The Return of MDROs: C diff Case Example

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Objectives

- To understand the emerging threat of multidrug resistant organisms
- Using Clostridioides difficile infection (C diff or CDI) as a case example, give a perspective on how emerging resistance will effect patient care

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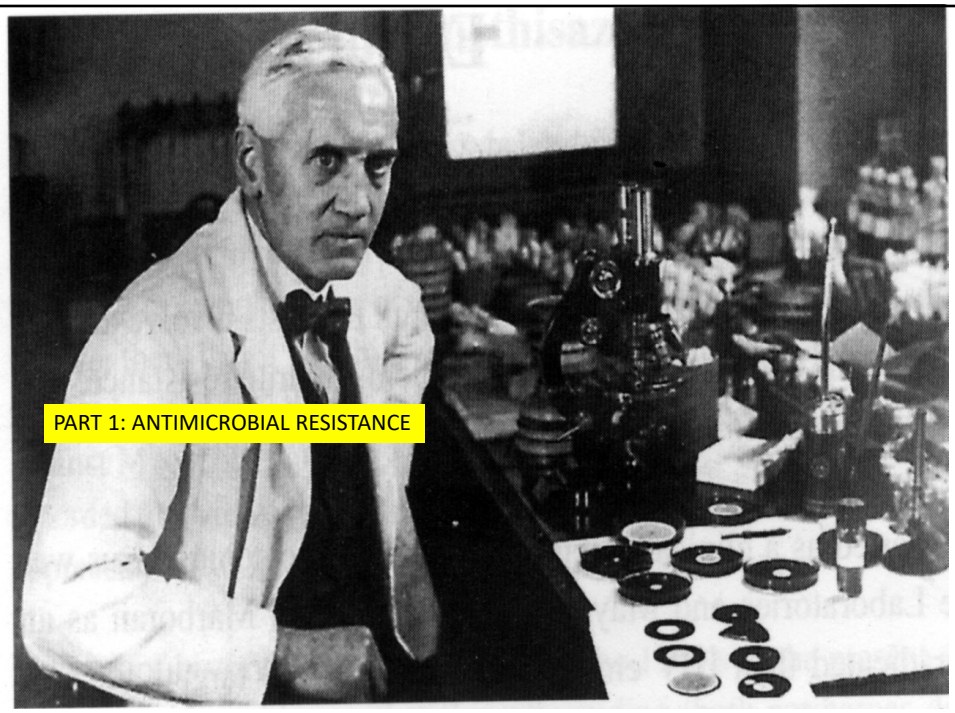

PART 1: ANTIMICROBIAL RESISTANCE

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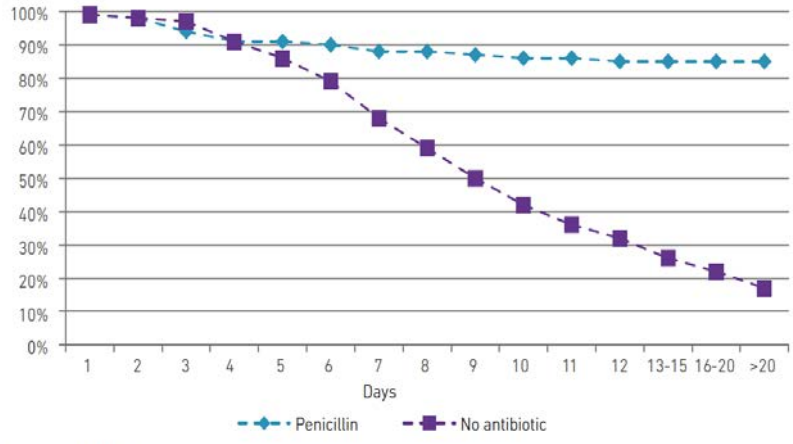
The Power of Antibiotics

Figure 9 Survival after pneumococcal pneumonia with bloodstream infection before and after penicillin treatment became available.



Adapted from Austrian et al. (5).

Antimicrobial resistance: global report on surveillance 2014, WHO

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The Power of Antibiotics

Disease	Pre-Antibiotic Death Rate	Death with Antibiotics	Change in Death
Community Associated Pneumonia[1]	~35%	~10%	-25%
Hospital Pneumonia[2]	~60%	~30%	-30%
Heart Infection[3,4]	~100%	~25%	-75%
Brain Infection[5,6]	>80%	<20%	-60%
Skin Infection[7,8]	11%	<0.5%	-10%
By comparison…treatment of heart attacks with aspirin or clot busting drugs[9]			-3%

1. Spellberg B, et al. Clin Infect Dis. 2008;47(S3):S249-65. 2, Clin Infect Dis. 2010; 51 (S1):S150-70
3. Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles Thomas, 1955.; 4. Lancet. 1935; 226:383-4.
5. Lancet. 1938;231:733-4.; 6. Am J Med. 1948;5:402-18; 7. Spellberg B, et al. Clin Infect Dis . 2009;49:383-91.
8. Madsen ST. Infection. 1973;1:76-81. 9. Lancet. 1988;2:349-60.

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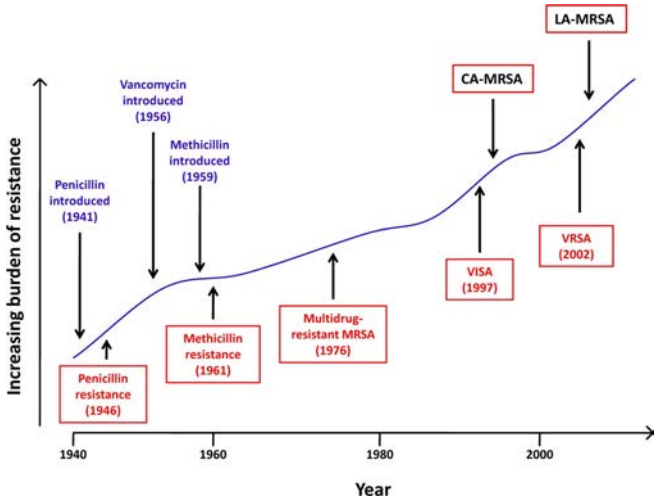
A brief history of MRSA

- Most staphylococci produce penicillinases → resistant to penicillin
  - Methicillin/oxacillin/nafcillin not inhibited by penicillinases, retain activity (MSSA)
- **M**ethicillin-**r**esistant ***S****taphylococcus* ***a****ureus* first identified in 1961
- **V**ancomycin-**r**esistant ***S****. **a**ureus* (VRSA) acquired vanA from VRE



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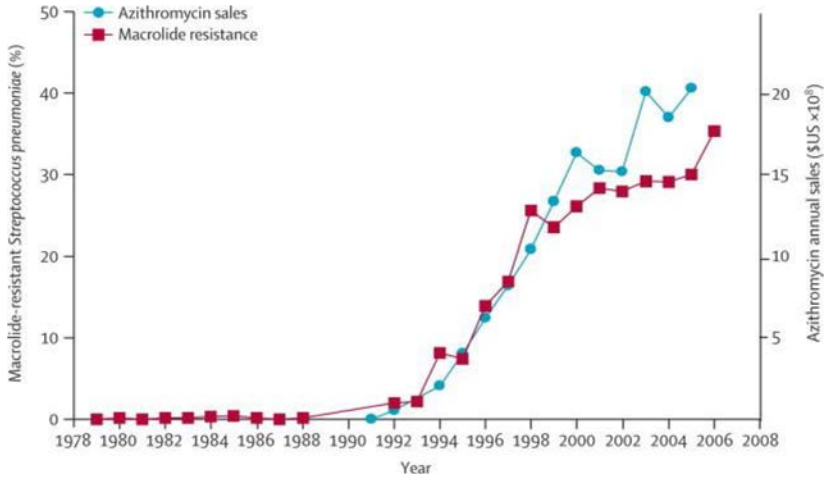
Correlation between antibiotic use and resistance



Serisier DJ. Lancet Respir Med. 2013;1:262-74.

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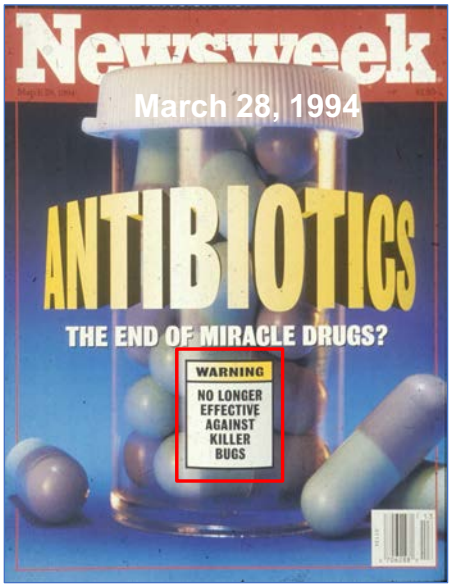
1994



2015

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CDC Threat Level Organisms

- 1. URGENT
  - Carbapenem-resistant Acinetobacter
  - Candida auris
  - Clostridioides difficile infection
  - Carbapenem-resistant Enterobacteriaceae
  - Drug-resistant Neisseria gonorrhoeae
- 3. Concerning Threats
  - Erythromycin-resistant group A Streptococcus
  - Clindamycin-resistant group B Streptococcus
- 2. Serious
  - Drug-resistant Campylobacter
  - Drug-resistant Candida
  - ESBL, VRE, MDR-PSA, MRSA
  - Drug-resistant nontyphoidal Salmonella and serotype Typhi
  - Drug-resistant Shigella
  - Drug-resistant Streptococcus pneumoniae
  - Drug-resistant Tuberculosis
- 4. Watch
  - Azole-resistant Aspergillus fumigatus
  - Drug-resistant Mycoplasma genitalium
  - Drug-resistant Bordetella pertussis

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Antibiotic Resistance is A Public Health Threat!

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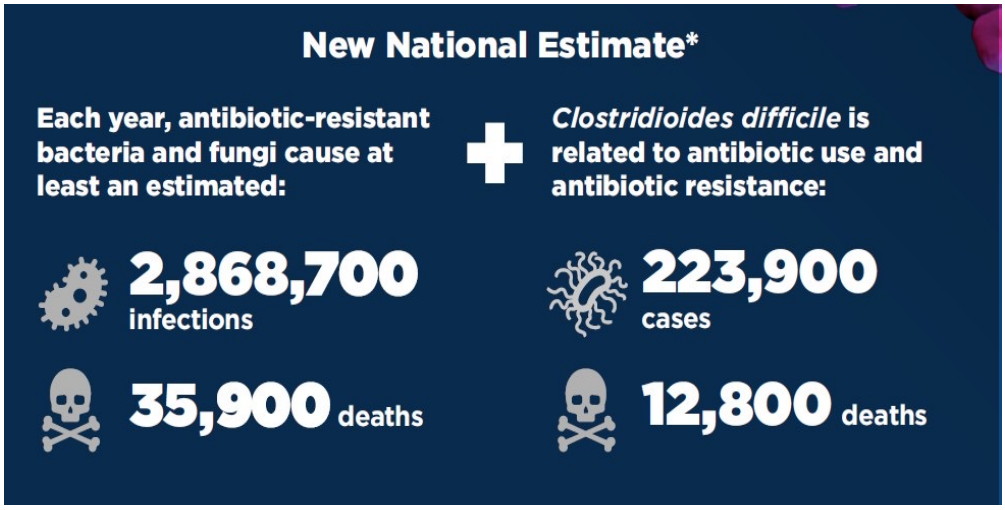
The Burden of Antibiotic Resistance



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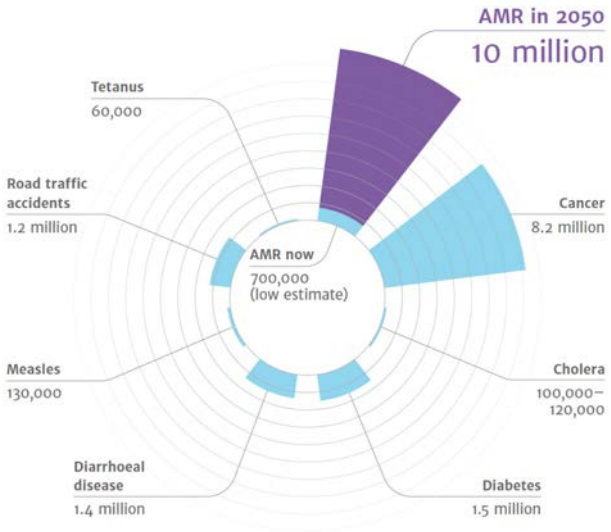
Projected Causes of Death 2050: UK Review on Antibiotic Resistance



https://amr-review.org/

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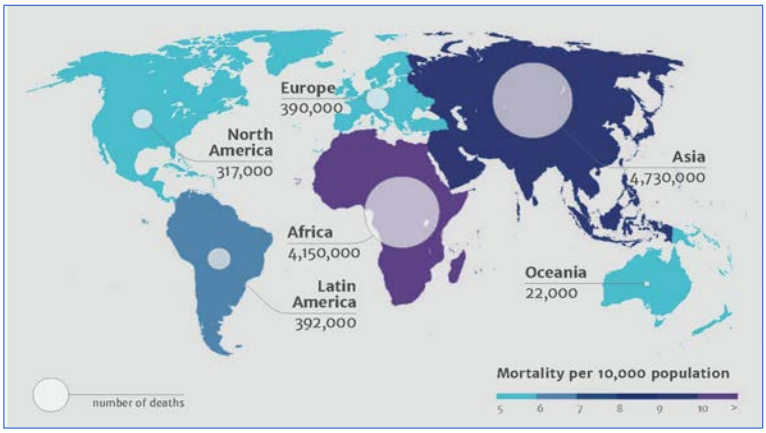
GLOBAL DIMENSIONS

Estimate: By 2050, 10 Million Deaths Attributed to AMR Every Year Costing World Economy $100 Trillion



Review on Antimicrobial Resistance (AMR), 2014. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. London, UK http://amr-review.org

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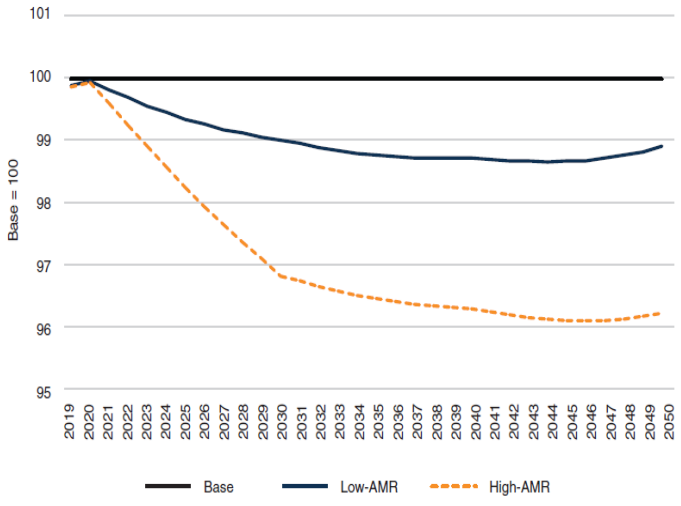
Economic Impact of Antibiotic Resistance



Global economic output is projected to be 1.0 percent lower by 2030 and 1.1 percent lower by 2050

Global economic output would be 3.2 percent lower in 2030 and then fall short further, so that in 2050, world GDP would be 3.8 percent smaller than in the base case

World Bank Group, September 2016

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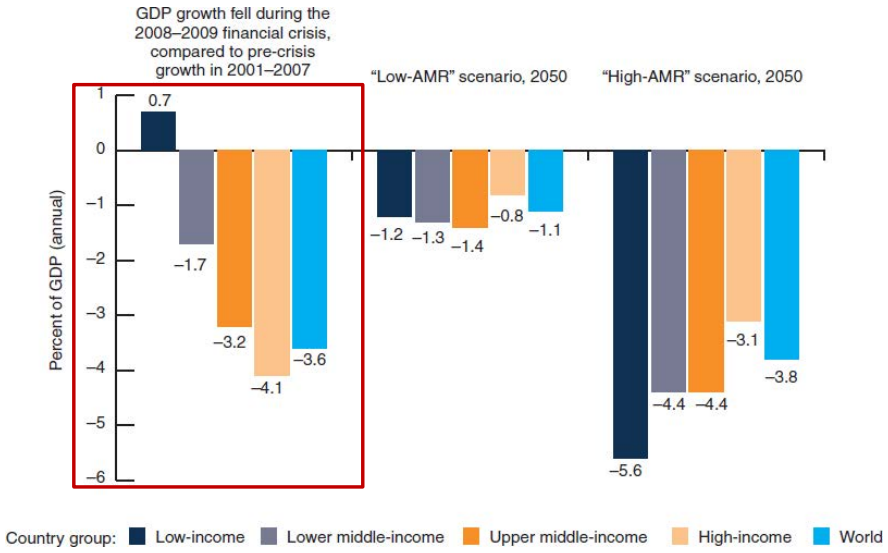
Economic Costs of AMR



World Bank Group, September 2016

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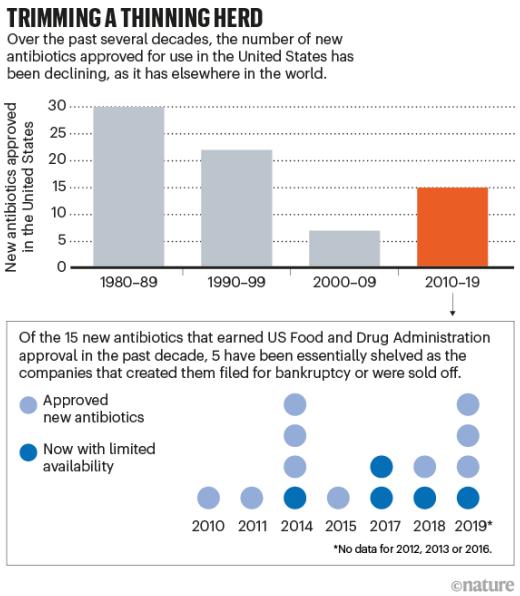
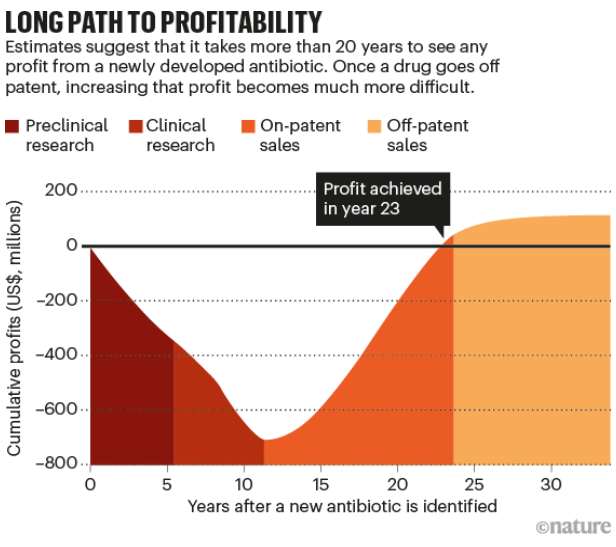
"Dry" Pipeline of Antibiotics





McKenna et al., *Nature* 2020;584:339-341

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Part 2. C difficile infection

- Historically, three effective antibiotics (now only 2)
- I'll give you a good summary of the current burden of C diff infection in which (most) antibiotics do not have an AMR problem
- Think about what will happen to these outcomes if it become untreatable.

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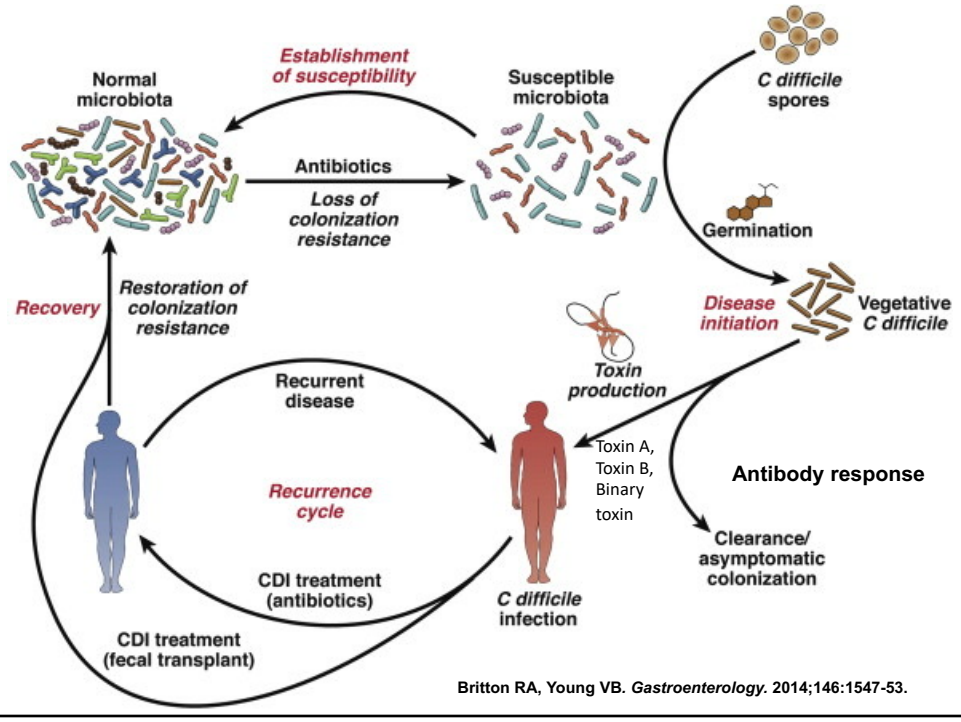

Britton RA, Young VB. *Gastroenterology.* 2014;146:1547-53.

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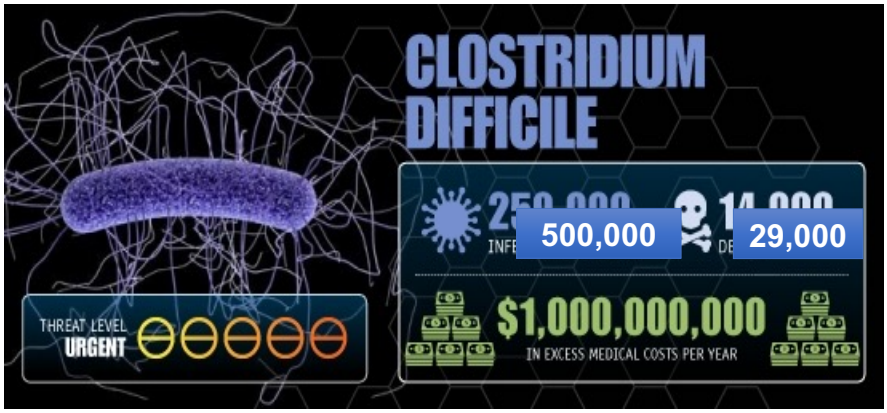
The Impact of *Clostridium difficile* Infections (CDI)



Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI
Up to 35% of all CDI is diagnosed in the community setting!

Source: CDC. Antibiotic Resistance Threats in the United States, 2013. Available: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.
Lessa CF, et al. *N Engl J Med.* 2015;372:825-34.

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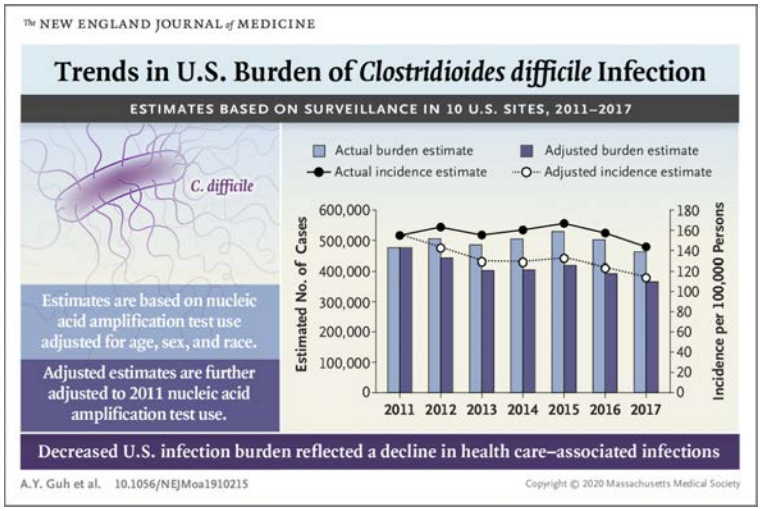
Update: Still lots of C diff out there



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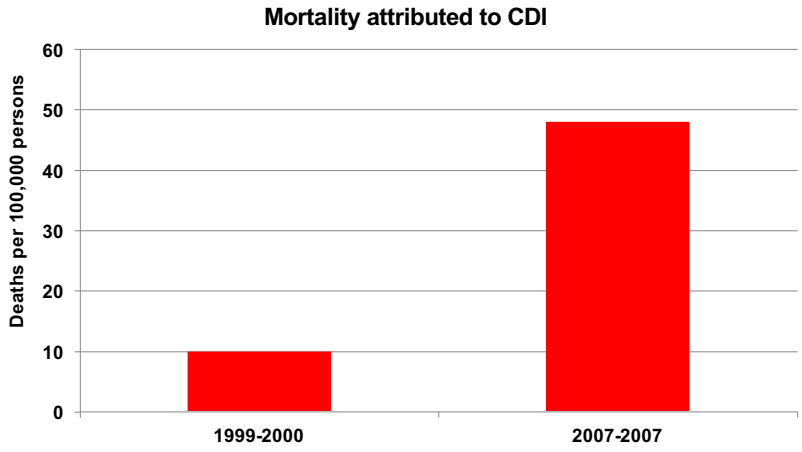
C. difficile is the Main Contributor to Gastroenteritis-associated Deaths in the USA



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 AJ, et al. *Clin Infect Dis.* 2012;55:216-23.

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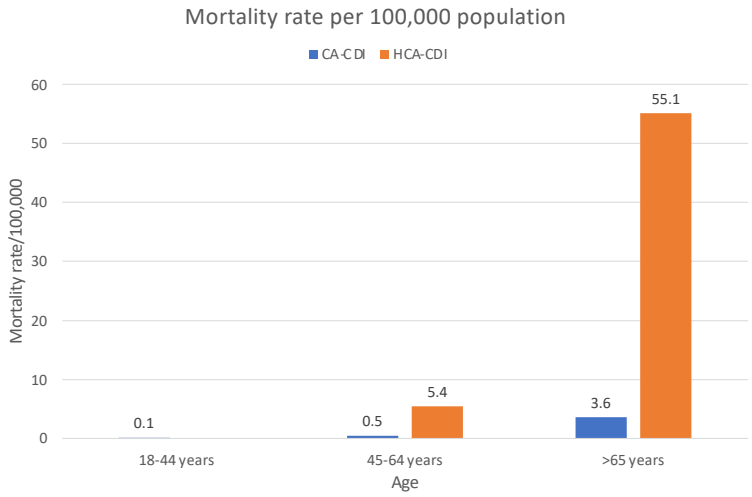
Mortality risk is especially pronounced in the elderly



CA-CDI: community-associated CDI; HCA-CDI: Health-care associated CDI

Lessa et al. N Engl J Med 2015;372:825-34

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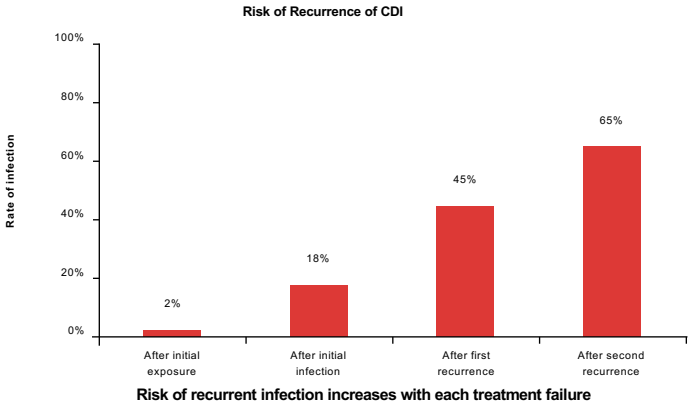
Recurrent CDI: Common and increases likelihood with each CDI episode

- Recurrence: most important risk factor for future recurrences
- Others: Advanced age, continued use of non-CDI antibiotics, and anti-ulcer meds (PPIs)



Adapted from Jiang et al. *Am J Gastroenterol.* 2006;101:112.

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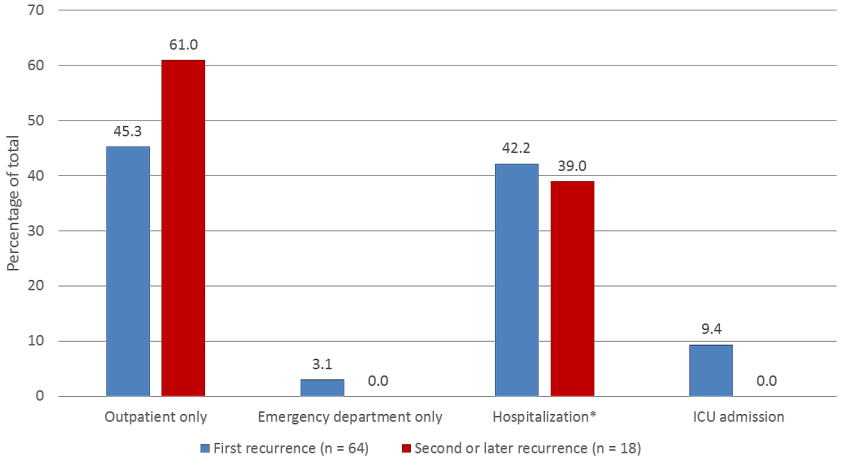
Recurrent CDI is costly: Healthcare utilization for recurrent CDI



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

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

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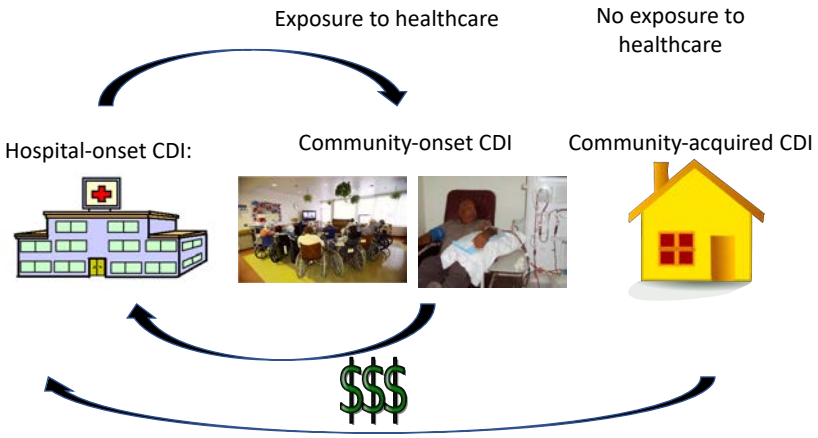
Costs of CDI will involve initial hospitalization costs + (re-)admission costs



[1]Lessa et al. N Engl J Med 2015;372:825-34
[2]Desai et al. BMC ID 2016;16:303

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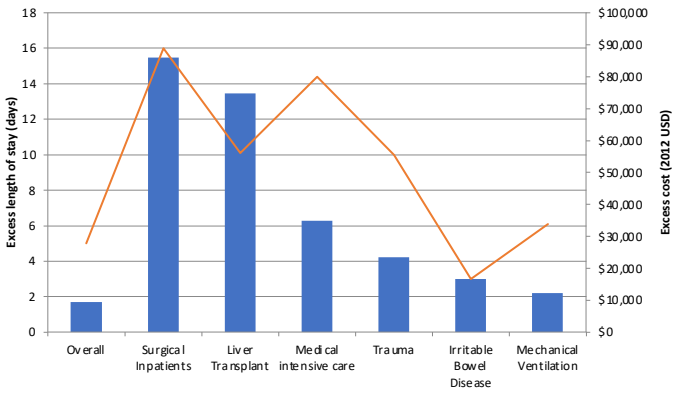
How much does CDI increase your length of stay (red lines) and hospitalization costs (blue bars)



Stewart et al. J Gastroenterol Surg 2011; Ali et al. Liver Tranpl 2012; Glance et al. Arch Surg 2011; Zerey et al. Surg Infect 2007; Lawrence et al ICHE 2007; Zilberberg et al. Chest 2009; Ananthakrishan Gut 2008

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Putting it all together: Best estimates for national economic burden (USA)

Population	CDI cases (N)	Total costs
US population (decision analysis)	606,000	$5.4 billion
Medicare (>65)	240,000	$6 billion
CDC Epicenter (US population)	500,000	$4.8 billion

Desai et al. BMC ID 2016; Shorr et al. ICHE 2016; Lessa et al. NEJM 2015

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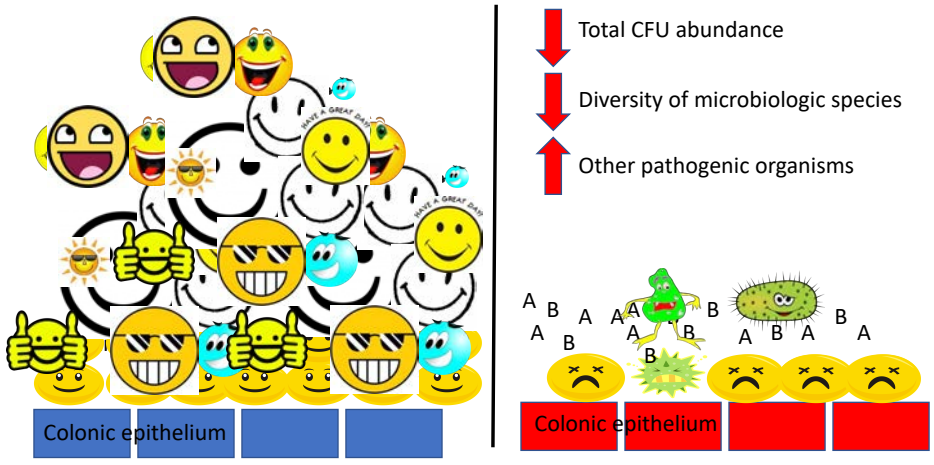
It's important to remember that recurrent CDI is more than about cost

Microbiome of non-CDI patients vs. CDI patients



Healthy Microbiome

Recurrent CDI Microbiome

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Six months post infection, almost ¼ of CDI patients will meet definitions for new onset IBS or FGID

	CDI cases (n, %)	Non-CDI controls (n. %)	P value*
IBS or FGID	9 (22.0%)	0 (0%)	P=0.0024
IBS	5 (12.2%)	0 (0%)	P=0.055
Functional Diarrhea	6 (14.6%)	0 (0%)	P=0.023
Functional Abdominal Bloating	4 (9.7%)	0 (0%)	P=0.12
Functional Abdominal Pain Syndrome	0 (0%)	0 (0%)	NA

Sethi et al. J Hosp Infect 2010

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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."

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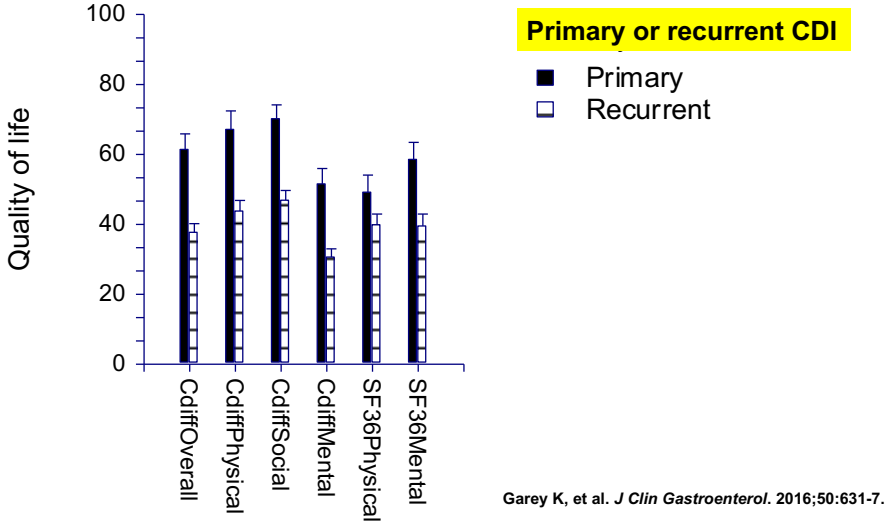
QOL Goes Down Considerably with Recurrent CDI



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

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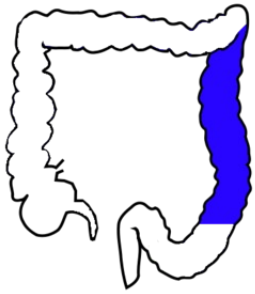
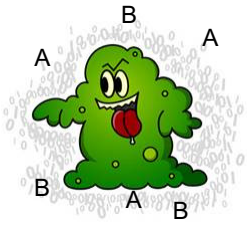
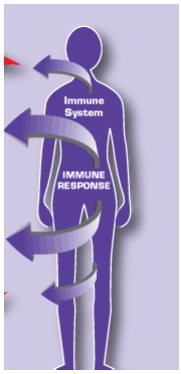
Therapeutic Goals for *C. difficile* Infection (CDI)







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

Adamu BO, Lawley TD. *Curr Opin Microbiol.* 2013;16:596-601.

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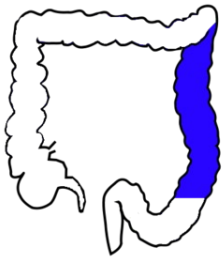
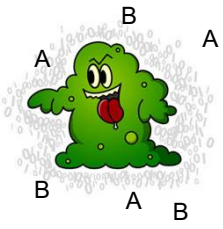
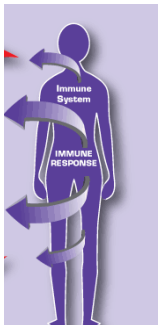
There Has Been an Explosion in Treatment Possibilities for CDI







Current:	Probiotics FMT Use narrow-spectrum antibiotics	Metronidazole Vancomycin Fidaxomicin	IVIG Bezlotoxumab
Future:	2nd-generation FMT Non-tox *C. difficile* M3 Ecobiotics	Ridinilazole Ibezapolstat	Toxoid vaccines

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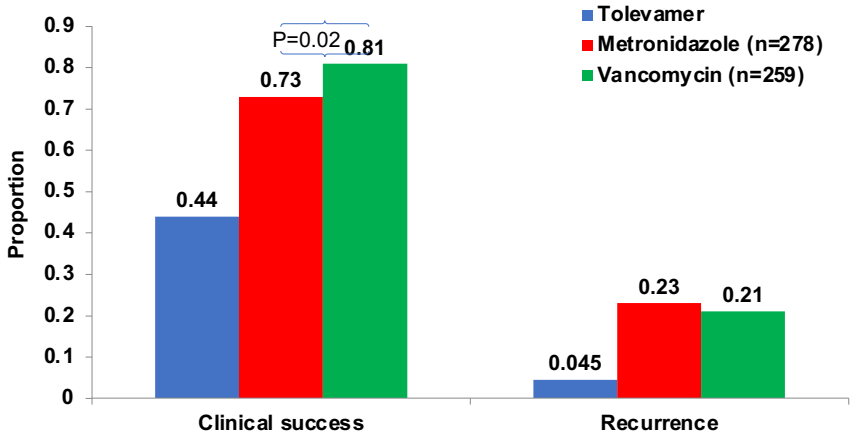
Metronidazole is Globally Inferior to Vancomcyin (Tolevamer Phase III RCT)



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

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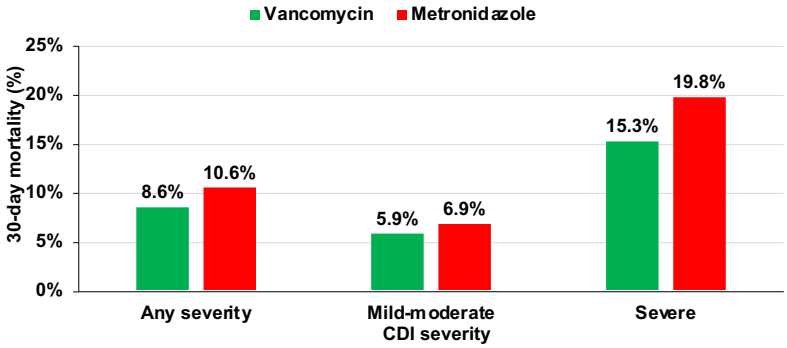
Increased Failure Rate of Metronidazole Also Associated with Increased 30-day Mortality



VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 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.

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There May Have Been MIC Creep With Metronidazole Over the Decades

Author	Location	Time period	Isolates	Metronidazole		
				MIC_{50}	MIC_{90}	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 D, et al. *Expert Rev Anti Infect Ther.* 2010;8:555-64.

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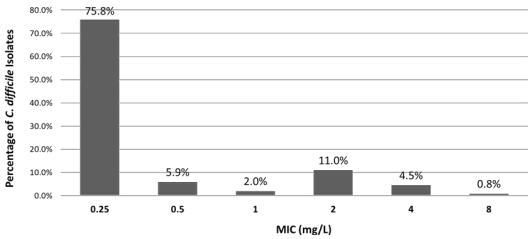
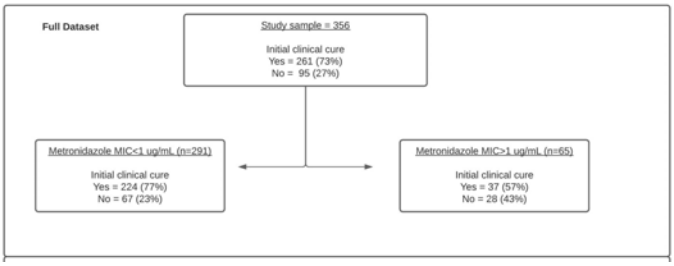
We recently completed a large-scale evaluation of metronidazole MIC and clinical outcomes in CDI patients





Gonzales-Luna et al. OFID 2021

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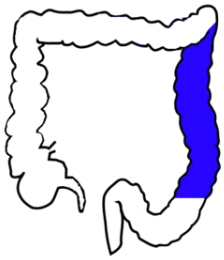
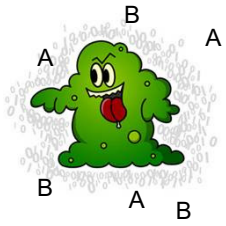
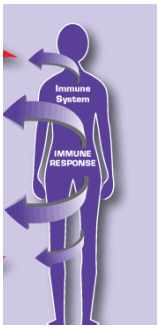
Explosion in Treatment Possibilities for CDI Minus 1







Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Vancomycin
Fidaxomicin

IVIG
Monoclonal antibodies vs. *C. difficile* toxins

Future: 2nd-generation FMT
Non-tox *C. difficile* M3
Ecobiotics

Ridinilazole
Ibezapolstat

Toxoid vaccines

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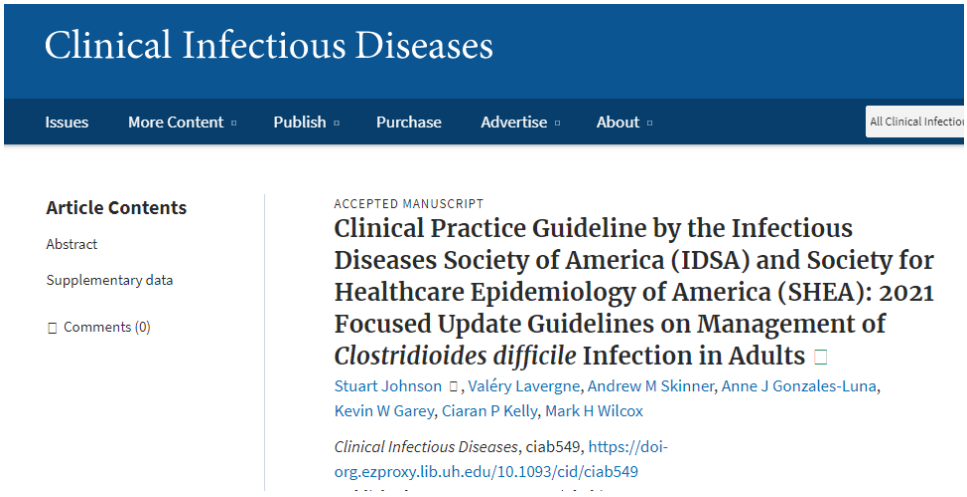
Anyone notice some new guidelines just got published!



Johnson S, et al. *Clin Infect Dis.* 2021; Jun 24;ciab549.doi:10.1093/cid/ciab549

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Recommendation for Initial Treatment of CDI in Adults, 2021

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin SD	Implementation depends on available resources
	Alternative: Vancomycin SD	Vancomycin remains an acceptable alternative
	Alternative for non-severe CDI, if above agents are unavailable: Metronidazole SD	Definition of non-severe is supported by the following lab parameters: White blood cell count of 15,000 cells/mL or lower and a serum creatinine level less than 1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin SD or Extend	
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Vancomycin 125 mg four times daily for 10-14 days, two times daily for seven days, and then every two to three days for two to eight weeks
	Alternative: Vancomycin SD	Consider a standard course of vancomycin if metronidazole was used from treatment of the first episode

SD, standard dose; Fidaxomicin SD: 200 mg given twice daily for 10 days; Vancomycin SD: 125 mg given four times daily by mouth for 10 days; Fidaxomicin Extend: 200 mg twice daily for 5 days followed by once every other day for 20 days

Johnson S, et al. *Clin Infect Dis.* 2021; Jun 24;ciab549.doi:10.1093/cid/ciab549

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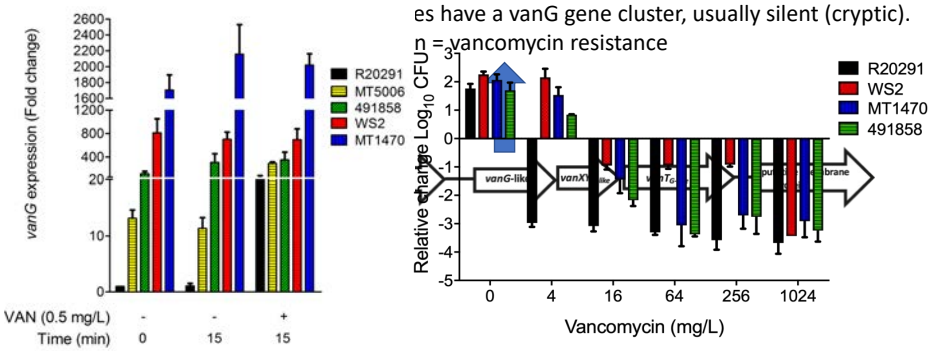
Vancomycin resistance, anyone?



Shen et al. J Antimicrob Chemother 2020

41

…and fidaxomicin is not immune from resistance development either

n=	MIC (ug/mL)	Eravacycline	Fidaxomicin	Metro	Vancomycin
234	MIC_{50}	≤ 0.0078	0.016	0.25	2
	MIC_{90}	0.016	0.0625	1	4

….but 4 isolates had fidaxomicin MIC ≥ 4 ug/mL

Basseres et al. JAC 2020

42

…and fidaxomicin is not immune from resistance development either

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5194–5199 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00625-11

Comparative Susceptibilities to Fidaxomicin (OPT-80) of Isolates Collected at Baseline, Recurrence, and Failure from Patients in Two Phase III Trials of Fidaxomicin against *Clostridium difficile* Infection

Ellie J. C. Goldstein,[1]* Diane M. Citron,[1] Pamela Sears,[2] Farah Babakhani,[2] Susan P. Sambol,[3] and Dale N. Gerding[3]

R. M. Alden Research Laboratory, Culver City, California[1]; Optimer Pharmaceuticals Inc., San Diego, California[2]; and Hines VA Hospital, Hines, Illinois[3]

Received 4 May 2011/Returned for modification 20 July 2011/Accepted 3 August 2011

A 10-day course of oral fidaxomicin (200 mg twice a day [b.i.d.]), a potent new macrocyclic drug, was compared to vancomycin (125 mg four times a day [q.i.d.]) in 1,164 adults (1,105 in the modified intent-to-treat [mITT] population) with *Clostridium difficile* infection in two phase III randomized, double-blind trials at sites in North America and 7 European countries. Of 1,105 mITT patients, 792 (71.7%), including 719/999 (72.0%) in the per-protocol (PP) population, provided a *C. difficile* strain at baseline, of whom 356 received fidaxomicin with 330 cures (92.7%) and 363 received vancomycin with 329 cures (90.6%). The susceptibilities (MIC_{90}) of baseline isolates did not predict clinical cure, failure, or recurrence for fidaxomicin (MIC_{90}, 0.25 μg/ml for both; range, ≤0.007 to 1 μg/ml [ran… g/ml … .9%) "rifa… tich incre… oped durin… d an elevated fidaxomicin MIC of 16 μg/ml at the time of recurrence. All isolates were susceptible to ≤4 μg/ml of metronidazole. When analyzed by restriction endonuclease analysis (REA) type, 247/719 (34.4%) isolates were BI group isolates, and the MICs were generally higher for all four drugs tested (MIC_{90}s: fidaxomicin, 0.5; vancomycin, 2.0; metronidazole, 2.0; and rifaximin, >256 μg/ml) than for the other REA types. There was no correlation between the MIC of a baseline clinical isolate and clinical outcome. MIC_{90}s were generally low for fidaxomicin and vancomycin, but BI isolates had higher MICs than other REA group isolates.

…. a single strain isolated from a cured patient had an elevated fidaxomicin MIC of 16 ug/mL

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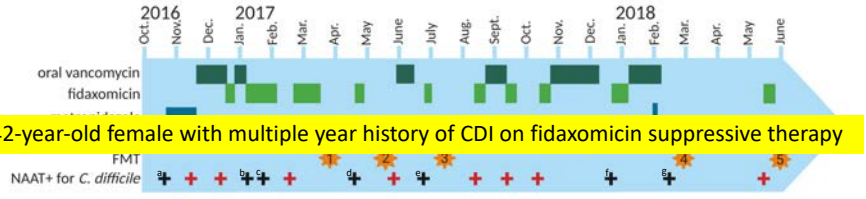
…and fidaxomicin is not immune from resistance development either



42-year-old female with multiple year history of CDI on fidaxomicin suppressive therapy

Sample	aMHS156	bMT4854	cMT4899	dMT5027	eMT5121	fMT5405	gMT5462
Ribotype	F078-126	F078-126	F078-126	F078-126	F078-126	F002/F054	F002
Description	Index case	Before 1st FMT	Before 1st FMT	Before 2nd FMT	Before 3rd FMT	Before 4th FMT	Before 4th FMT
Episode	1	3	4	6	11	12	13
MIC (24 hr)							
Colonies tested (no.)	1	6	6	ND	1	2	1
vancomycin	0.5	1.0-2.0	0.5-				
metronidazole	0.125	0.25-2	0.125				
fidaxomicin	0.016	0.03125-0.016	0.016-0.				
eravacycline	0.03125	0.016-0.0625	0.016-0.0625		0.016-0.03125	0.03125	0.016
							2
							8
							Yes

Now not responding to fidaxomicin therapy

WGS results: A single cgSNV differentiated the index case from the genome of isolate MT5121 occurred within the **RNA polymerase β subunit (*rpoB*) gene**.

Sample	MHS156	MT4854	MT4899	MT5121
Fidaxomicin	0.016	0.03125-0.016	0.016-0.0625	0.016

Gonzales-Luna AJ et al. Anaerobe 2021

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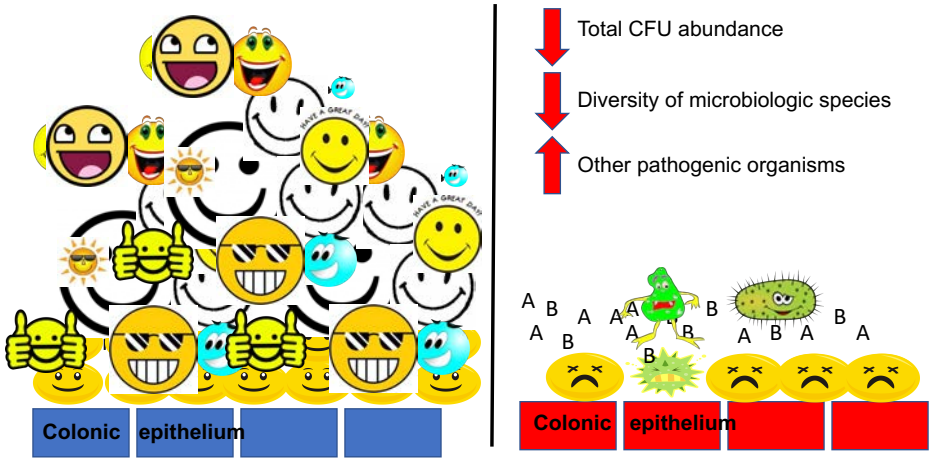
Restore the Microbiome

Microbiome of non-CDI patients vs. CDI patients



Healthy Microbiome

Recurrent CDI Microbiome

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Recommendation for Second or Subsequent Recurrence of CDI in Adults

Clinical presentation	Recommended and Alternative Treatments	Comments
Second or subsequent recurrences	Fidaxomicin SD or Extend	
	Vancomycin by mouth in a tapered and pulsed regimen	
	Vancomycin SD followed by rifaximin 400 mg three times daily for 20 days	
⇨	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatment for at least two recurrences should be tried prior to offering FMT

SD, standard dose; Fidaxomicin SD: 200 mg given twice daily for 10 days; Vancomycin SD: 125 mg given four times daily by mouth for 10 days; Fidaxomicin Extend: 200 mg twice daily for 5 days followed by once every other day for 20 days

Johnson S, et al. *Clin Infect Dis.* 2021; Jun 24;ciab549.doi:10.1093/cid/ciab549

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FMT is common in the veterinary world (transfaunation)

YouTube video: Baby elephants eating dung – BBC wildlife

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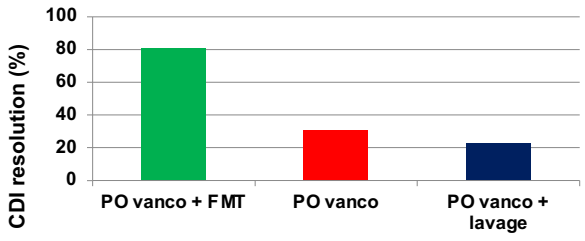
Duodenal Infusion of Donor Feces for Recurrent *C. difficile* Infection

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.

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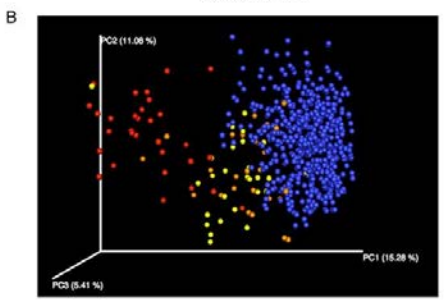
Next generation FMT (microbial consortium): SER-109

SER-109 is a consortium of purified bacterial spores of multiple Firmicute species, manufactured by fractionating targeted bacteria from the stool of healthy human donors with further steps to inactivate potential pathogens.



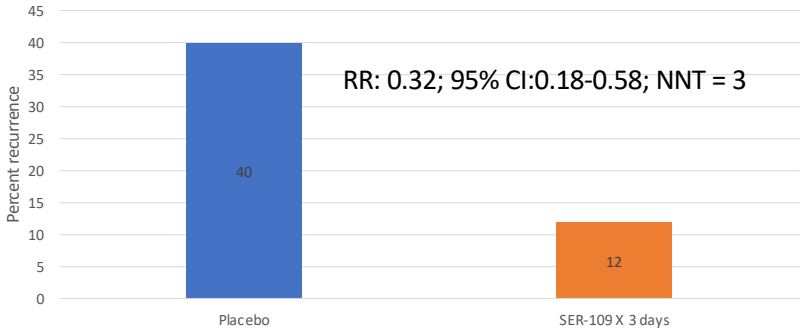
Red represents microbiome prior to SER-109, yellow represents after SER-109, and blue represents samples from the human microbiome project

Khanna et al. JID 2016

49

SER-109 Phase III results just became available

RCT: 182 patients with multiply recurrent CDI diagnosed via EIA given SER-109 or placebo (1:1)followed for 8 weeks for CDI recurrence



Feuerstadt et al. N Eng J Med 2022 Jan 20;386(3):220-229. doi: 10.1056/NEJMoa2106516

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There are a ton of next generation FMT products in development!

Company	Study Name	Product Description	Phase	Study Population	Primary Outcome
Rebiotix/Ferring		RBX7455	Phase 1	Recurrent CDI	Absence of CDI diarrhea without re-treatment at 8 weeks
Rebiotix/Ferring	PUNCH CD 3	RBX2660 Enema	Phase 3	Recurrent CDI	Absence of CDI diarrhea without re-treatment at 8 weeks
Seres Therapeutics	ECOSPOR III	SER-109 Oral capsule (Firmicutes spores)	Phase 3	Recurrent CDI	CDI recurrence at 8 weeks
Finch Therapeutics Group	PRISM3	CP101 Oral capsule	Phase 2	Recurrent CDI	CDI recurrence at 8 weeks
Vedanta Bioscience	CONSORTIUM	VE303	Phase 2	Recurrent CDI	CDI Recurrence at 8 weeks

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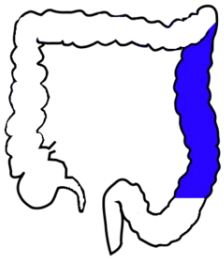
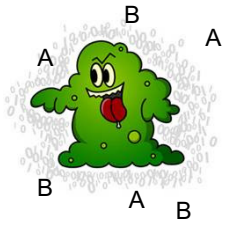
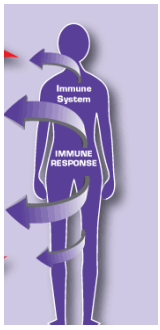
Explosion in Treatment Possibilities for CDI: <u>Augment Immune Response!</u>







Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Vancomycin
Fidaxomicin

IVIG
Monoclonal antibodies vs. *C. difficile* toxins

Future: 2nd-generation FMT
Non-tox *C. difficile* M3
Ecobiotics

Ridinilazole

Toxoid vaccines

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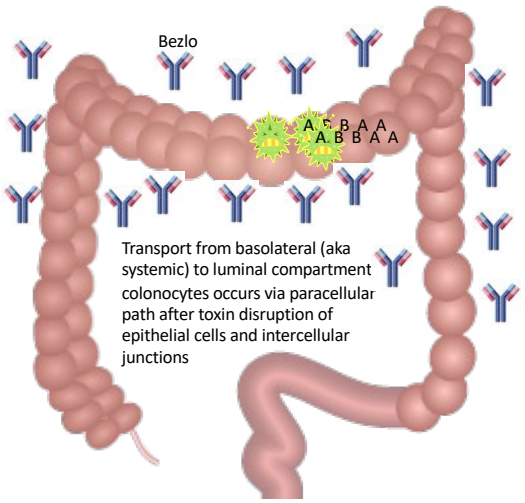
Bezlotoxumab



Fully human IgG1 monoclonal antibody against *C. difficile* toxin B

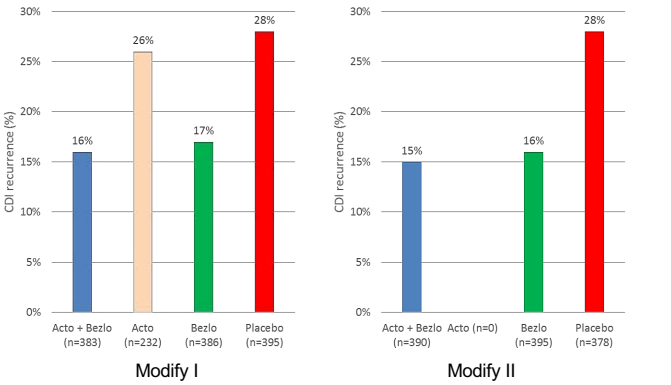
Single infusion (10 mg/kg) over 60 minutes while receiving standard of care antibiotics

$T_{1/2}$ = 20 days

Infect Dis Ther 2020;9:481-94

53

Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo)



Wilcox et al. N Eng J Med 2017;376(4):305-17

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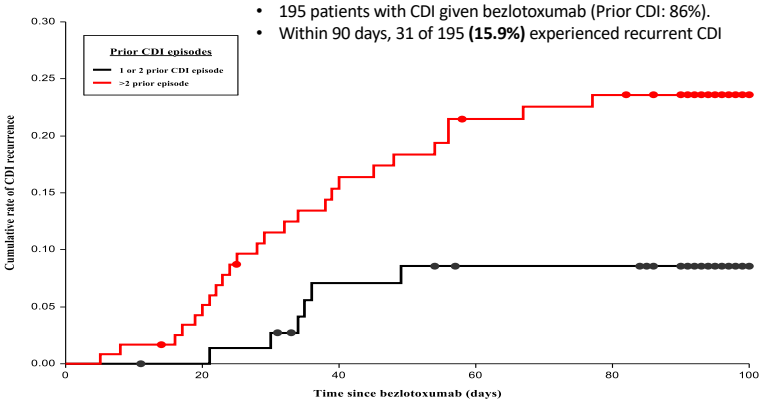
Real world data has mimicked the clinical trial results

- 195 patients with CDI given bezlotoxumab (Prior CDI: 86%).
- Within 90 days, 31 of 195 **(15.9%)** experienced recurrent CDI



Hengel et al. OFID 2020

55

Recommendation for Treatment of CDI in Adults, 2021

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin SD	Implementation depends on available resources
	Alternative: Vancomycin SD	Vancomycin remains an acceptable alternative
	Alternative for non-severe CDI, if above agents are unavailable: Metronidazole SD	Definition of non-severe is supported by the following lab parameters: White blood cell count of 15,000 cells/mL or lower and a serum creatinine level less than 1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin SD or Extend	
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Vancomycin 125 mg four times daily for 10-14 days, two times daily for seven days, and then every two to three days for two to eight weeks
	Alternative: Vancomycin SD	Consider a standard course of vancomycin if metronidazole was used from treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure
Second or subsequent CDI recurrences	FMT	
	Adjunctive treatment: Bezlotoxumab	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure

SD, standard dose; Fidaxomicin SD: 200 mg given twice daily for 10 days; Vancomycin SD: 125 mg given four times daily by mouth for 10 days; Fidaxomicin Extend: 200 mg twice daily for 5 days followed by once every other day for 20 days; SOC: standard of care

Johnson S, et al. *Clin Infect Dis*. 2021; Jun 24;ciab549.doi:10.1093/cid/ciab549

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Conclusions

- We are in the world of rising MDROs
  - This will increase healthcare burden on a global scale
- Using C diff as an example
  - AMR will complicate an already difficult disease state
  - BUT: also provides hints that we can tackle this problem

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The Return of MDROs: C diff Case Example

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