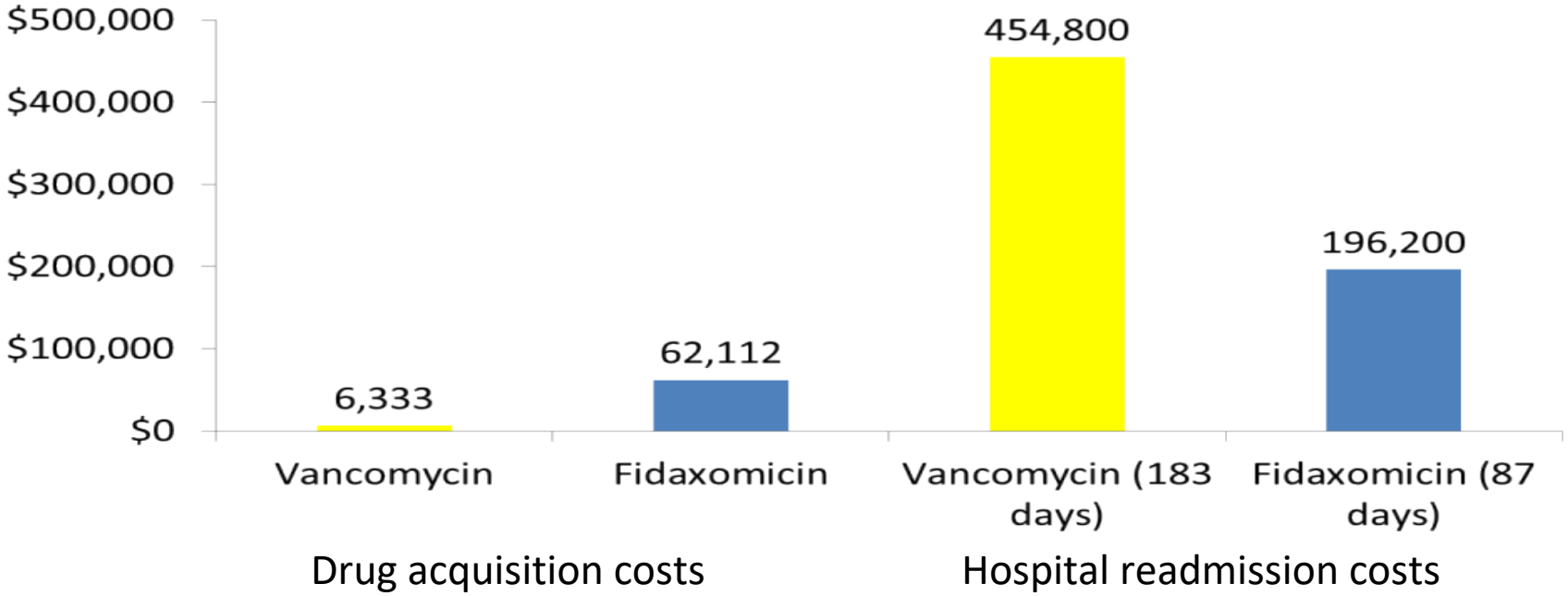
Cost in US dollars; median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment*	$60 (23 - 200)	$140 (30 - 260)
CDI-attributable hospitalization^	$13,168 (7,525 - 24,455)	$28,218 (15,049 - 47,030)
Total hospitalization^	$20,693 (11,287 - 41,386)	$45,148 (20,693 - 82,772)

Shah et al. *J Hosp Infect*. 2016; 93:286-9.

Any evidence that fidaxomicin may reduce these costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for selected patients.

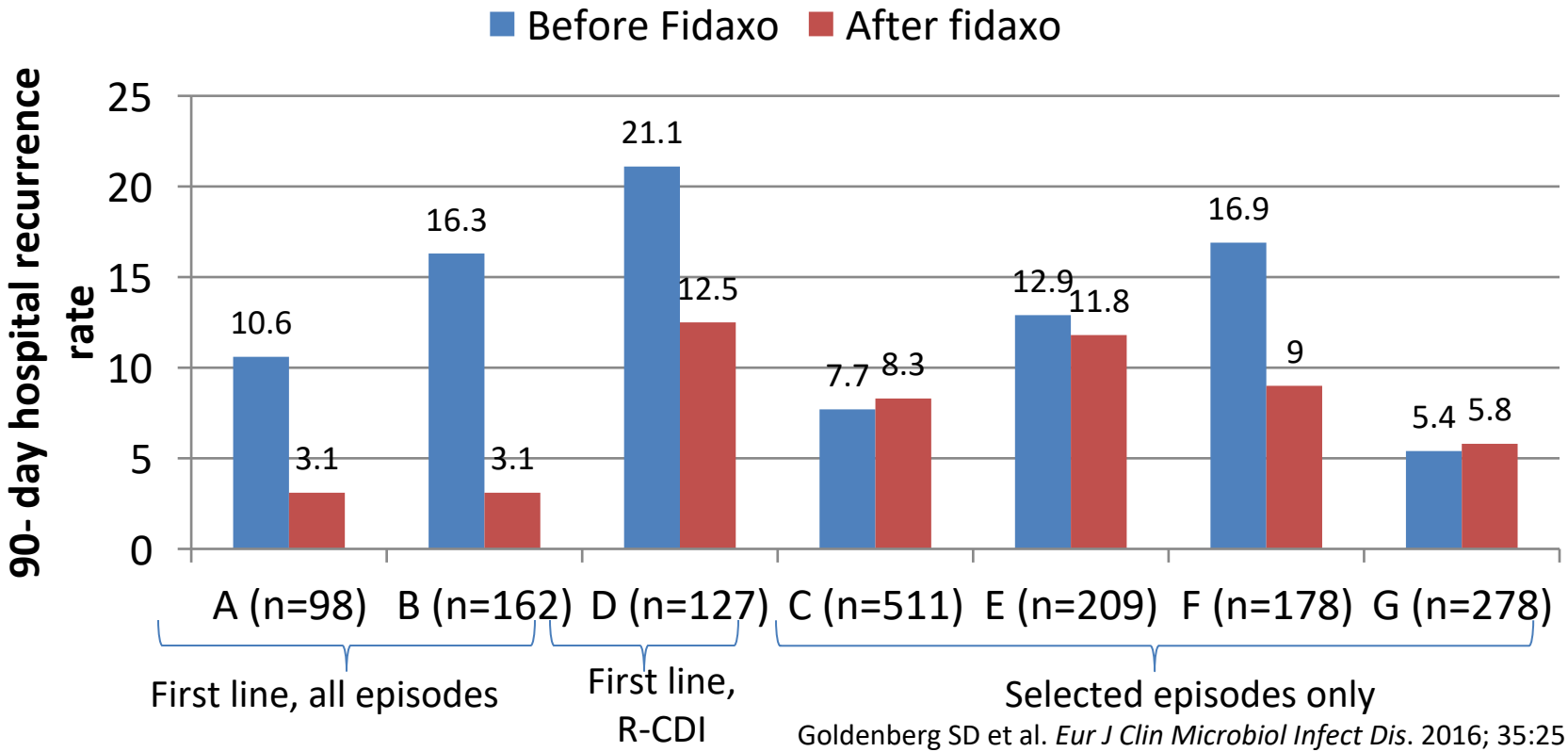
CDI-related readmissions: Fidaxo: 20.4%; Vanco: 41.3%



Gallagher JC et al. *Antimicrob Agents Chemother*. 2015; 59:7007-10.

Real-world evidence that fidaxomicin may reduce these costs?

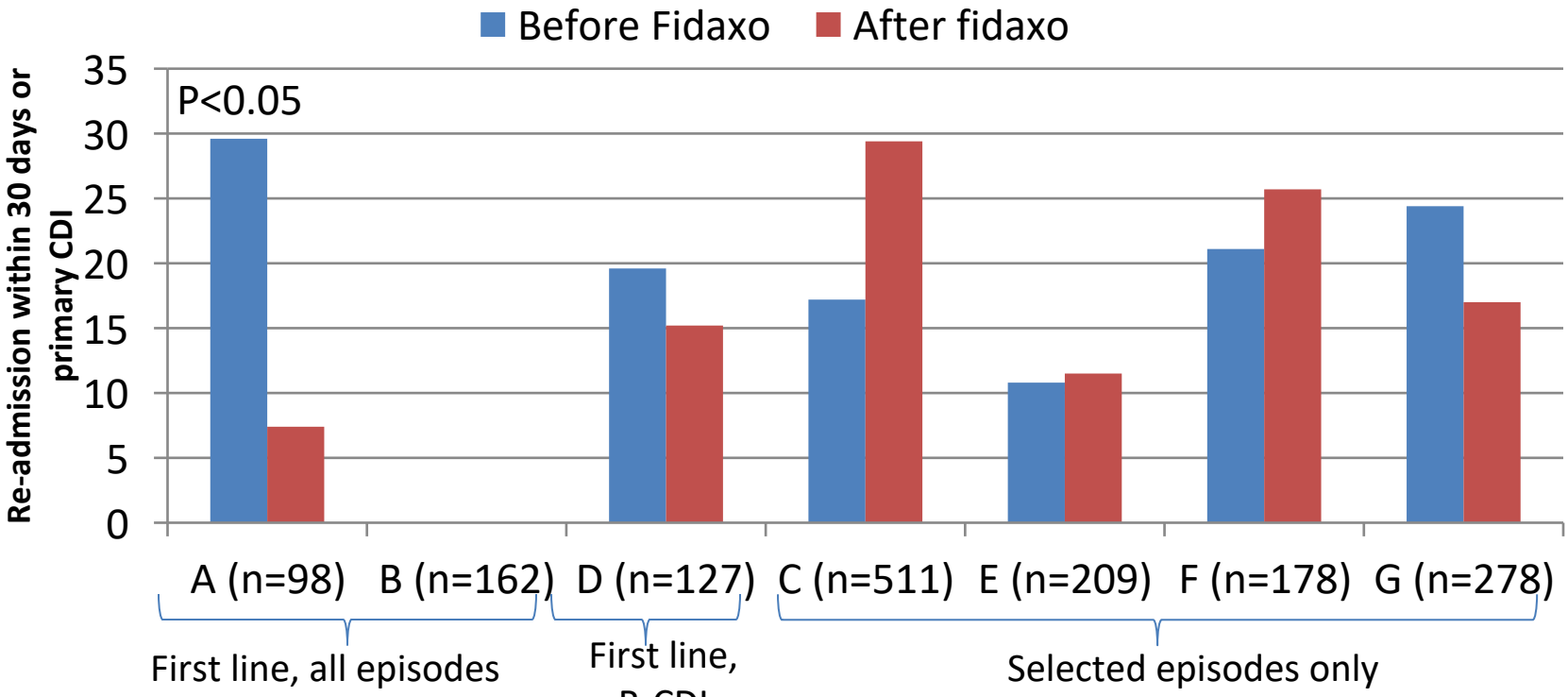
UK, 2012-13: seven hospitals incorporated fidaxomicin into clinical protocols. Letters below indicate individual hospitals



Goldenberg SD et al. *Eur J Clin Microbiol Infect Dis*. 2016; 35:251-9.

Real-world evidence that fidaxomicin may reduce these costs?

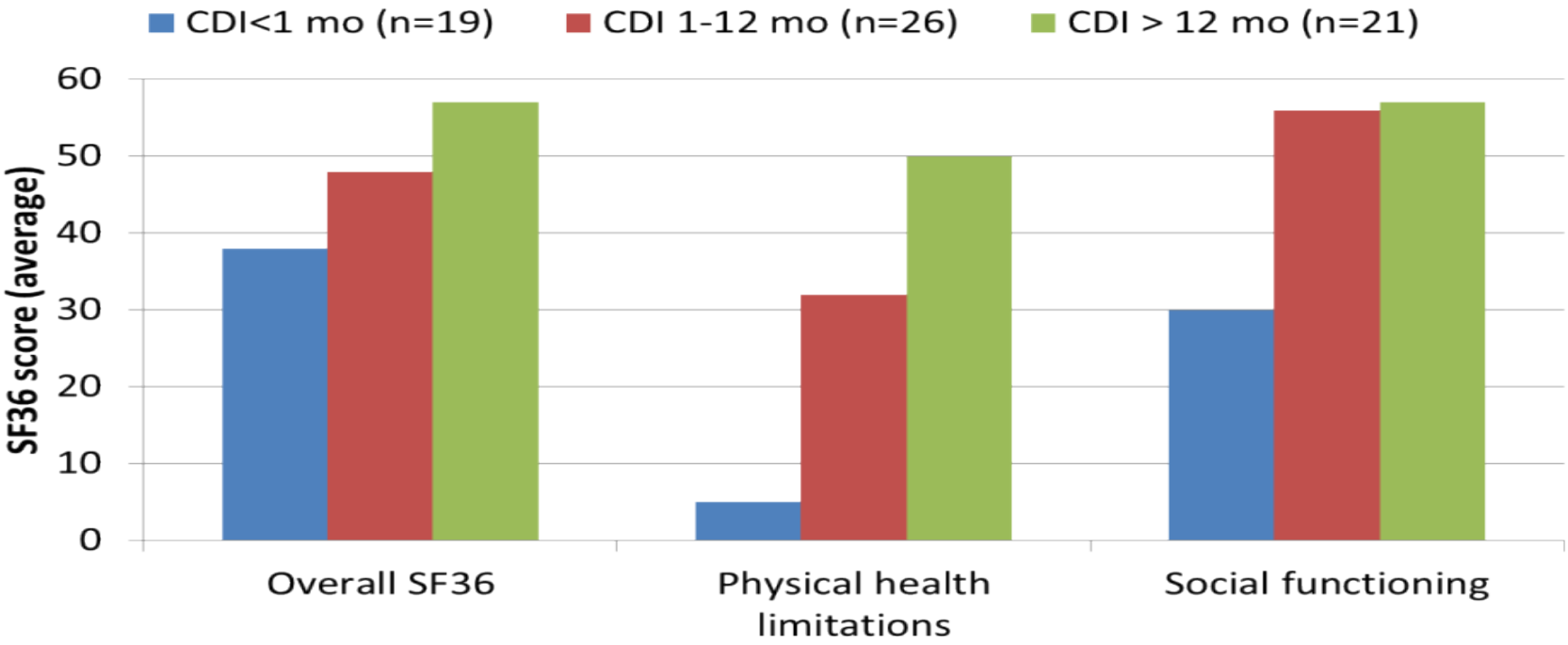
UK, 2012-13 : seven hospitals incorporated fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)



Goldenberg SD et al. *Eur J Clin Microbiol Infect Dis*. 2016; 35:251-9.

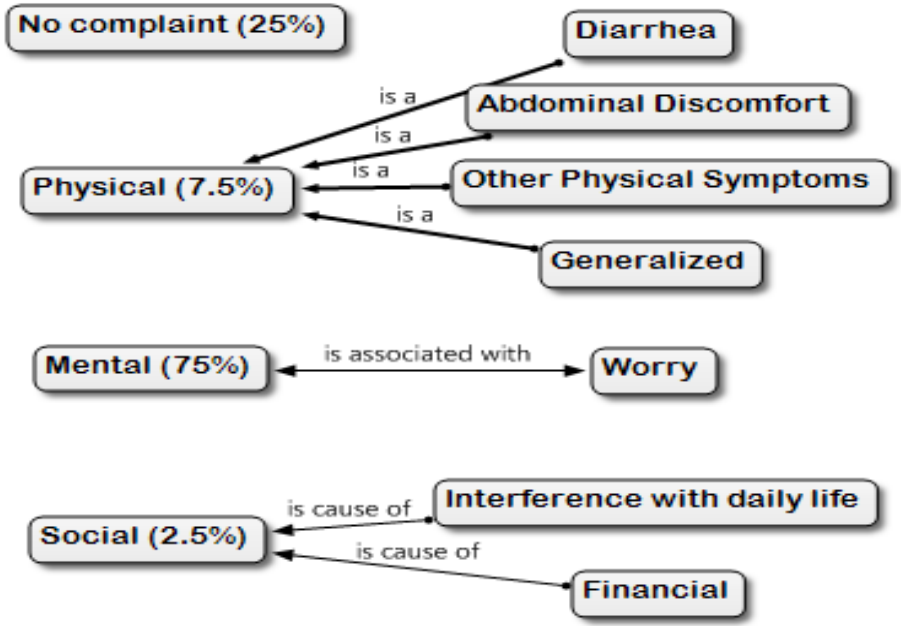
And last but not least, the patient perspective

I wonder if we are missing the most important endpoints?



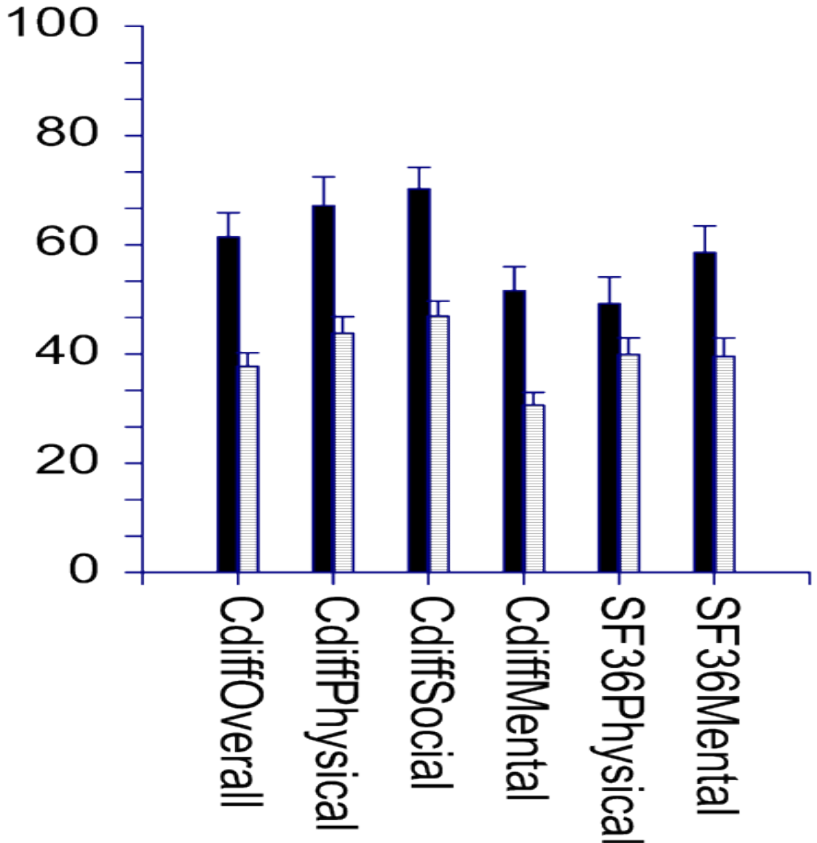
Aitken et al. ICAAC 2014 Poster #K-360, Sat, Sept 6, 2014.

The driver for decreased quality of life (QOL) is not so much physical as a worry/anxiety of transmissibility or symptom persistence



Goddu S, Bozorgui S et al. Presented at ISPOR 20th Annual International Meeting, Philadelphia, PA, May 2015.

Quality of Life (QOL) goes down considerably with recurrent CDI



Primary or recurrent CDI

Primary
Recurrent

Garey et al. *J Clin Gastroenterol.* 2016; 50:631-7.

Patient perspective

"It was a little over a year ago I was diagnosed and treated with metronidazole, then treated again in April with vancomycin for it as tested positive again, and am 50 years old and otherwise healthy except for hypertension issues. I think I acquired it as a caretaker for my elderly mother (who has since passed away), and having antibiotics for dental issues. I wouldn't wish this illness on my worst enemy, and it's been a life changer for me."

Should fidaxomicin be used first-line?

Question	Answer	Why
Is fidaxomicin a superior drug?	Yes	Decreased recurrence rate by 50%
Is fidaxomicin a safer drug?	Yes	Decreased VRE colonization
Is fidaxomicin a more cost-effective drug?	Yes	Decreased hospitalization costs due to recurrent CDI
Is patient satisfaction higher if you don't have recurrence?	Yes	Significantly increased anxiety in patients with recurrent CDI

Kevin GAREY PRO – CON debate

- PRO Vancomycin

Vancomycin is remarkably effective at day 7-10 cure rates

Study years	Study drug	Comparator	Study phase	N	Clinical cure rate (%)		Recurrence rate (%)	
					Study drug	Vanco	Study drug	Vanco
<2005	Ramoplanin	Vancomycin	II	89	71	78		
2006-08	Fidaxomicin	Vancomycin	III	629	88	90	15	25
2007-09	Fidaxomicin	Vancomycin	III	535	88	87	13	27
2010-11	Surotomycin	Vancomycin	II	209	87-92	89	17-28	36
2012-15	Surotomycin	Vancomycin	III	608	79	84	18	23
2012-15	Surotomycin	Vancomycin	III	608	83	82		
2011-12	Cadazolid	Vancomycin	II	84	68-80	68	18-25	50
2011-12	LFF571	Vancomycin	II	72	85	80	31	30
2014-15	Ridinilazole	Vancomycin	II	100	78	70	14	35

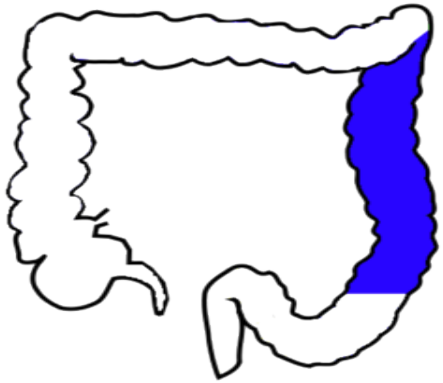
Basseres et al. *Curr Opin Gastroenterol*. 2017; 33:1-7

I would use vancomycin routinely if:

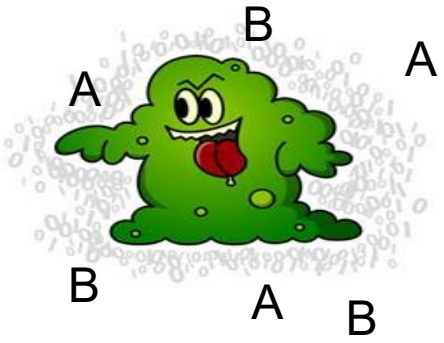
- I could get the recurrence rate similar to fidaxomicin or other ‘newer’ antibiotics
- Is this possible?

- (I’m ignoring the VRE overgrowth stuff)

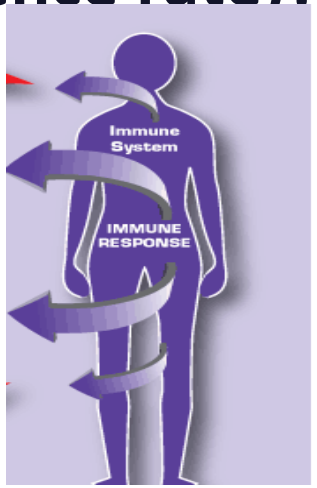
Can we use our knowledge of CDI treatment goals to better use vanco (aka, drop recurrence rate)?



Current: Can we combine with a probiotic



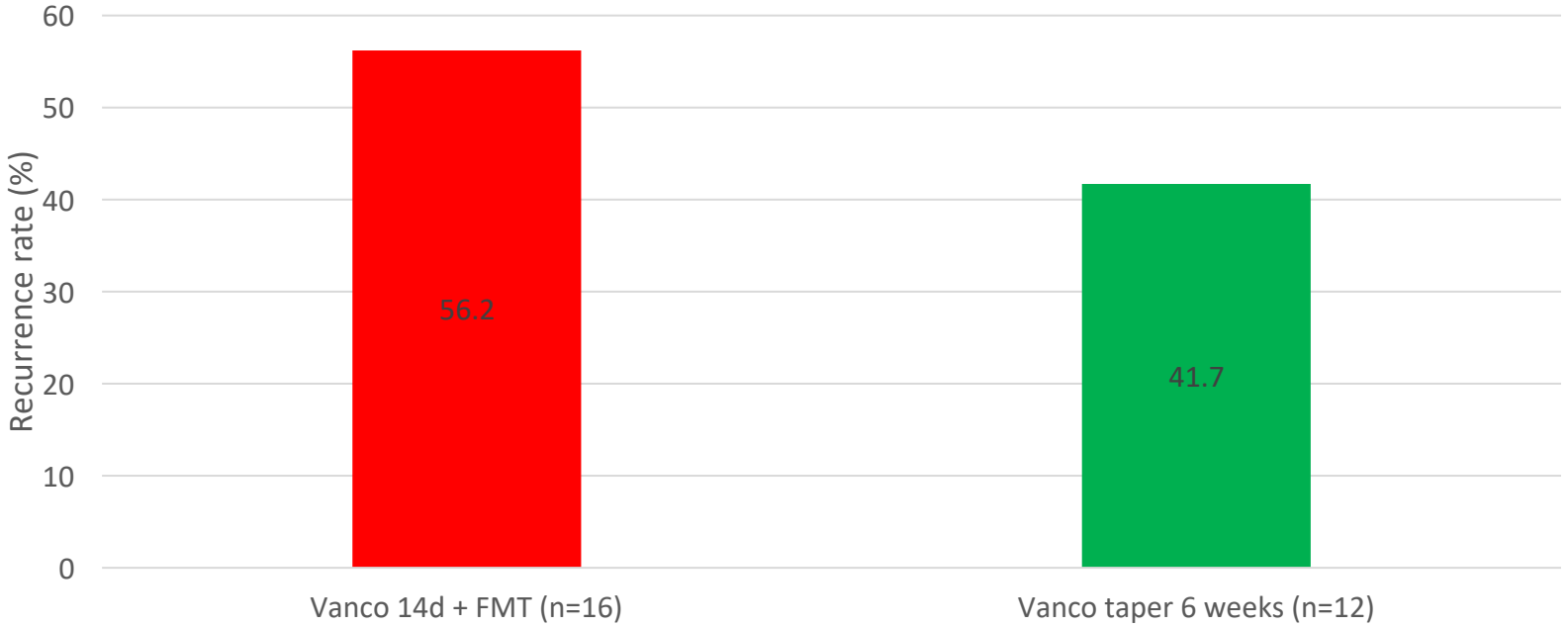
Are there novel ways to use vanco?



Vanco + immune stimulation?

Six week taper of vanco was as good as an FMT enema

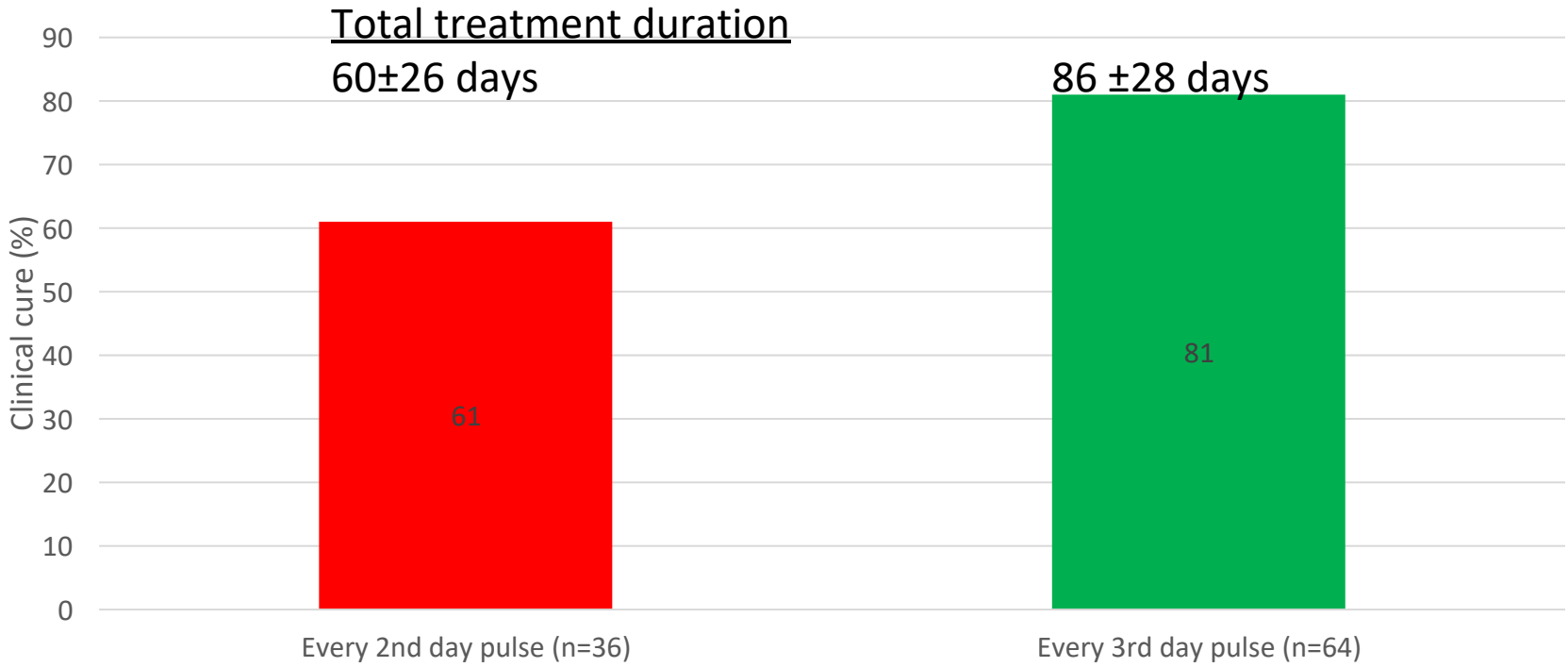
Ontario, Canada. Patients experiencing recurrent CDI randomized to standard course vanco + FMT enema vs. vanco taper regimen (6 weeks)



Early termination at interim analysis

Hota et al. *Clin Infect Dis*. 2017; 64:265-71.

Possibility #1: Extend out the pulse taper regimen to every 3rd day



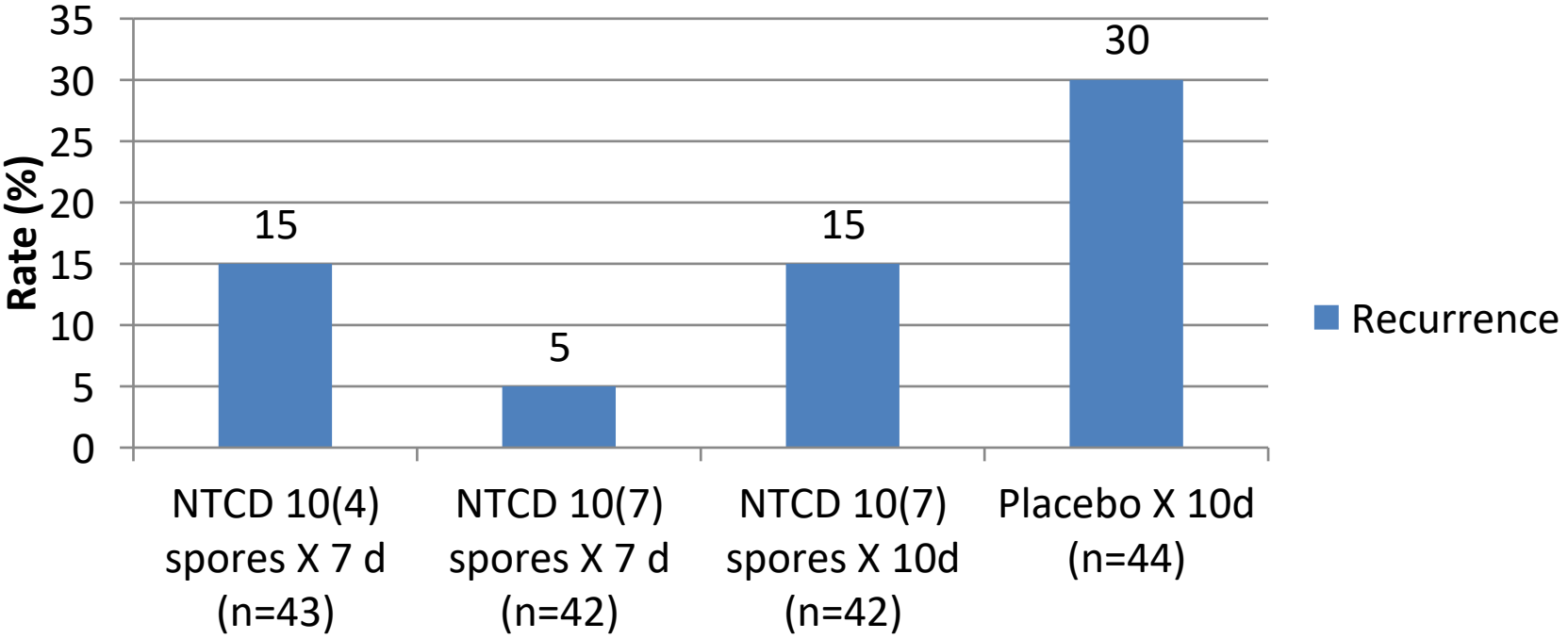
Chicago, IL: 100 patients with recurrent CDI treated with vanco pulse taper regimen

Sirbu et al. *Clin Infect Dis*. 2017; 65:1396-9.

Possibility #2: Use a probiotic

Non-toxigenic *C. diff* (NTCD): phase II study

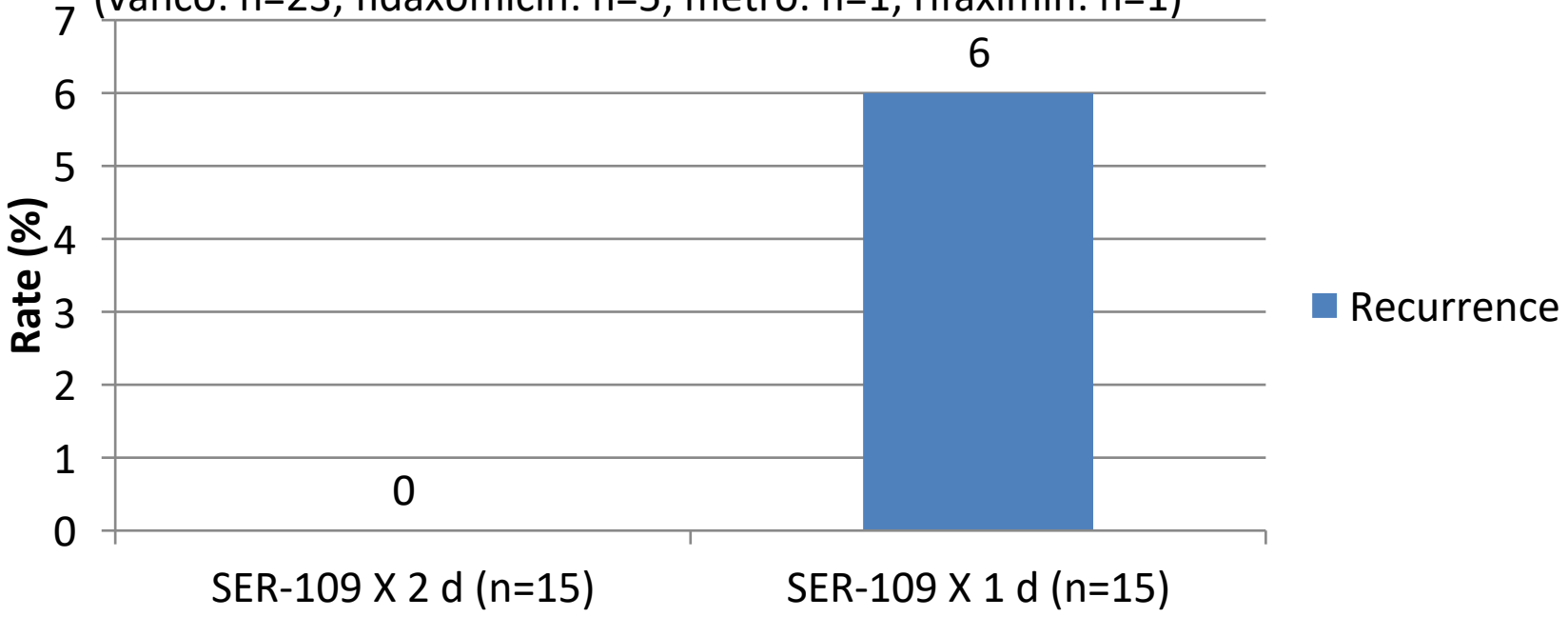
CDI patients given NTCD or placebo immediately after finishing antibiotic therapy
(metro only: 53-60%; vanco only: 14-32%; metro+vanco: 12-26%)



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

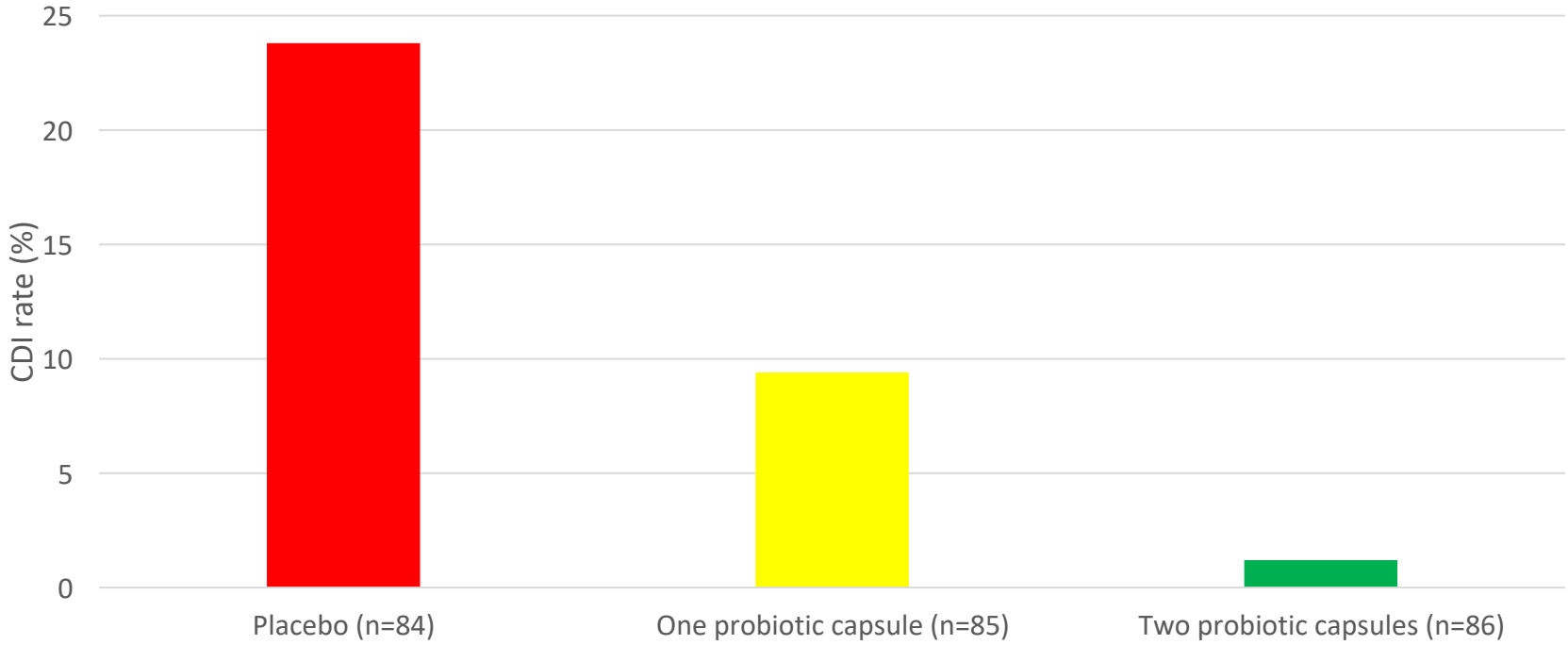
SER-109. Fractionated and encapsulated spores from healthy donor stools

CDI patients given SER-109 immediately after finishing antibiotic therapy
(vanco: n=23; fidaxomicin: n=5; metro: n=1; rifaximin: n=1)



Khanna et al. *J Infect Dis*. 2016; 214:173-81.

A probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R decreased CDI rates



Gao et al. *Am J Gastroenterol*. 2010; 105:1636-41.

Protocol utilizing a staggered and tapered antibiotic regimen for the treatment of recurrent *Clostridium difficile* infection that has failed to respond to standard antibiotic therapy.

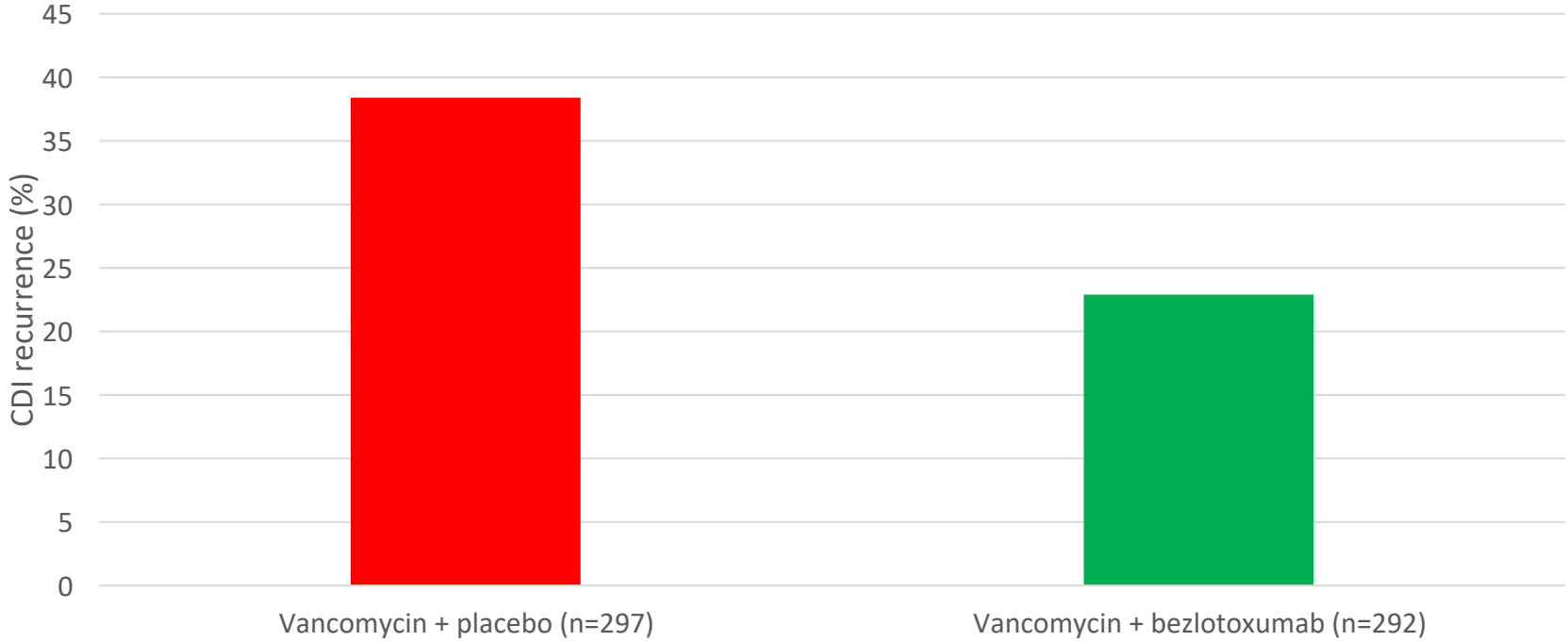
25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

Antibiotic Time Course	Metronidazole Dose/Frequency		Vancomycin Dose/Frequency		Kefir
Weeks 1-2	250 mg Q 6h		125 mg Q 6h		150 mL TID
Weeks 3-4	750 mg Q 72h		375 mg Q 72h		150 mL TID
Weeks 5-6	500 mg Q 72h	OR	250 mg Q 72h	PLUS	150 mL TID
Weeks 7-8	250 mg Q 72h		125 mg Q 72h		150 mL TID
Weeks 9-15					150 mL TID

Bakken JS. *Clin Infect Dis*. 2014; 59:858-61.

Possibility #3: Improve antibody response

Combined phase III clinical trial results of bezlotoxumab in patients who received vancomycin as standard therapy



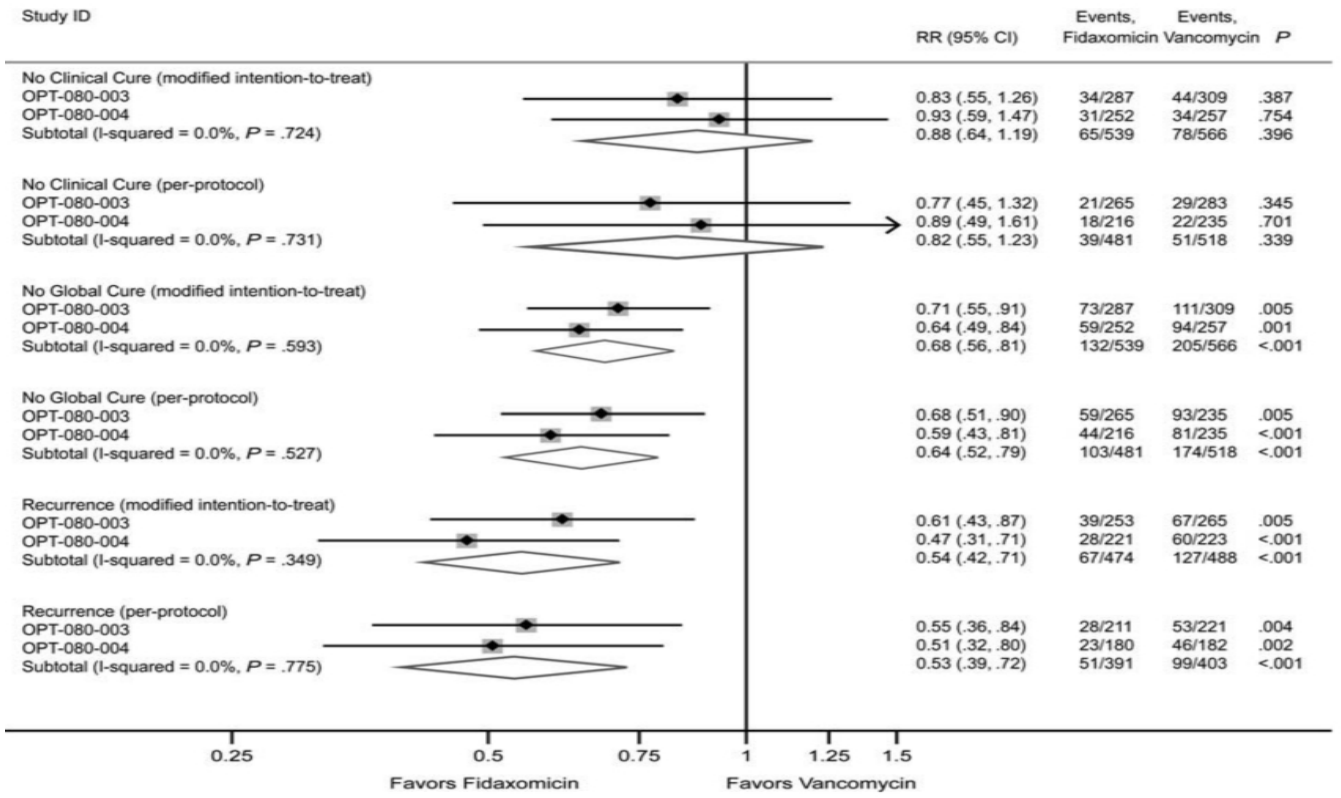
Dubberke et al. ID-week 2017.

Should vancomycin be used first line?

- Remarkably effective for initial clinical cure
- Decades of experience, has withstood the tests of time
- With a little creativity, can lower recurrence rates similar to what is observed with fidaxomicin

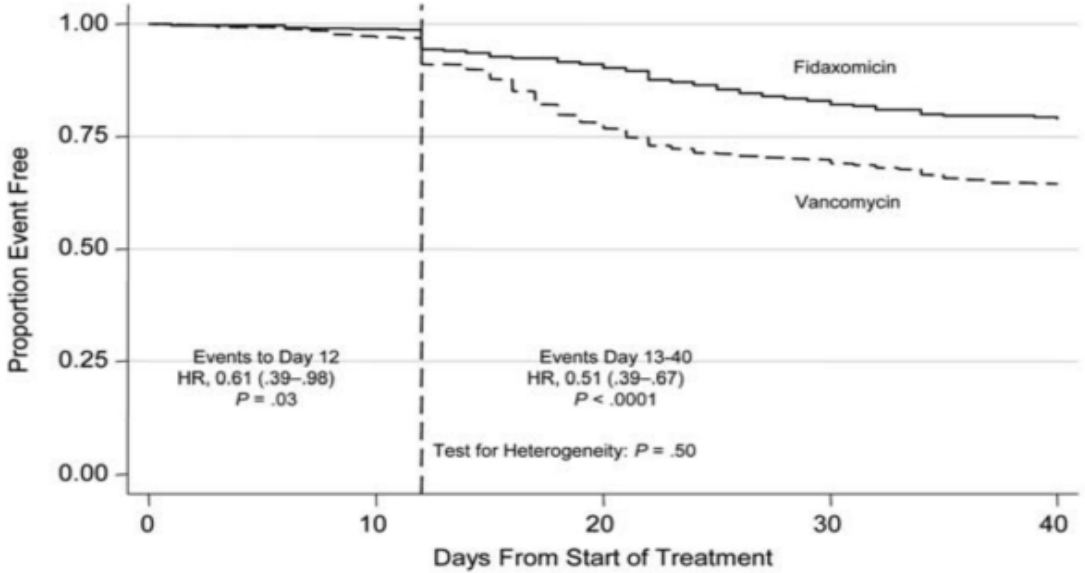
A. KRISHNA RAO
PRO FIDAXOMICIN

Fidaxomicin: clinical trials



Crook DW et al. *Clin Infect Dis*. 2012; 55(Suppl 2):S93-103.

Fidaxomicin: clinical trials

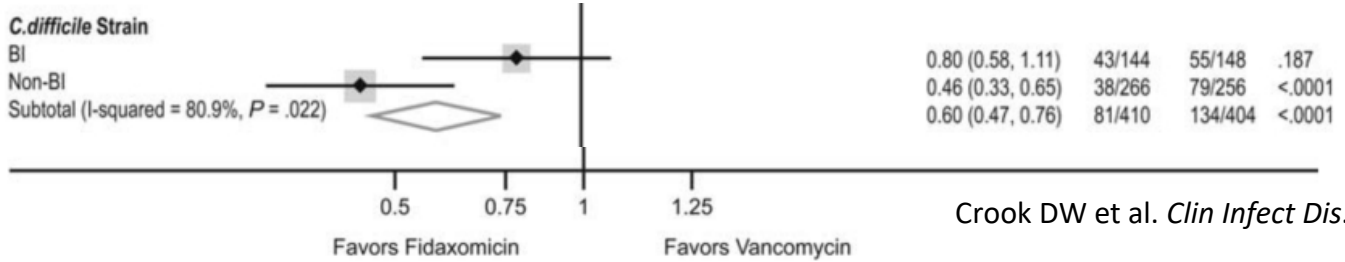


Number at Risk	(events)								
Fidaxomicin	572	(6)	515	(41)	472	(42)	427	(21)	405
Vancomycin	592	(14)	527	(104)	416	(44)	365	(27)	334

Note: Patients first assessed for persistent diarrhea 8 to 12 days after start of treatment: those with diarrhea considered as events on day 12.

Crook DW et al. *Clin Infect Dis*. 2012; 55(Suppl 2):S93-103.

Fidaxomicin: strain specific benefit?



Crook DW et al. *Clin Infect Dis*. 2012; 55(Suppl 2):S93-103.

- Reduced relapse (HR 0.40 [.25–.66]; *P* = .0003)
- Reduced reinfection (HR 0.33 [0.11–1.01]; *P* = .05)

Eyre DW et al. *J Infect Dis*. 2014; 209:1446-51.

Fidaxomicin for the critically ill?

- Penziner et al. 2014:
  - 30 patients on the wards compared with 20 in ICUs
  - All received fidaxomicin for CDI

TABLE 2 Factors associated with probability of lack of fidaxomicin treatment response

Characteristic	No. (%) of patients with: Treatment failure ($n = 18$)	Treatment response ($n = 32$)	Univariate, OR (95% CI); P value[a]	Multivariate, OR (95% CI); P value
Age > 60 yr	14 (77.8)	14 (43.8)	4.5 (1.21–16.72); 0.04	4.7 (0.9–23.4); 0.06
CDI due to NAP1 strain	10 (55.6)	11 (35.5)	2.3 (0.69–7.44); 0.3	1.5 (0.36–6.55); 0.6
Severe and severe complicated CDI	13 (72.2)	11 (34.4)	4.9 (1.4–17.56); 0.02	5.1 (1.02–25.46); <0.05
Fever when fidaxomicin therapy commenced	5 (27.8)	3 (9.4)	3.7 (0.77–17.94); 0.1	2.6 (0.27–25.48); 0.4
Fidaxomicin in combination with other anti-CDI drugs[b]	11 (61.1)	7 (21.9)	5.6 (1.58–19.87); 0.014	4.9 (0.95–25.43); 0.06
CCU level of care during fidaxomicin treatment	8 (44.4)	12 (37.5)	1.3 (0.412–4.31); 0.8	0.8 (0.12–3.74); 0.6

[a] OR, odds ratio; CI, confidence interval.

[b] Including metronidazole ($n = 9$), oral vancomycin ($n = 4$), or both ($n = 5$).

Fidaxomicin: the microbiota

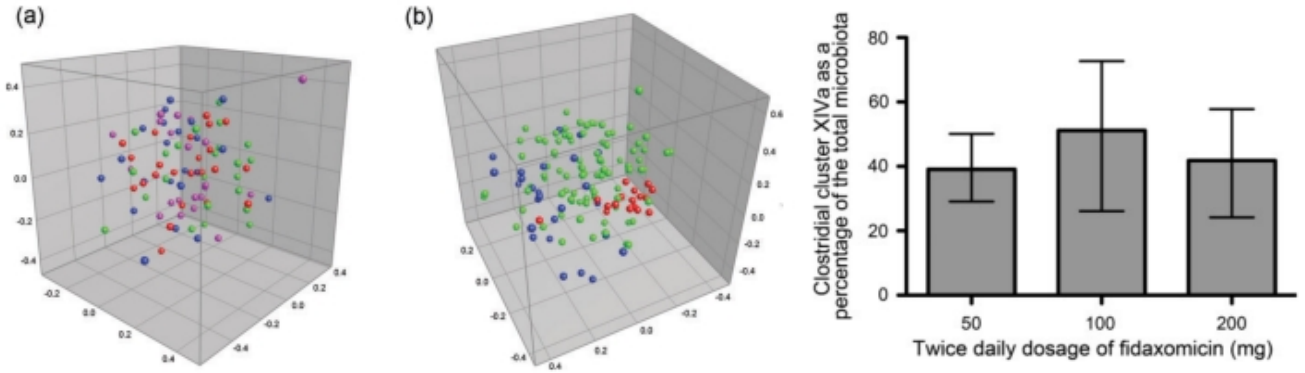


Table 1. Quantification of *Enterococcaceae–Lactobacillaceae* (probe Lab158) as a proportion of the total faecal microbiota

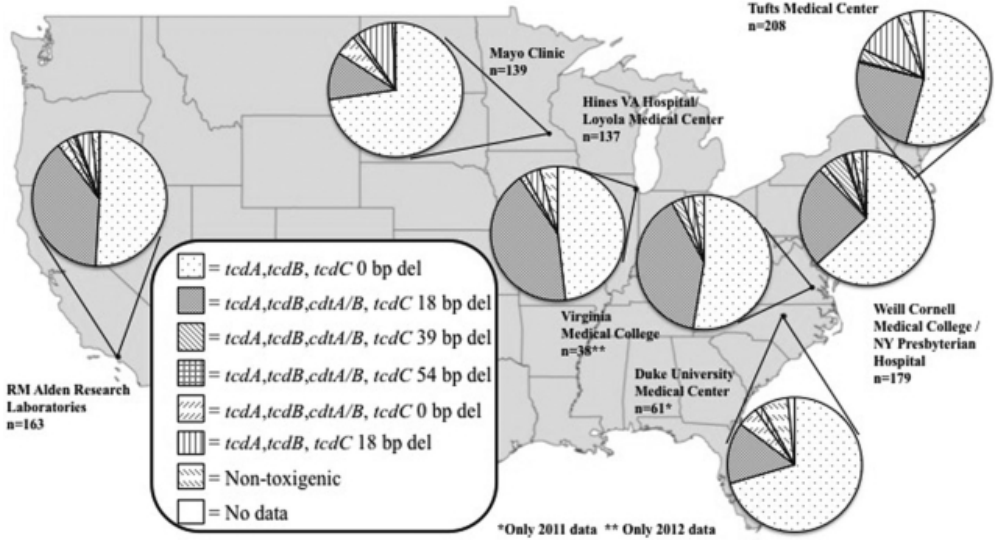
Data are means ± SE of percentage values. ND, No samples; NA, not applicable.

Treatment	Percentage of total faecal microbiota on day:			
	0	7	10	21
Fidaxomicin	4.06 ± 1.37	5.93 ± 2.03	6.40 ± 2.36	7.96 ± 3.18
Vancomycin	6.04 ± 2.66	ND	27.27 ± 4.53	18.68 ± 6.23
None (healthy controls)	4.72 ± 1.50	NA	NA	NA

Tannock GW et al. *Microbiology*. 2010; 156(Pt 11):3354-9.

Fidaxomicin: no resistance…yet

- Snydman et al. 2015
  - 7 geographically dispersed medical centers 2011-2012
  - 925 isolates
  - MIC90 ≤ 0.5 µg/mL across regions and over 1 year after licensure



Snydman et al. *Antimicrob Agents Chemother.* 2015; 59:6437-43.

Fidaxomicin: cost-effective? probably...

- Bartsch et al. 2013
  - Incremental cost-effectiveness ratio (ICER) >$43.7 million per quality-adjusted life year (QALY)
  - Assuming 50% ribotype 027, not cost-effective until ≤$150 per course
- Stranges et al. 2013
  - ICER $67,576 per QALY
  - Simulation: 80% chance of being cost-effective at $100K threshold
- Nathwani et al. 2014
  - ICER £16, 529 ($23,952) per QALY for severe CDI
  - Dominant (more effective & less costly) for 1st recurrence
  - Simulation: 60% probability of cost-effectiveness for severe CDI and 68% for first recurrence at £30 000 threshold

Bartsch et al. *J Antimicrob Chemother*. 2014; 69:2901-12; Stranges et al. *Value Health.* 2013; 16:297-304; Nathwani et al. *Clin Infect Dis.* 2013; 57:555-61.

Fidaxomicin: Overview

- Narrow spectrum, non-absorbable antibiotic
- Studied for 1st or 2nd episode
- Noninferior to vancomycin for cure[1]
- 50% reduction in recurrent CDI[1]
- Possible role at the end of a taper (chaser) in place of rifaximin[2]

[1] Crook DW et al. *Clin Infect Dis*. 2012; 55(Suppl 2):S93-103.
[2] Johnson AP and Wilcox MH. *J Antimicrob Chemother*. 2012; 67(12):2788-92.

A. KRISHNA RAO
PRO VANCOMYCIN

Fidaxomicin is too expensive

- Outpatients:
  - Fidaxomicin cost is over $2000 out of pocket in most settings
  - There are still many insurers that will not cover it without prior authorization / failure of other agents
  - There is a coupon program but many patients do not qualify for it
- Inpatients:
  - Too costly to keep on most formularies without restriction
  - Many programs restrict only to failures / multiple recurrences (less evidence in this setting)
  - There is a special incentive through CMS: new technology add-on payment, but remaining cost is still over $1000
- Vancomycin oral can be compounded from the IV formulation
  - Resulting cost is essentially nominal for most insurers
- Even vancomycin oral tablets are usually several fold less expensive

Fidaxomicin is not necessarily cost effective at the individual hospital level

- Bartsch et al. 2013
  - Incremental cost-effectiveness ratio (ICER) >$43.7 million per quality-adjusted life year (QALY)
  - Assuming 50% ribotype 027, not cost effective until ≤$150 per course
- Stranges et al. 2013
  - ICER $67,576 per QALY
  - Simulation: 80% chance of being cost-effective at $100K threshold
- Gallagher et al. 2015
  - Fidaxomicin costs totaled $62,112
  - Vancomycin costs totaled $6,646
  - Hospital lost $3,286 per fidaxomicin-treated patient and $6,333 per vancomycin-treated patient
  - However, savings depend on local epidemiology and rates of recurrence, readmission to the same facility

Bartsch et al. *J Antimicrob Chemother*. 2014; 69:2901-12; Stranges et al. *Value Health.* 2013; 16:297-304; Gallagher JC et al. *Antimicrob Agents Chemother*. 2015; 59 (11):7007-10.

Precision health is not mature enough to move away from vancomycin yet

- Cost is an issue but what if we could risk stratify people better?
- Severity/Complications? Nope

TABLE 4. Concordance of Severity Score Indices for Severe *Clostridium difficile* Infection

Index	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Kappa score (95% CI)
Beth Israel	63.2	87.3	36.4	95.4	0.38 (0.24–0.52)
UPMC version 1	68.4	93.9	56.5	96.3	0.57 (0.43–0.71)
University of Calgary version 1	68.4	90.3	44.8	96.1	0.48 (0.34–0.62)
Hines VA	73.7	93.4	70.0	97.0	0.69 (0.54–0.83)
Modified University of Illinois	84.2	59.4	19.3	97.3	0.18 (0.08–0.27)
University of Calgary version 2	73.7	72.7	23.7	96.0	0.24 (0.13–0.36)
UPMC version 2	73.7	88.5	42.4	96.7	0.47 (0.33–0.61)
University of Temple	68.4	71.5	21.7	95.2	0.20 (0.09–0.32)

NOTE. CI, confidence interval; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; UPMC, University of Pittsburgh Medical Center.

Fujiotani S et al. Infect Control Hosp Epidemiol. 2011; 32:220-8..

- Recurrence? Double nope.
  - Retrospective cohort
  - Entire VA 2006-2012
  - 56,273 CDI cases, 7446 rCDI
  - Overall results were not encouraging

	Hu (2009)		Zilberberg (2014)	
Predictor	Original	Modified	Original	Modified
Age	≥ 65 years		Continuous	
Acuity	Horn Index 3/4	90th %-ile of Charlson-Elixhauser	≥2 hospitalizations in the last 60 days	No Modification
Antibiotics	Any antibiotic after CDI diagnosis	Any antibiotics within 48 hours prior to CDI	Within 48 hours prior to CDI: Fluoroquinolones	No Modification
			High Risk Antibiotics: Cephalosporins, Clindamycin, Aminopenicillins	No Modification
Gastric Acid Suppressors	Not Included		New Onset Proton Pump Inhibitors and Histamine-2 receptor blockers within 48 hours of CDI	Any Proton Pump Inhibitor and Histamine-2 Receptor Blockers within 48 hours of CDI
Onset of CDI	Not Included		Community-Onset Healthcare Associated	No Modification
Model Performance (C-statistic)	0.89 Derivation / 0.62 Validation	0.55	0.64 Derivation / 0.63 Validation	0.71

Stevens et al., ID Week 2015.

Vancomycin is more versatile

1. Capsules that can be opened
2. Liquid formulation upon compounding the IV form
3. Varying doses from 125-500 mg
4. Used orally and can be infused rectally for ileus
5. Useful in severe AND complicated CDI

We have more evidence and experience with vancomycin

- Has been used for CDI for three decades now
- Non-inferior for cure compared with fidaxomicin
- Many edge cases have been tested
  - Severe, complicated with multiple recurrences
  - Immune compromised patients
- Can be given as a taper for recurrence and may be even better than FMT?
  - FMT no better than vancomycin taper in recent RCT[1] of acute CDI patients, although enema only
  - The authors on difference with prior RCTs not using a placebo control arm (emphasis mine):

    "Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free ***had their antibiotics been simply discontinued***."

[1]Hota SS et al. *Clin Infect Dis.* 2017; 64:265-71.

Audience response question (for rebuttal period only)

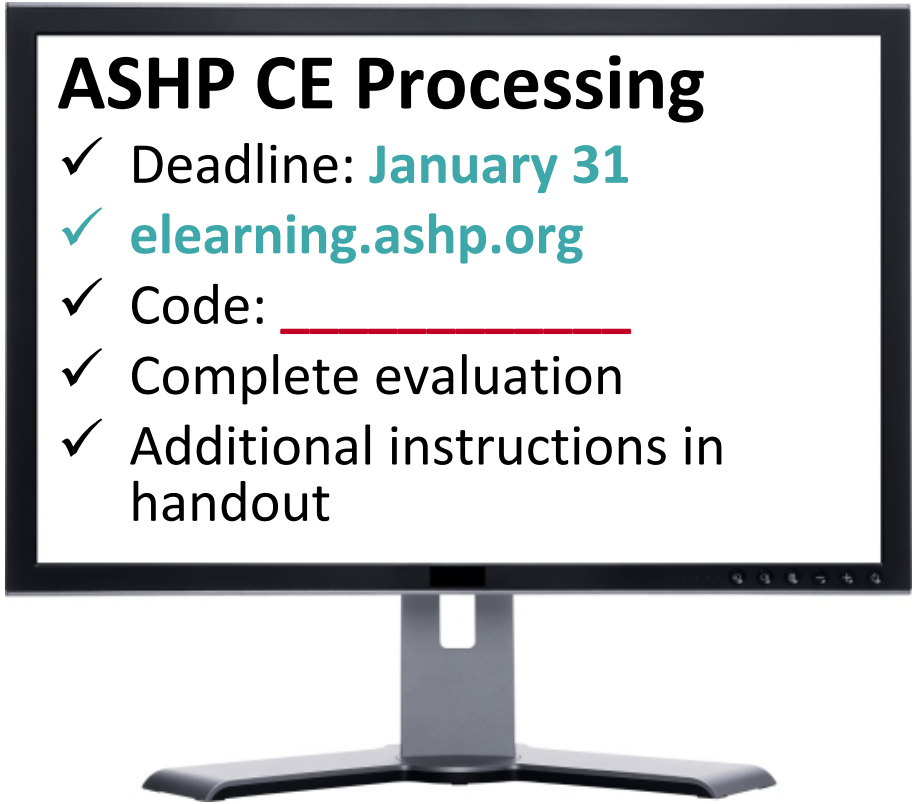
You are treating a 50-year-old man with his initial episode of CDI. He started fidaxomicin but by day 5 is not doing much better with continued diarrheal stools 7-10 times per day. Against the advice of your colleagues in ID, you sent a repeat test and it was positive for toxin A/B by ELISA again. What do you do next?

a. Continue fidaxomicin and reassess in a couple of days
b. Stop fidaxomicin and start vancomycin 125 mg orally four times daily
c. Stop antibiotics and move to fecal transplant
d. Send for endoscopy to look for alternative diagnoses

Which of these practice changes will you consider making?

- Discuss with colleagues the disease burden of CDI
- Educate staff on the emerging and current treatment options for managing patients with CDI
- Incorporate most current evidence-based guidelines into practice when treating patients with CDI
- Apply emerging evidence and treatment recommendations for managing patients with CDI
- Collaborate with other healthcare professionals to achieve optimal outcomes for preventing and treating patients with CDI

Thank You for Joining Us



Coming Soon

On-demand archive of today's presentation

- Available early March 2019

E-Newsletter

- Spring 2019

Download the handout at **www.ashpadvantage.com/cdiff/midyear**