Cost-effective Treatment of *Clostridium difficile* Infection in the ICU

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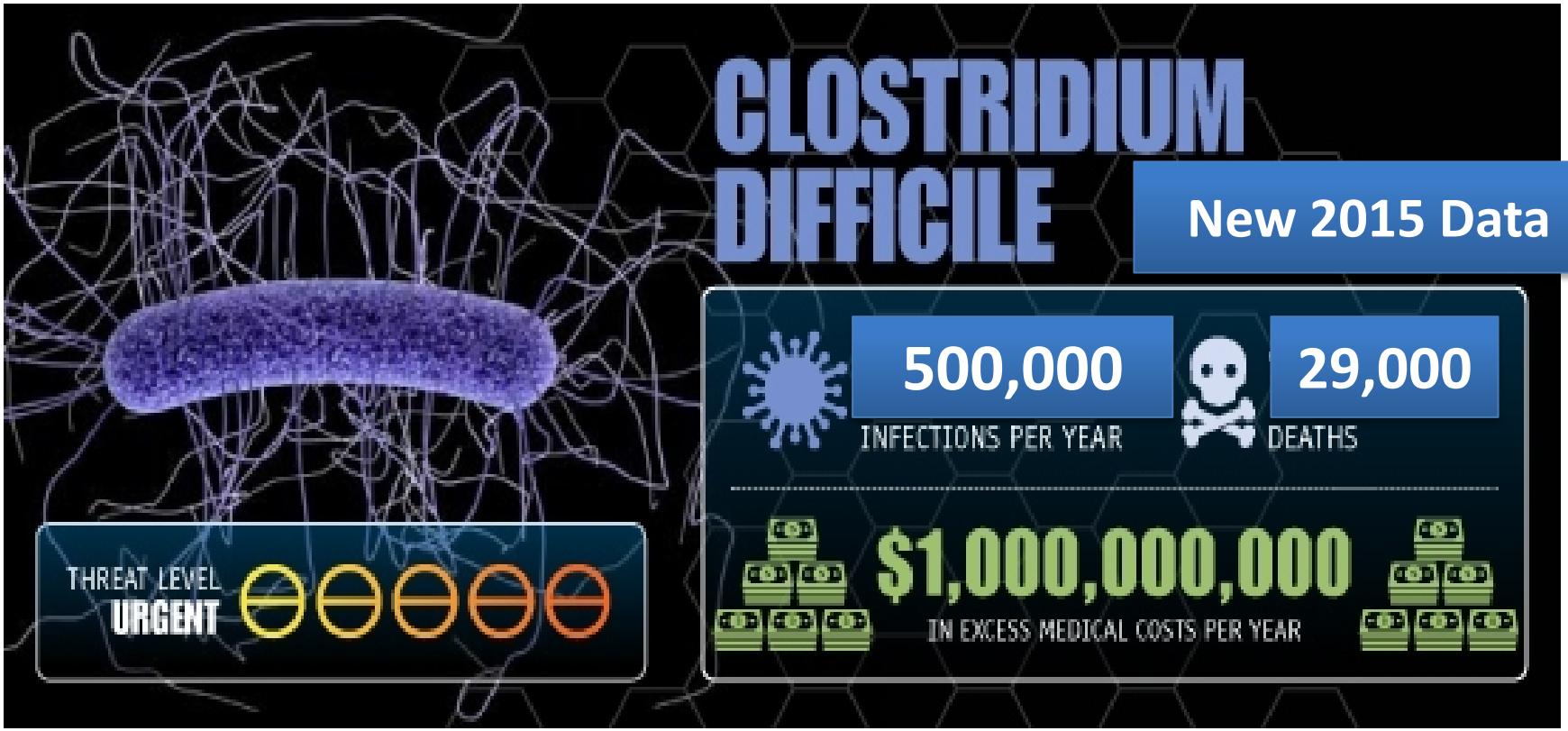


Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

Source: CDC Report "Antibiotic Resistance Threats in the United States, 2013"
Lessa CF et al. NEJM 2015;372:825-34.

Acknowledgements

- Research Funding:
  - Merck & Co
  - Summit PLC
  - Texas Department of State Health Services

Objectives

1. Discuss the epidemiology and presentation of *C. diff* in critically ill patients
2. Compare and contrast pharmacotherapy treatment options for *C. diff* based on efficacy, availability, and cost

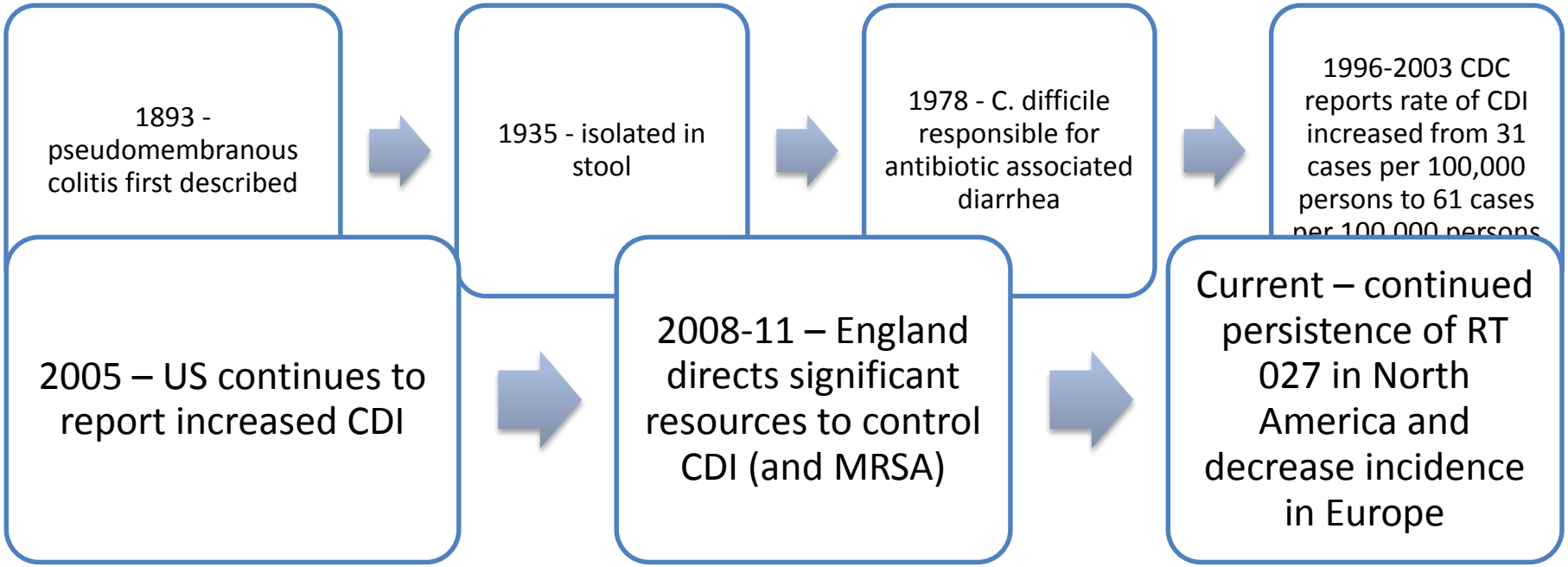
Learning assessment questions

- Learning Assessment Questions

- Which severity measure is associated with mortality?
  - Leukocytosis
  - Volume depletion due to diarrhea
  - Low albumin
  - All of the above

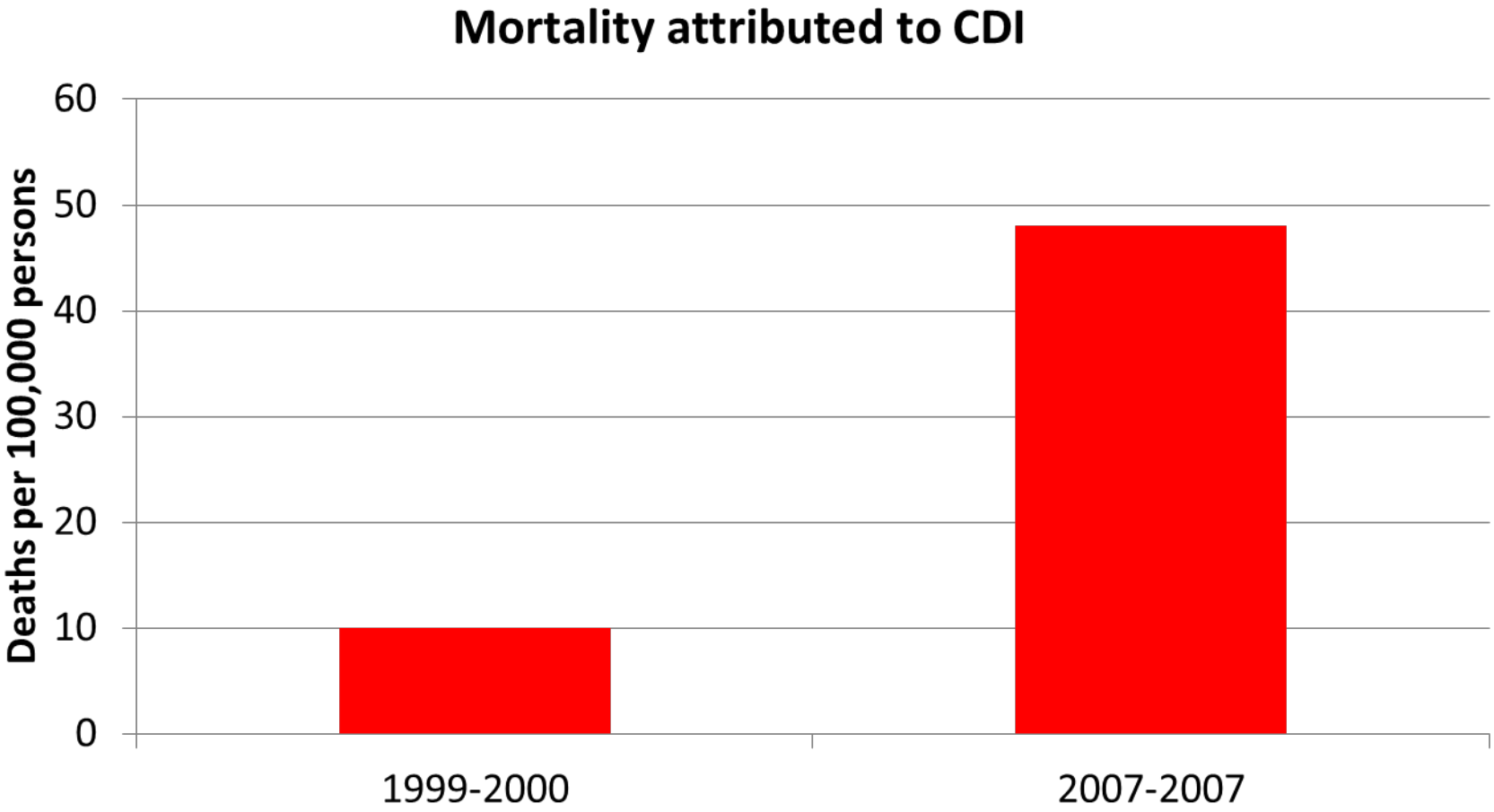
- Which of the following antibiotics should NOT be used in patients with severe CDI?
  - Metronidazole
  - Oral vancomycin
  - Fidaxomicin

A History of *C. difficile*



1. Heinlen L, Ballard JD. *Clostridium difficile* Infection. *The American journal of the medical sciences*. 2010;340(3):247-252. doi:10.1097/MAJ.0b013e3181e939d8.
2. The *Clostridium difficile* PCR ribotype 027 lineage: a pathogen on the move Valiente, E. et al. Clinical Microbiology and Infection , Volume 20 , Issue 5 , 396 - 404

C. difficile is the main contributor to gastroenteritis-associated deaths in the USA



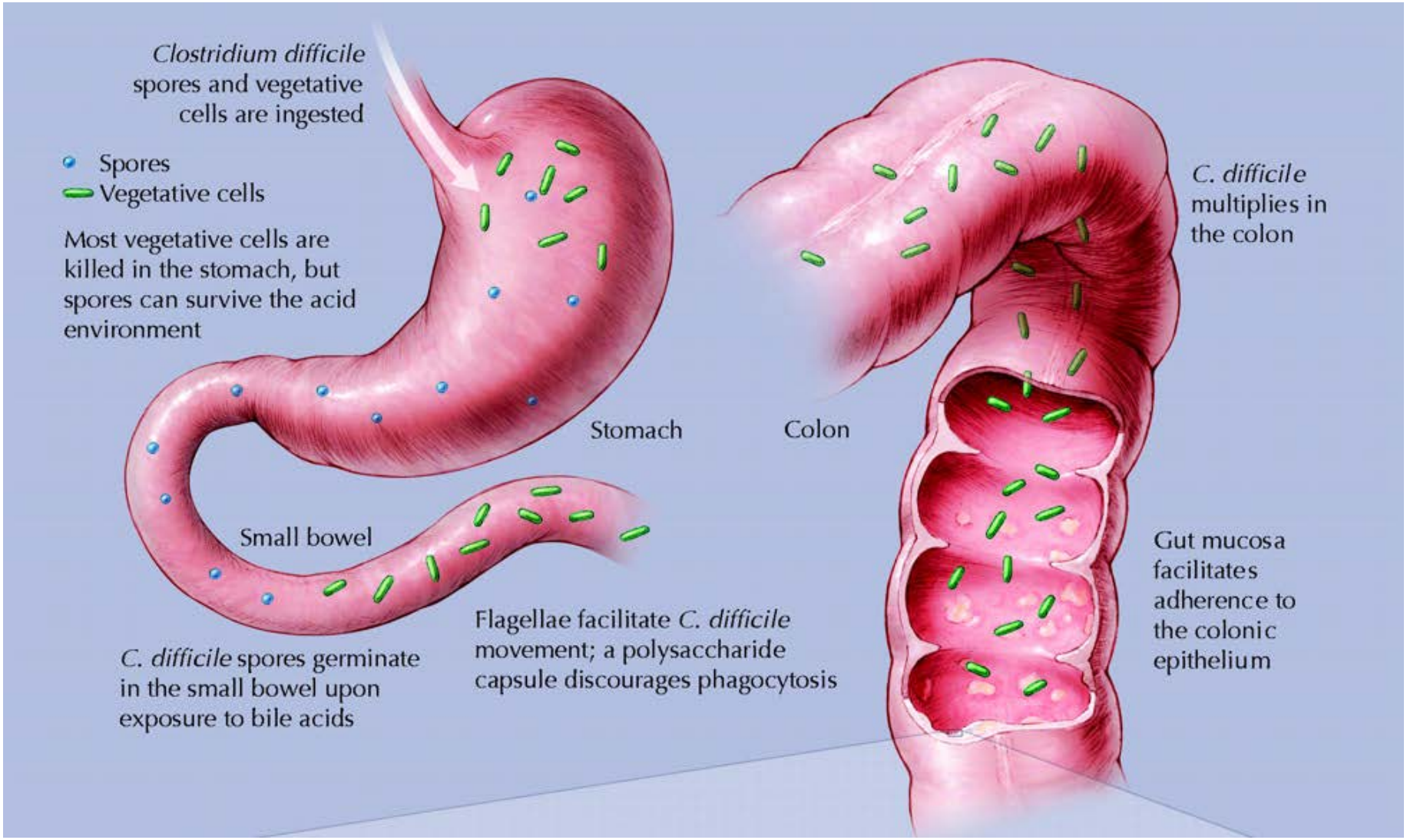
Analysis of National Center for Health Statistics (NCHS) multiple-cause-of-death mortality data for the years 1999–2007, a 5-fold increase in mortality attributed to CDI was noted

Hall et al. CID 2012;55:216-23

How did we get here?

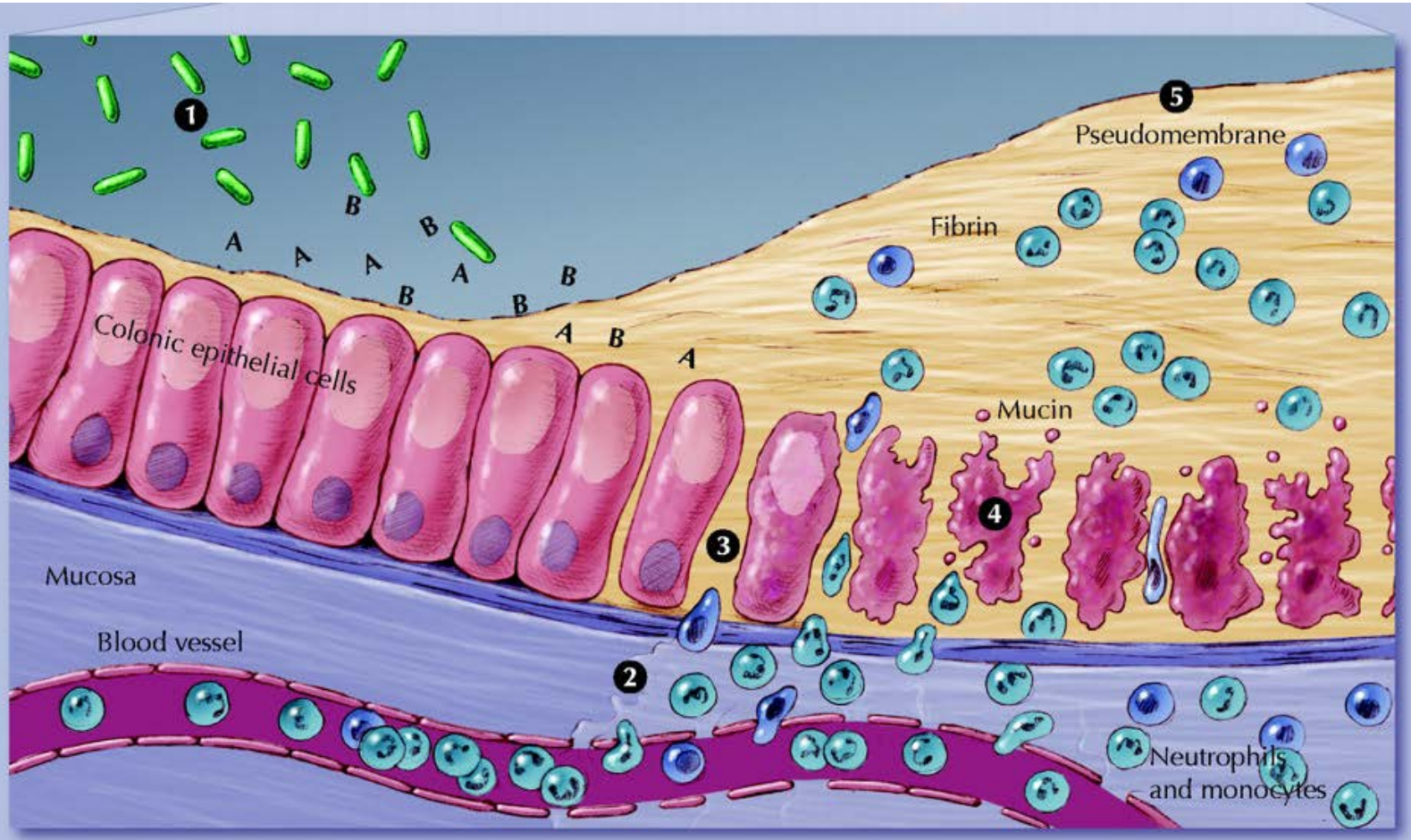
- Let's review a few key concepts on CDI to get everyone up to speed
  - Pathogenesis
  - Emergence of 'hypervirulent' strains

Pathogenesis of Clostridium difficile-associated diarrhea in adults



Poutanen, S. M. et al. CMAJ 2004;171:51-58

Pathogenesis of Clostridium difficile-associated diarrhea in adults



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.

Poutanen, S. M. et al. CMAJ 2004;171:51-58

Hypervirulent *C. difficile*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2005 VOL. 353 NO. 23

An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

L. Clifford McDonald, M.D., George E. Killgore, Dr.P.H., Angela Thompson, M.M.Sc., Robert C. Owens, Jr., Pharm.D., Sophia V. Kazakova, M.D., M.P.H., Ph.D., Susan P. Sambol, M.T., Stuart Johnson, M.D., and Dale N. Gerding, M.D.

Incidence of hypervirulent strains of *C. difficile*, 2005

Table 1. Isolates of *Clostridium difficile* According to Health Care Facility and the Proportion of Isolates Belonging to the BI/NAP1 Strain.

Health Care Facility	Date of Onset of Outbreak	No. of Isolates Tested	BI/NAP1 Strain
			no. (%)
Georgia	Oct. 2001	46	29 (63)
Illinois	July 2003	14	6 (43)
Maine, Facility A	March 2002	13	9 (69)
Maine, Facility B	July 2003	48	30 (62)
New Jersey	June 2003	12	9 (75)
Oregon*	April 2002	30	3 (10)
Pennsylvania, Facility A	2000–2001	18	7 (39)
Pennsylvania, Facility B	Oct. 2003	6	3 (50)
Total		187	96 (51)

* Isolates were not collected until after the peak of the outbreak.

McDonald et al. N Eng J Med 2005;353:2433-2441

Increasing mortality and complications due to CDAD

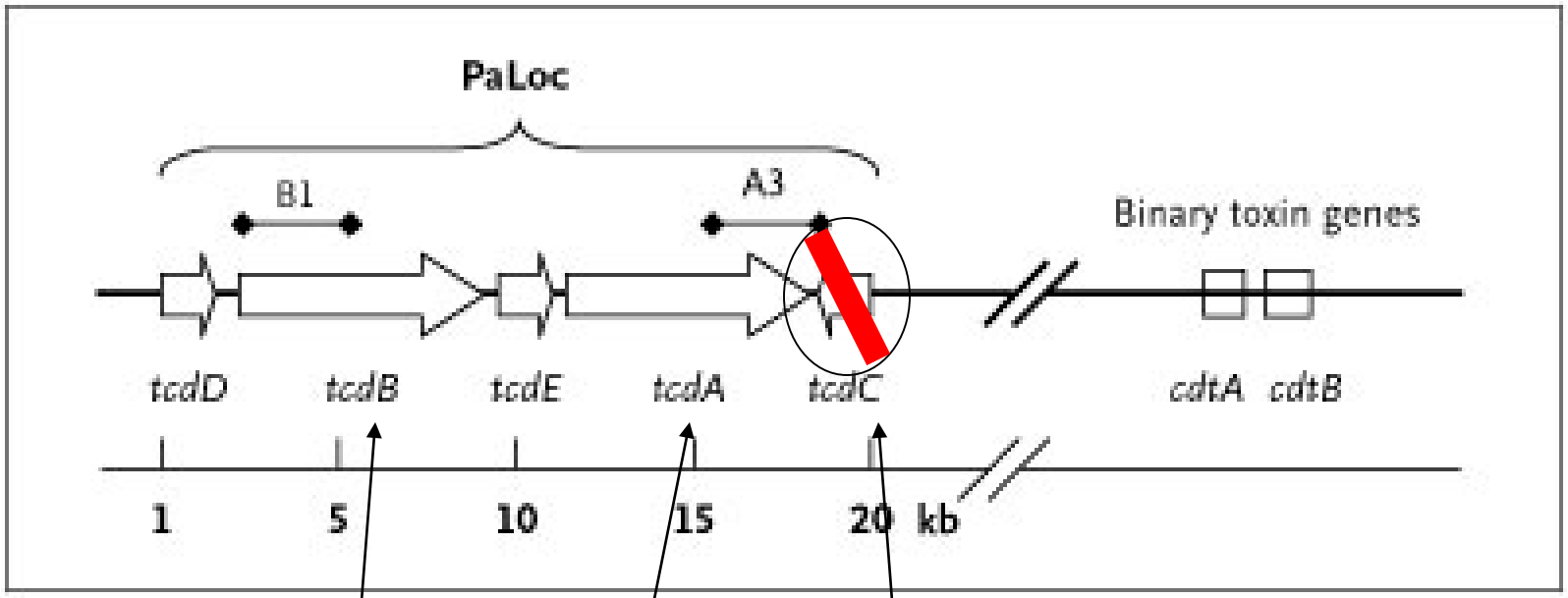
Table 1: Patients with *Clostridium difficile*-associated diarrhea (CDAD) in the Estrie region of Quebec who died within 30 days after diagnosis or who had complicated CDAD, 1991–2003

Period	No. of patients with CDAD*	No. (%) who died within 30 days after diagnosis	Adjusted OR (95% CI)†	No. (%) who had complicated CDAD‡	Adjusted OR (95% CI)†
1991–1992	169	8 (4.7)	1.0	12 (7.1)	1.0
1993–1994	217	11 (5.1)	1.7 (0.5–5.3)	14 (6.5)	1.0 (0.4–2.7)
1995–1996	215	13 (6.0)	1.6 (0.5–5.0)	17 (7.9)	0.9 (0.3–2.2)
1997–1998	192	11 (5.7)	1.1 (0.4–3.7)	13 (6.8)	0.6 (0.3–1.7)
1999–2000	248	19 (7.7)	1.5 (0.5–4.6)	28 (11.3)	1.2 (0.5–2.9)
2001–2002	244	21 (8.6)	1.6 (0.5–4.7)	28 (11.5)	1.1 (0.5–2.5)
2003	390	54 (13.8)	3.0 (1.1–8.4)	71 (18.2)	2.2 (1.0–4.9)
p value		< 0.001§	< 0.001¶	< 0.001§	0.001¶

Note: OR = odds ratio, CI = confidence interval.
*Includes only patients for whom enough information was available to assess these outcomes.
†Adjusted for age, sex, initial treatment, immune status, and tube feeding and surgery in the 2 months preceding diagnosis; 1991–1992 was used as the baseline period.
‡Presence of one or more of the following: megacolon, perforation, colectomy, shock requiring vasopressor therapy, death within 30 days after diagnosis.
§χ^2 test for trend.
¶χ^2 test, comparing 2003 with all other years.

Pepin, J. et al. CMAJ 2004;171:466-472

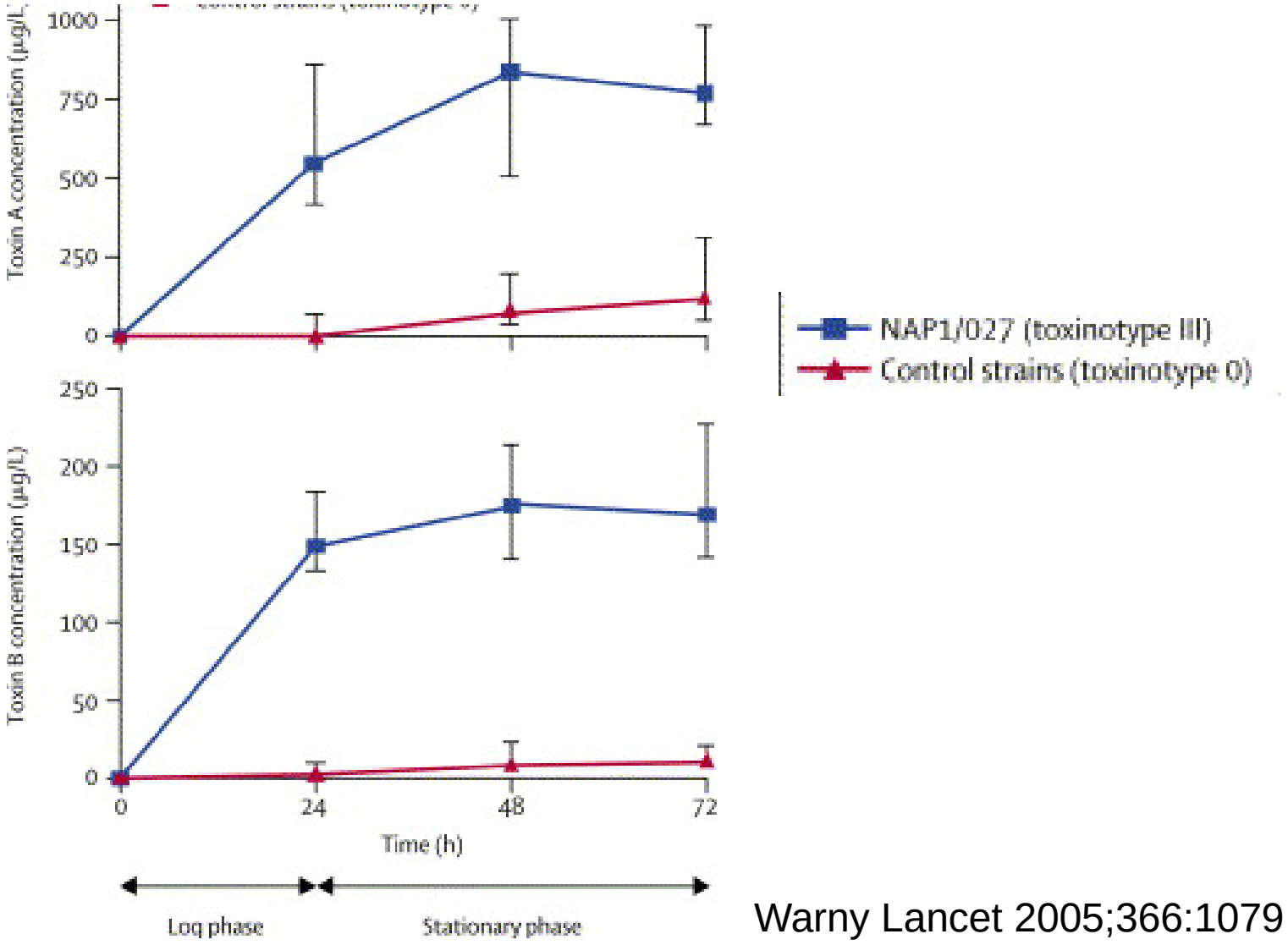
Toxins A and toxin B are produced in the Pathogenicity Locus (PaLoc) of *C. difficile*



tcdC deficient strain = Lots more production of toxins A and B!

McDonald et al. N Eng J Med 2005;353:2433-2441

Time course of toxin production by hypervirulent strain compared to control



Warny Lancet 2005;366:1079

Who you calling “hypervirulent”

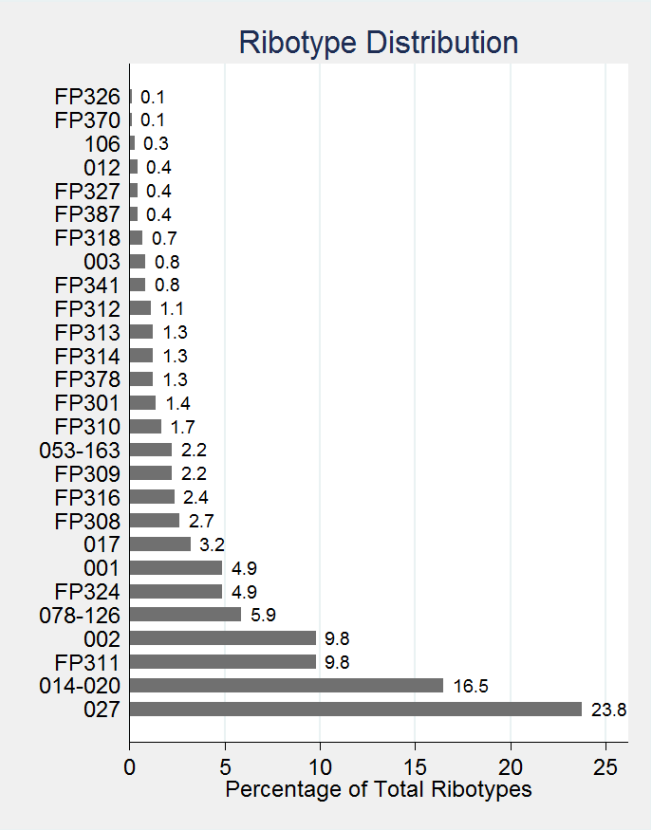
Michigan: Derivation (n=310/34 severe) and validation (n=433/45 severe) of predictors of severe CDI (ICU admission, colectomy, or death). After accounting for disease presentation severity, ribotype did not predict outcome

Predictor[a]	**Derivation OR (95% CI)**	**P Value**	**Validation OR (95% CI)**	**P Value**
Hypervirulent ribotype:				
027/078 vs non-027/078 (reference)	0.82 (.07–10.0)	.874	1.34 (.53–3.16)	.516
White blood cell count: Leukocytosis (>12 000 cells/mL) or leukopenia				
(<4000 cells/mL) vs normal (reference)	4.27 (1.14–19.46)	.041	2.32 (1.07–5.18)	.035
Low albumin level (g/dL)	0.25 (.07–.77)	.025	0.47 (.25–.87)	.018

Walk et al. CID 2012;doi:10.1093/CID/CIS78

..and there are more ribotypes than just 027

A lot of ribotypes are associated with CDI



Many ribotypes are virulent, including 027

Ribotype	Severe CDI presentation	Severe CDI outcome
027 (n=170)	54.7%	18.9%
014-020 (n=118)	22.9%	4.2%
FP11 (n=70)	31.4%	8.6%
078-126 (n=42)	21.4%	9.5%
001 (n=35)	42.9%	8.6%
FP24 (n=35)	37.1%	22.9%
17 (n=23)	39.1%	17.4%
FP8 (n=19)	36.9%	10.5%
053-163 (n=16)	37.5%	6.25%
FP16 (n=16)	35.3%	11.8%
FP9 (n=16)	25.0%	18.8%

Aitken et al. ICHE 2015

So, why do you really have bad outcomes due to CDI?

Table 5 (European guidelines): Prognostic markers to determine severe CDI

Characteristic	SoR	Associated poor outcomes	Associated with	Associated with	Why?
Comorbidity	B	30-d mortality	Yes	Yes	Vulnerable population

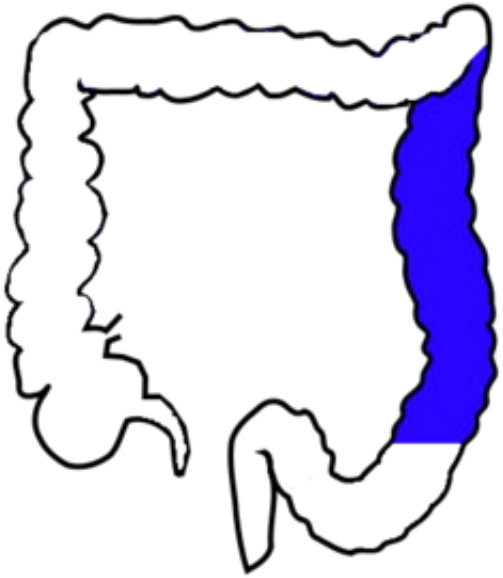
Major goal of treatment:

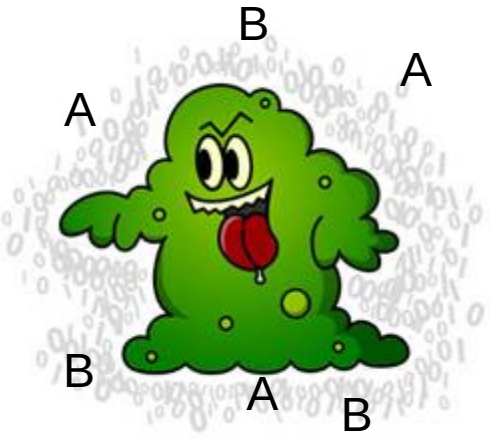
Stop the fluid loss (diarrhea) and make sure it doesn't come back!

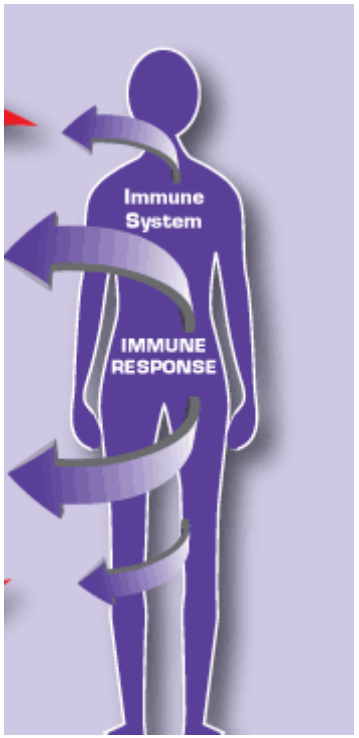
You are all now expert C diff ribotypers

- 027 is definitely a virulent ribotype
- …..but, there are lots of ribotypes that are equally virulent
  - Treat the patient, not the bug!
- Without a doubt, the ribotype 027 strain has put a large focus on the value of strain typing in *C. difficile*.
- Now, let's use some antibiotics!

Expanding treatment goals for CDI



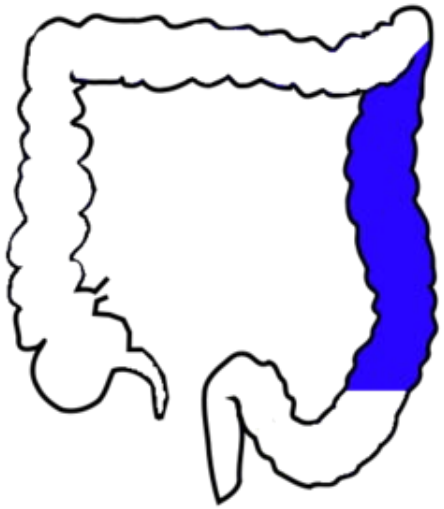


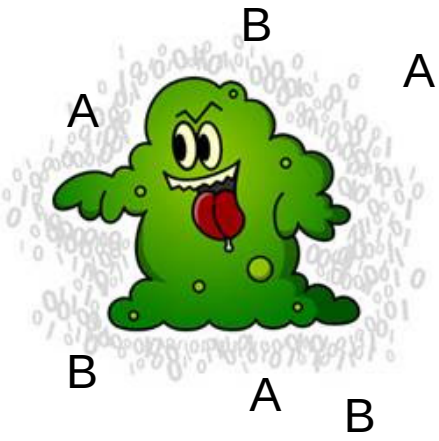


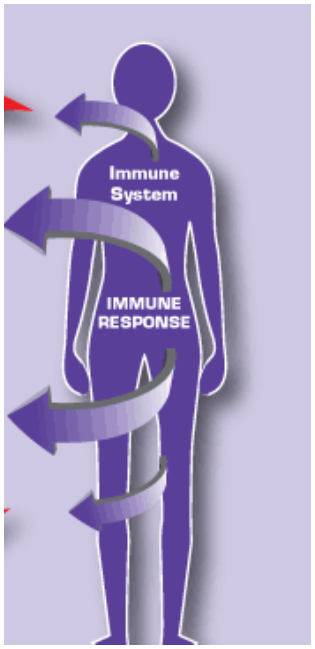
Essential:	Correct dysbiosis	Kill the organism	Adaptive immunity
Optional but nice:	Safe and convenient	Also affects toxins and spores	Short vs. long-term

Adamu and Lawley. Curr Opin Microbiol 2013

There has been an explosion in treatment possibilities for CDI







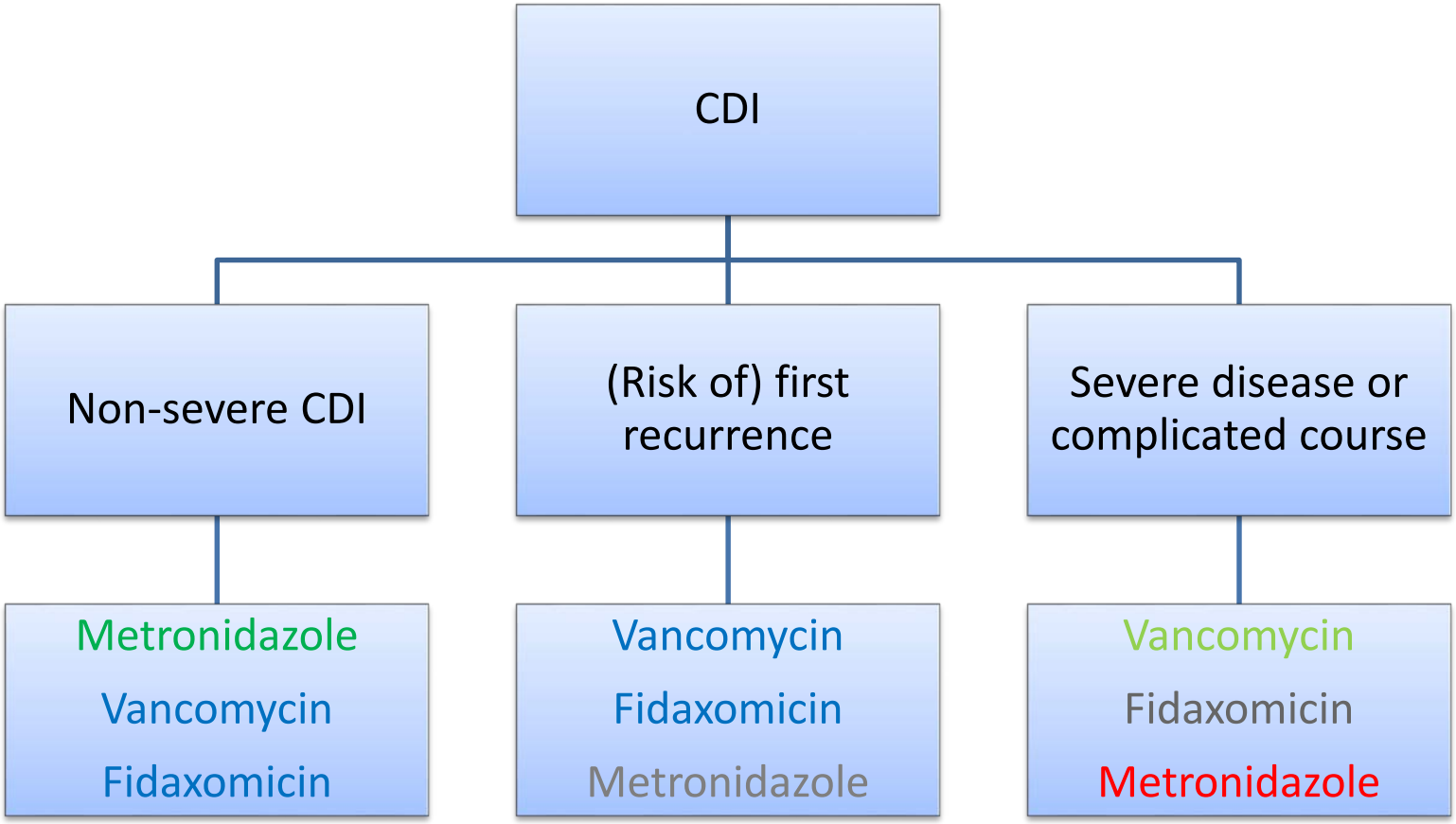
Current:	Probiotics FMT	Metronidazole Vancomycin Fidaxomicin	IVIG
Future:	2nd generation FMT non-tox C diff M3 Ecobiotics	Surotomycin Cadazolid SMT-19969	Monocloncal antibodies vs. C diff toxins Toxoid vaccines

Current US IDSA CDI guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC < 15,000 and SrCr < 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 SrCr ≥ 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 q8hours. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1^{st} recurrence)	----------	----------	Same as initial	Same as initial	A-II
Third (2^{nd} recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed	B-III

Cohen SH, Gerding DN, et al. Infection control and hospital epidemiology. 2010 (May); 31(5)

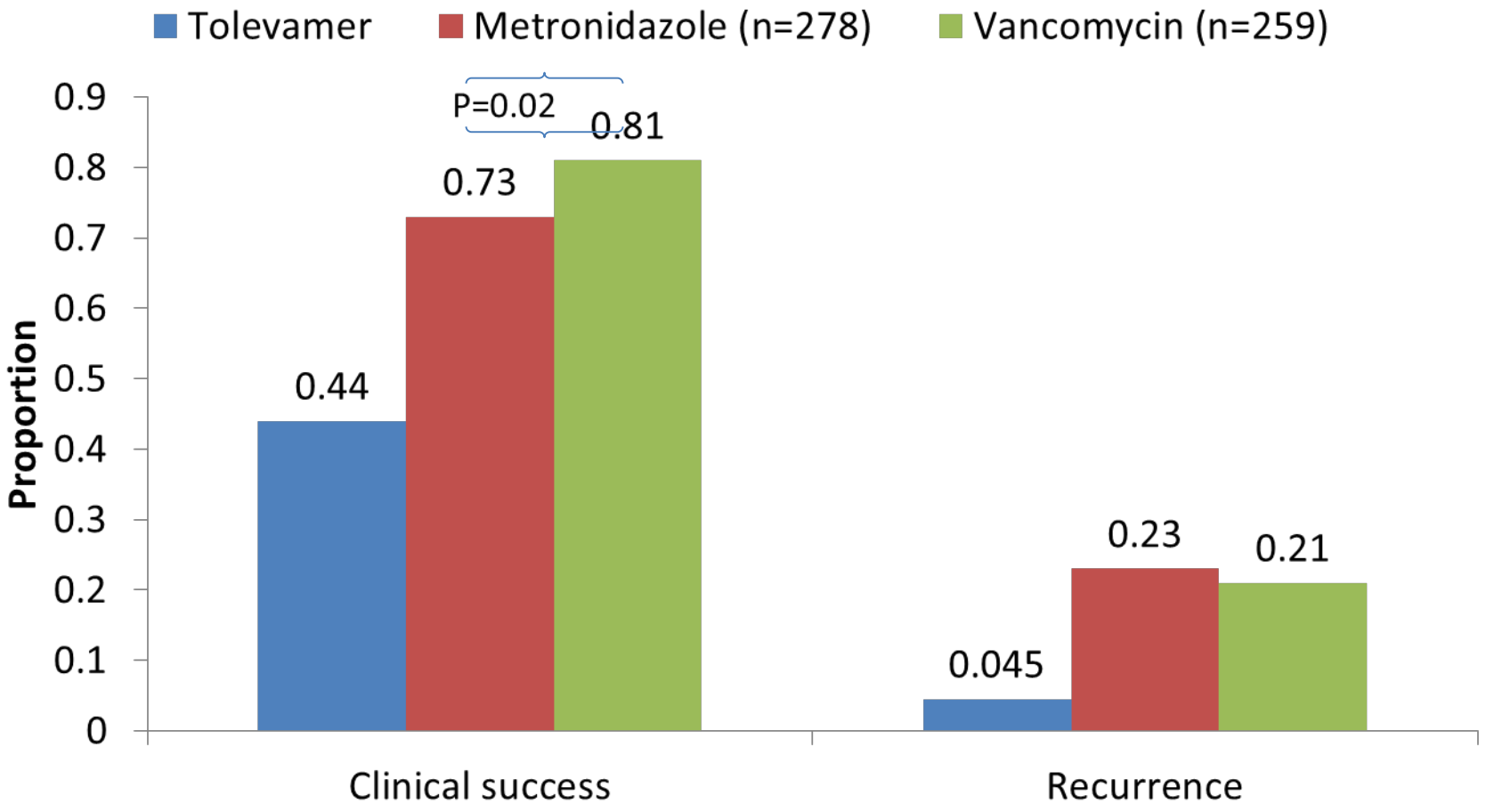
Current European CDI guidelines



Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use

Clin Microbiol Infect 2014

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

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

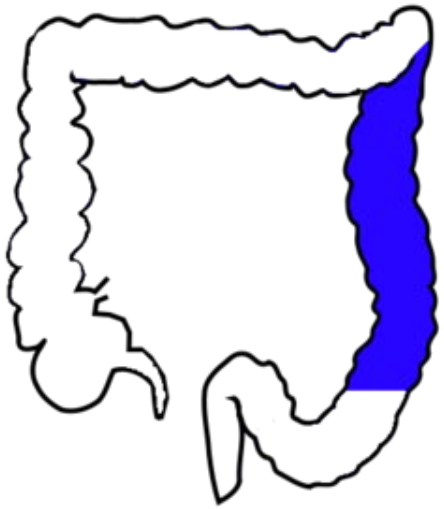
Shah et al. Expert Rev Anti Infect Ther 2011

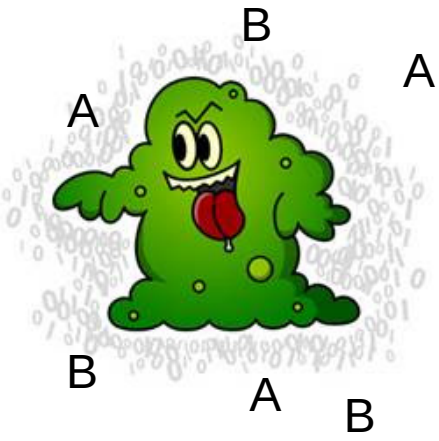
Bottom line: this may simply be a PK/PD problem

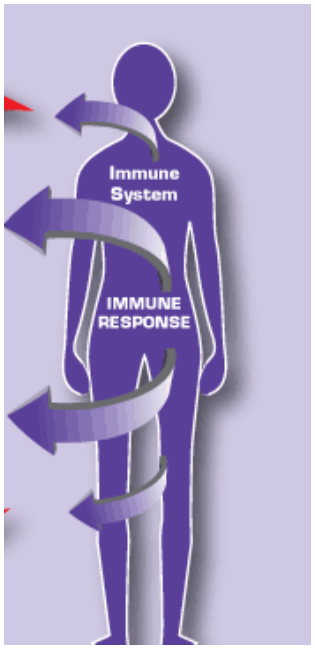
- Mean concentrations of metronidazole in stool: <0.25-9.5 ug/g
- MIC50: 1 ug/ml MIC90: 2 ug/ml
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Bolton et al. Gut 1986

Explosion in treatment possibilities for CDI minus 1







Current: Probiotics
FMT

Vancomycin
Fidaxomicin

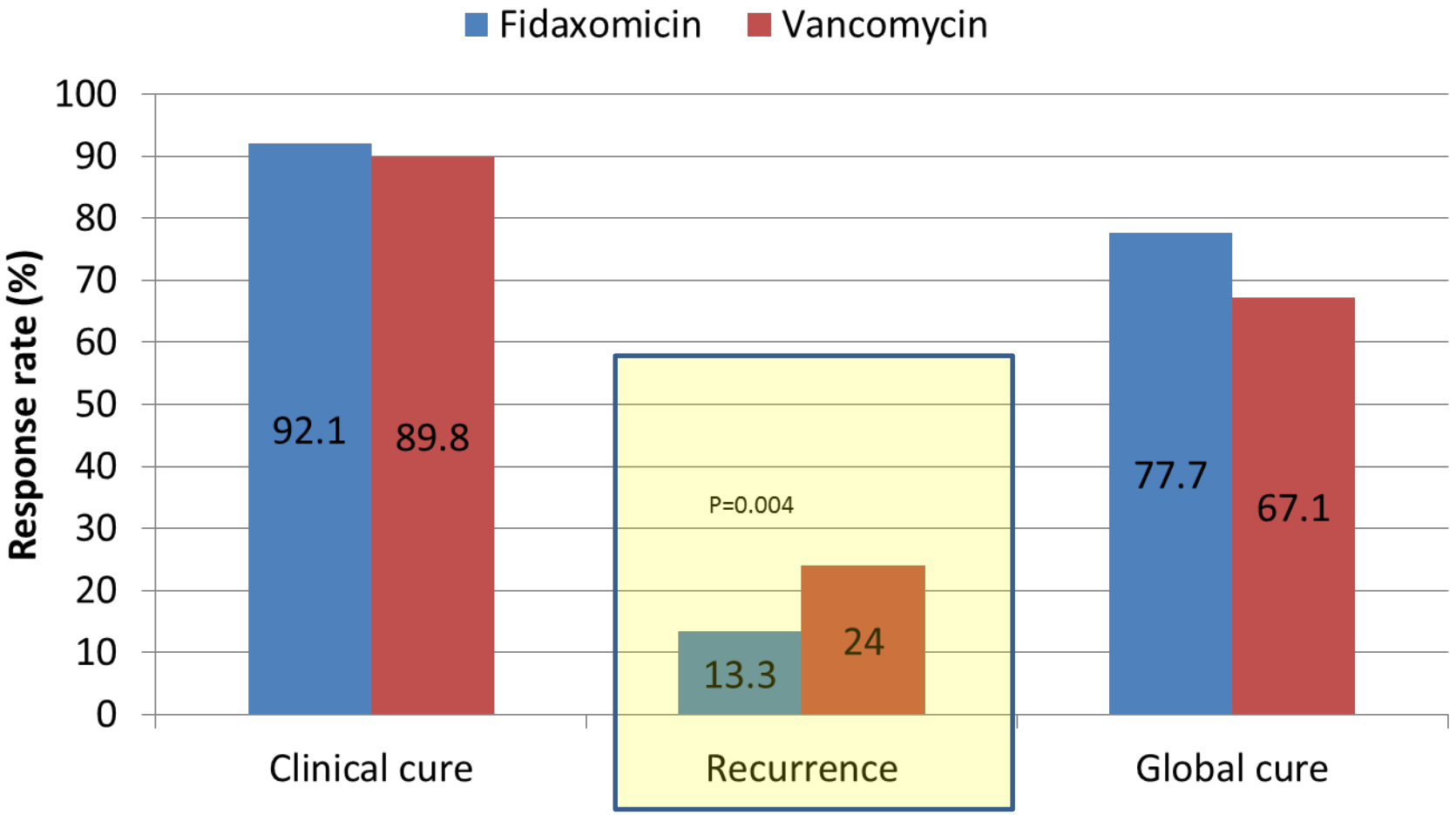
IVIG

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

Surotomycin
Cadazolid
SMT-19969

Monoclonal antibodies vs. C diff toxins
Toxoid vaccines

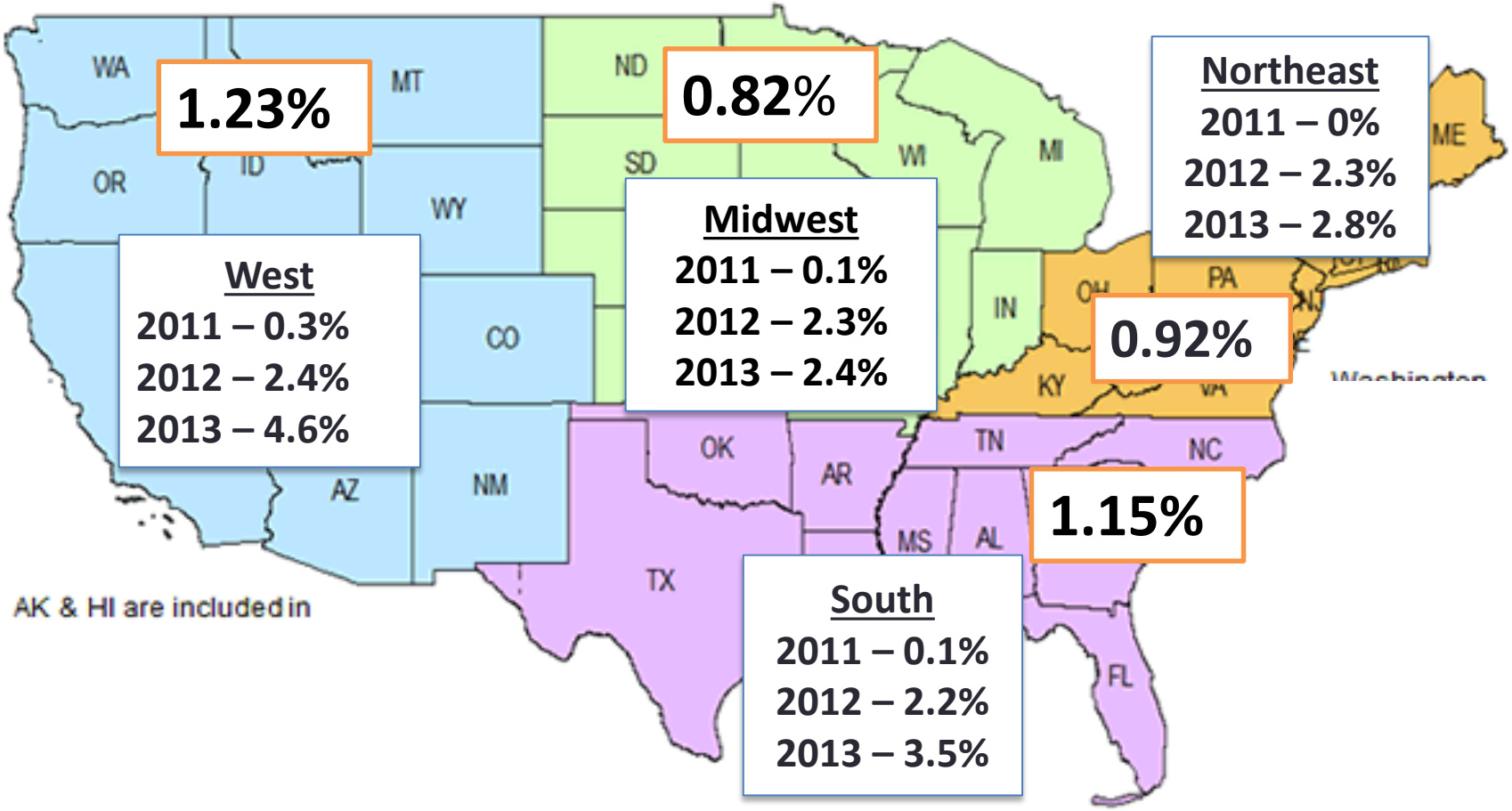
Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence



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

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

However, this drug is quite costly: Fidaxomicin Use By Region



Shah, Chan, Garey. Springer Plus 2016

Appropriate use of fidaxomicin

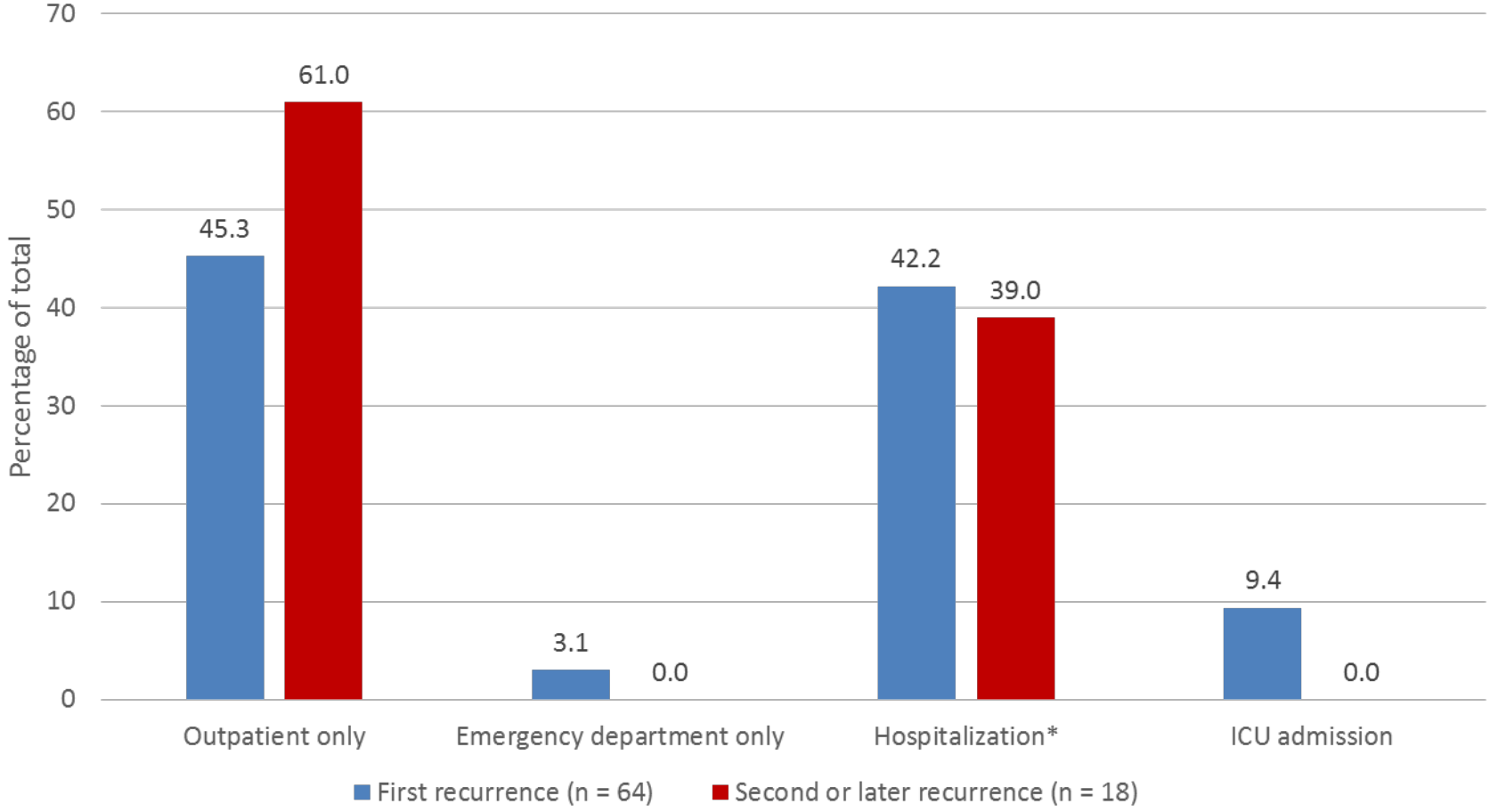
- Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population almost always in combination with other C diff or other antibiotics
- Remember: fidaxomicin's primary MOA is its narrow spectrum of activity preserving host microbiota
- Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?

Shah, Chan, Garey. Springer Plus 2016

How do we decide who to give fidaxomicin to?

- As far as I can tell, 100% of the money we have used on fidaxomicin has been a waste of money (only kind of kidding).
- Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?

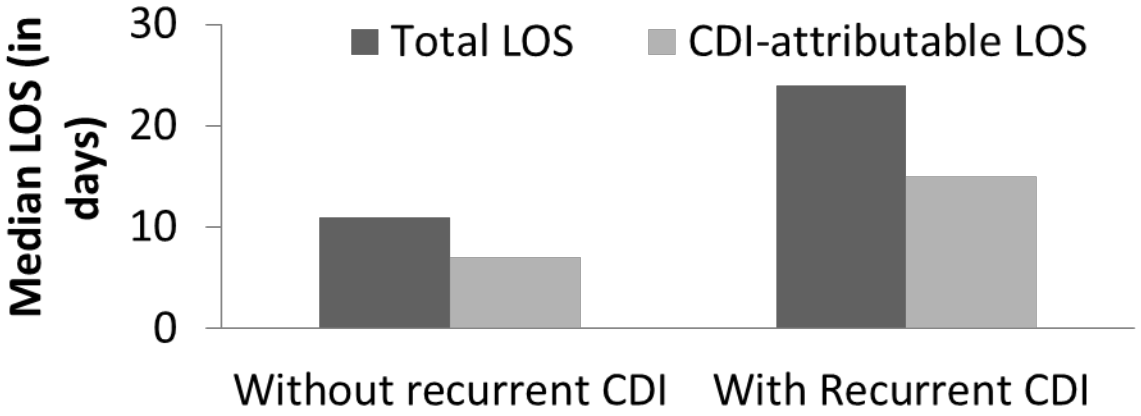
Recurrent CDI is costly: Healthcare utilization for recurrent CDI



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

Aitken, DuPont, Garey. PLOS One 2014 July 24;9(7)

Increased healthcare utilization = increased healthcare costs



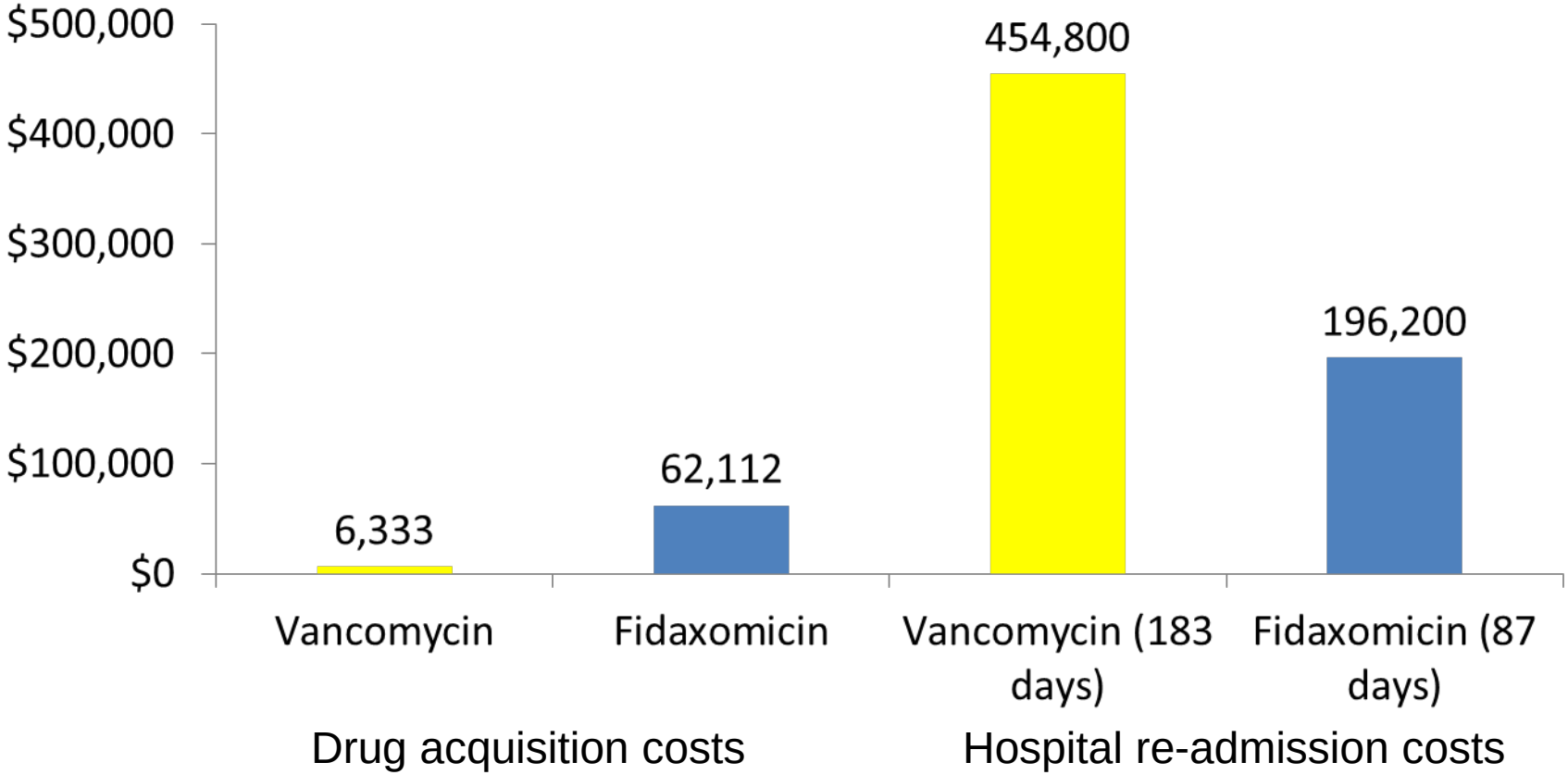
Cost in US dollars; median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment*	$60 (23 - 200)	$140 (30 - 260)
CDI-attributable hospitalization^	$13, 168 (7,525 - 24,455)	$28, 218 (15, 049 – 47,030)
Total hospitalization^	$20, 693 (11, 287 - 41, 386)	$45, 148 (20, 693 - 82,772)

Shah et al. ICAAC 2014 Poster #K-356, Sat, Sept 6, 2014

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 select patients.

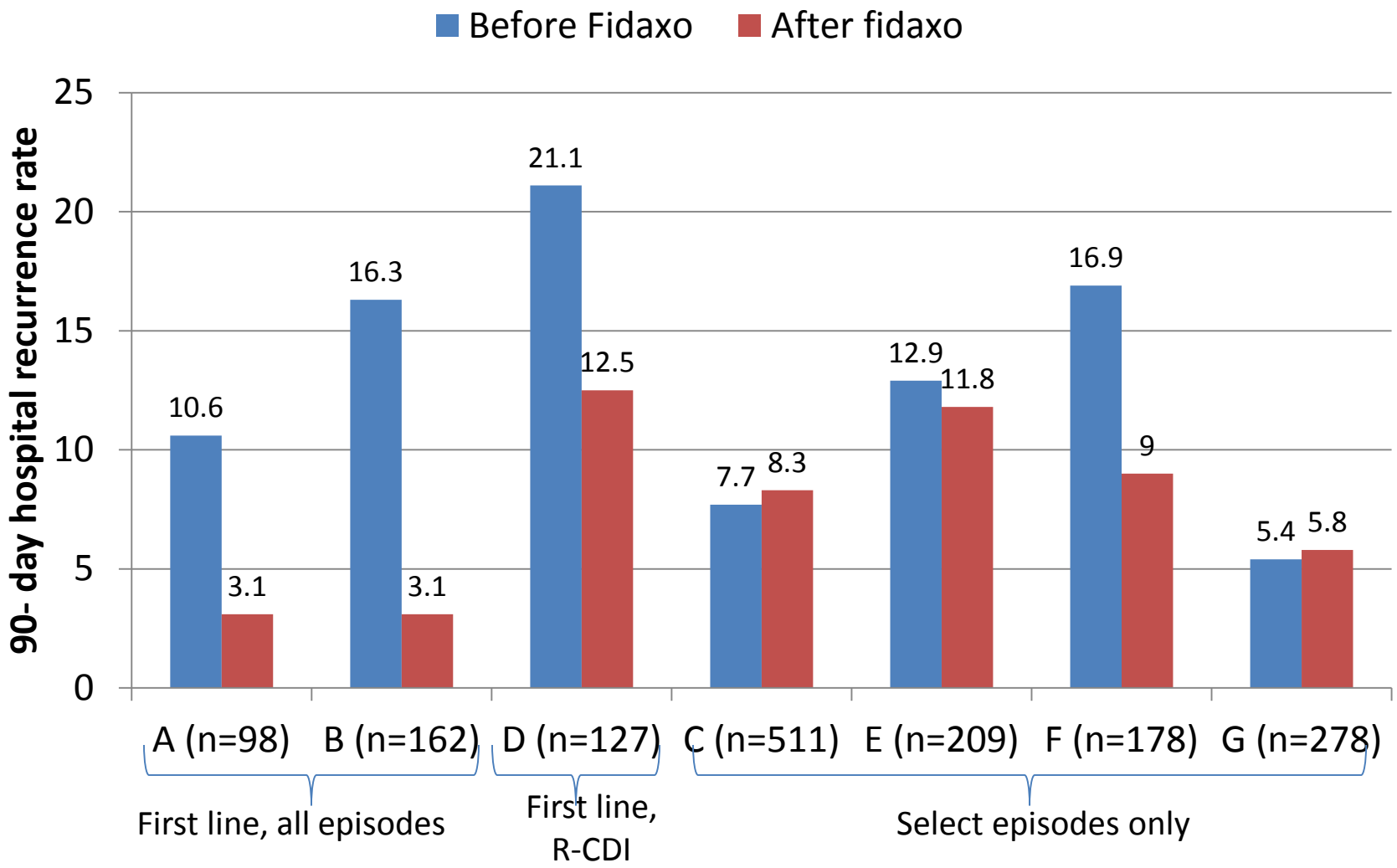
CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%



Gallagher et al. AAC 2015

Real-world evidence that fidaxomicin may reduce these costs?

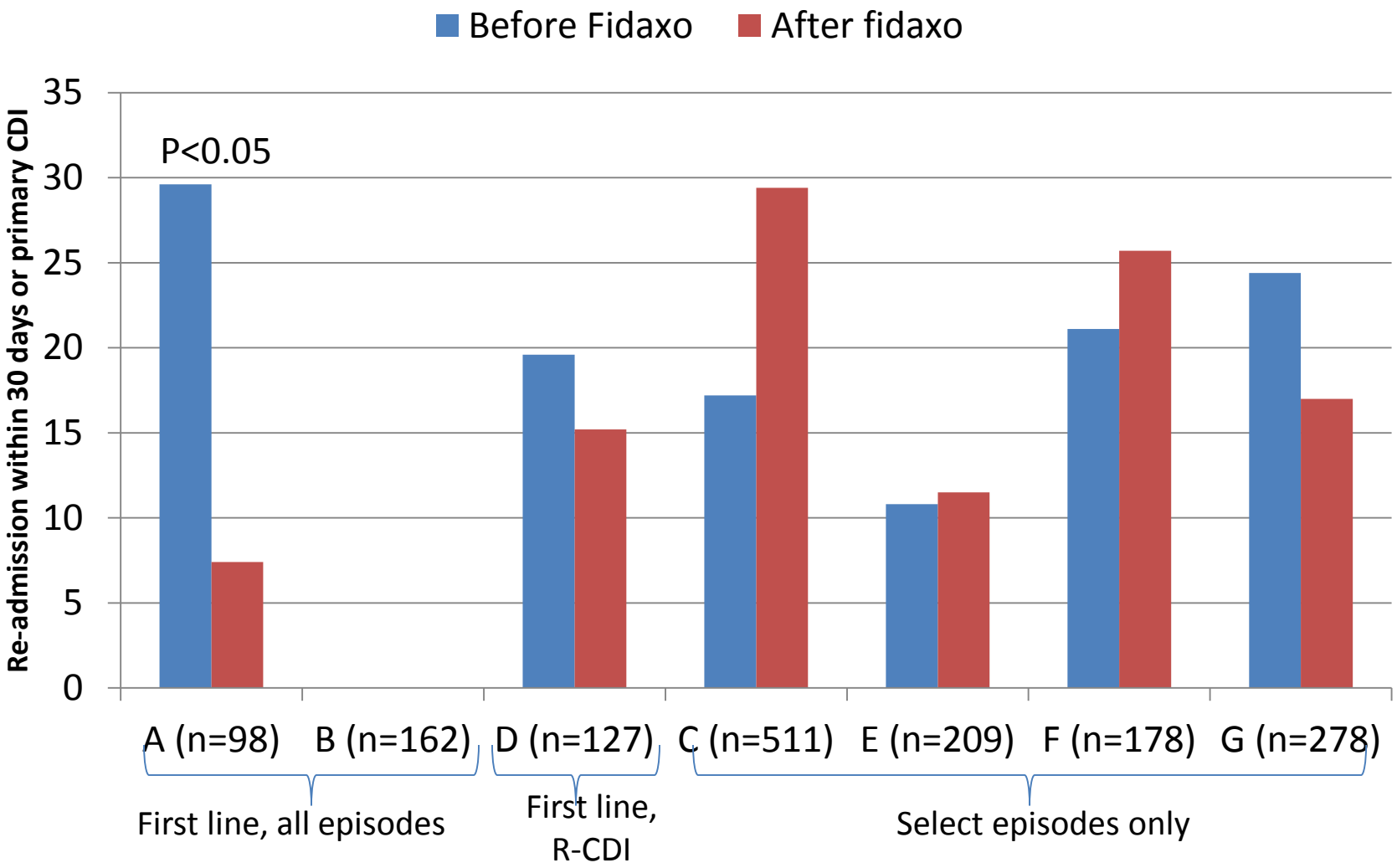
UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals



Goldenberg, Eur J Clin Microbiol Infect Dis 2016

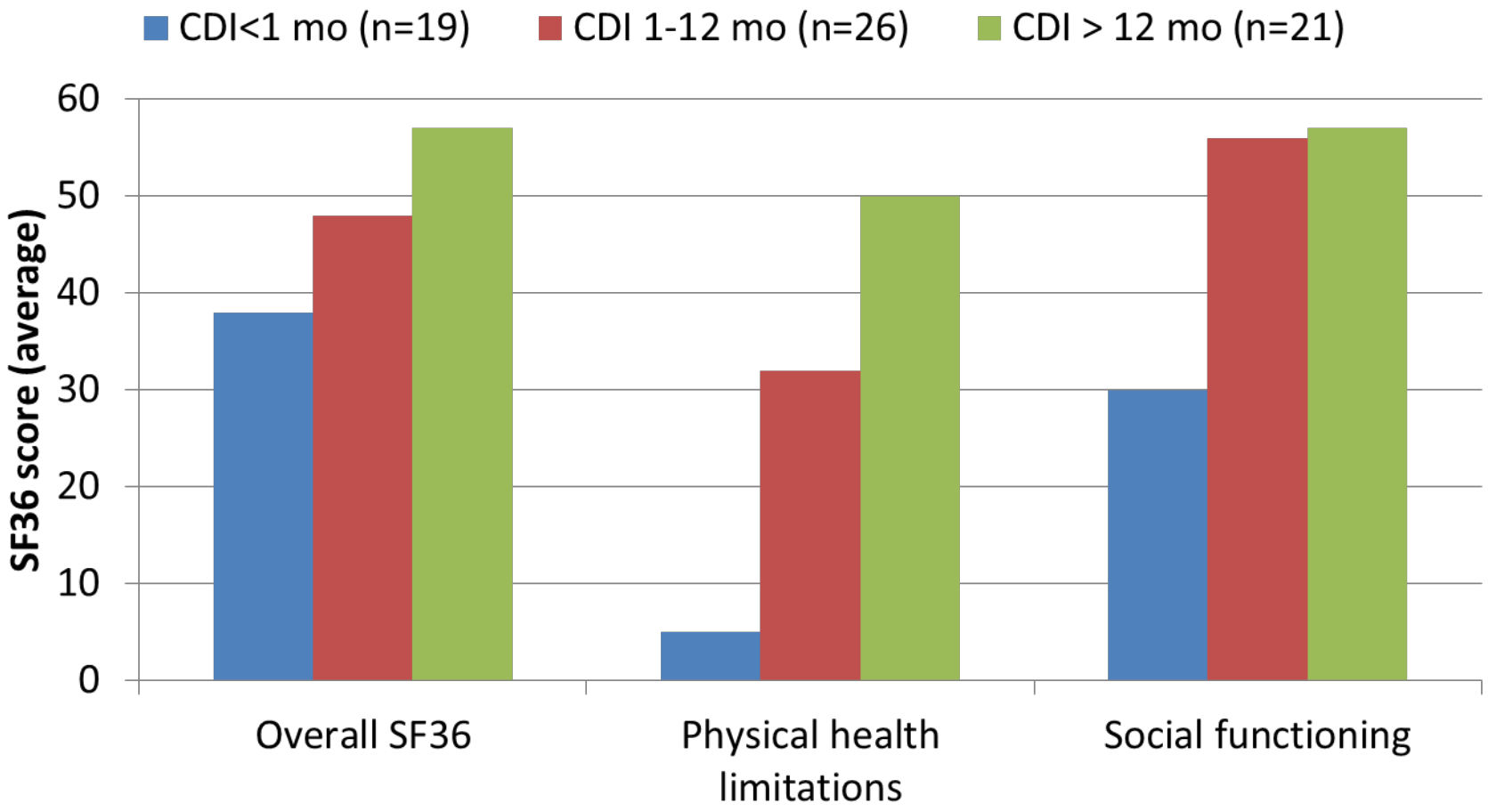
Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13 : seven hospitals incorporate 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, Eur J Clin Microbiol Infect Dis 2016

I do also wonder if we are missing the most important endpoints?



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

Final thoughts on antibiotic treatment

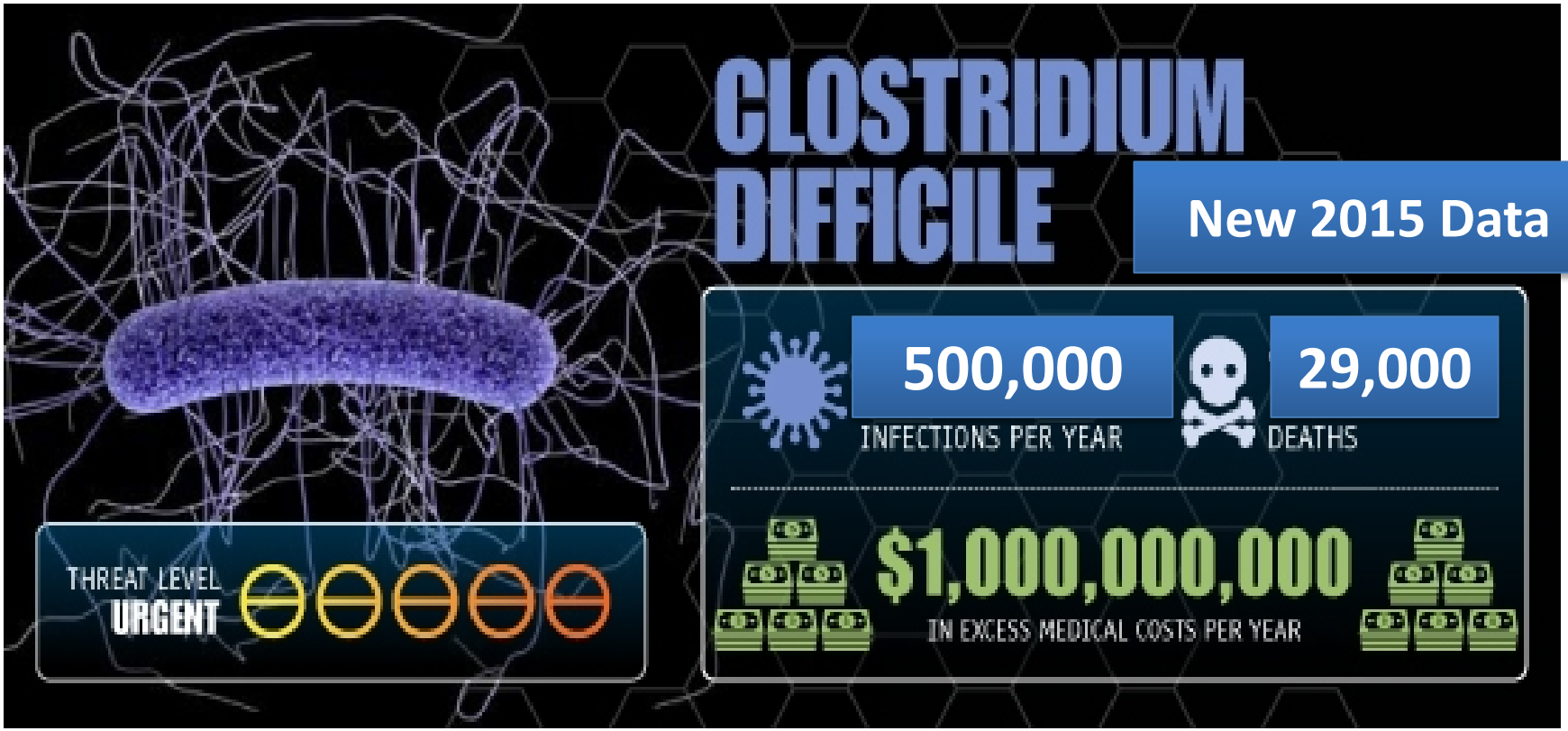
- Limit use of metronidazole as alternative agent
- Consider a certain budget that you can afford to prove the worth of fidaxomicin and then use it for that purpose (first recurrence?).
- As more narrow-spectrum branded drugs become available, may have to prove themselves in other pharmacologic niches (decreased toxin expression).
  - This assumes similar phase III results

Conclusion

- As long as we live in a world of elderly, hospitalized patients given broad spectrum antibiotics, CDI is here to stay
- With a coordinated effort and contemporary epidemiologic techniques, we can likely control and respond to future changes in the pathogenesis of CDI
- With a little luck and good science, we may also be able to discover new insights into strategies to prevent and control CDI.

Cost-effective Treatment of *Clostridium difficile* Infection in the ICU

Kevin W. Garey, PharmD, MS. Professor and Chair
University of Houston College of Pharmacy



Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

Source: CDC Report "Antibiotic Resistance Threats in the United States, 2013"
Lessa CF et al. NEJM 2015;372:825-34.