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Clostridium Difficile Infection: Applying New Treatment Guidelines and Strategies to Reduce Recurrence Rate

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Objectives

- Summarize the changing epidemiology and demographics of patients at risk for *Clostridium difficile* infection (CDI) recurrence
- More knowledgeably select therapeutic regimens for patients at high risk for recurrent CDI, including validated non-antibiotic agents
- Analyze the impact of the recent changes made to the Infectious Diseases Society of America guidelines on CDI diagnosis accuracy and patient outcomes

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Faculty Information

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Dr. Dubberke receives consulting fees from Merck, Rebiotix, Summit, and Synthetic Biologics; and has contracted research for Pfizer.

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Dept of Pharmacy Practice and Translational Research
Houston, TX

Dr. Garey receives consulting fees from Merck, Summit PLC, and Seres Therapeutics.

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C. diff Incidence Rate

- CDC list of pathogens with pathogens at highest level of risk — based on high incidence and mortality rates
  - Roughly 500,000 cases of *C. diff* per year; 29,000 deaths
  - *C. diff* is the #1 cause of infectious diarrhea for patients hospitalized in all developed countries
  - Often not tested for, more of an emerging disease
  - Considered a global pathogen

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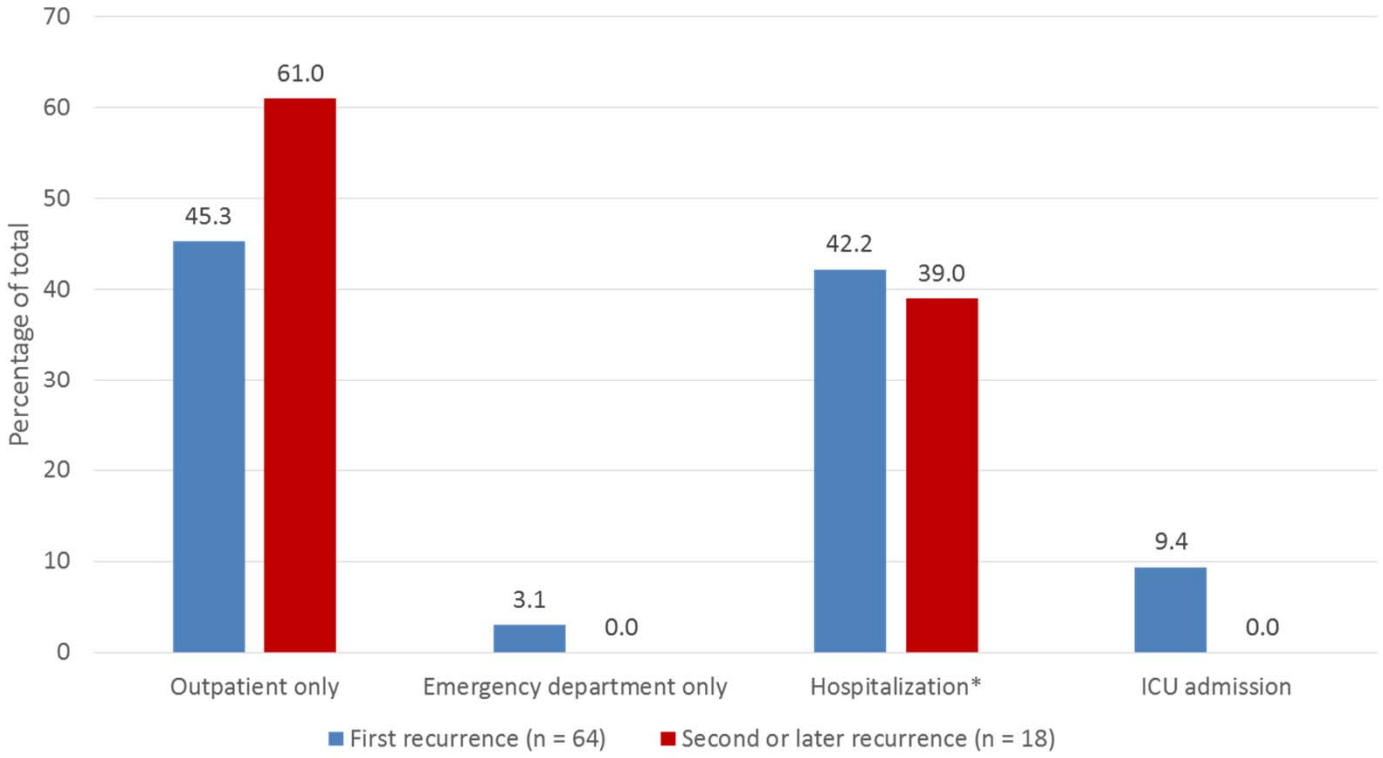
Recurrent CDI is Costly: Healthcare Utilization for Recurrent CDI



Aitken SL et al. *PLoS One*. 2014;9(7):e102848.

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

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What Factors Place Patients at Higher Risk for CDI?

- Patients have 2 main lines of defense against *C. diff*
  - Microbiome — first line of defense
  - Immune system — second line of defense
- Most important risk factor for CDI is antibiotic use
  - Alters the microbiome to where it may no longer protect against CDI
- Conditions, states, or medications that impact immune function place a patient with an altered microbiome at even greater risk for CDI

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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)

L. Clifford McDonald,[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] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

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PCR Diagnostic Strategies May Detect Patients Colonized with CDI but Not Infected

UK: prospective, multicenter study of suspected CDI patients; fecal samples were evaluated using cytotoxicity assay (CTA), cytotoxigenic culture (CC), or nucleic acid amplification test (NAAT)

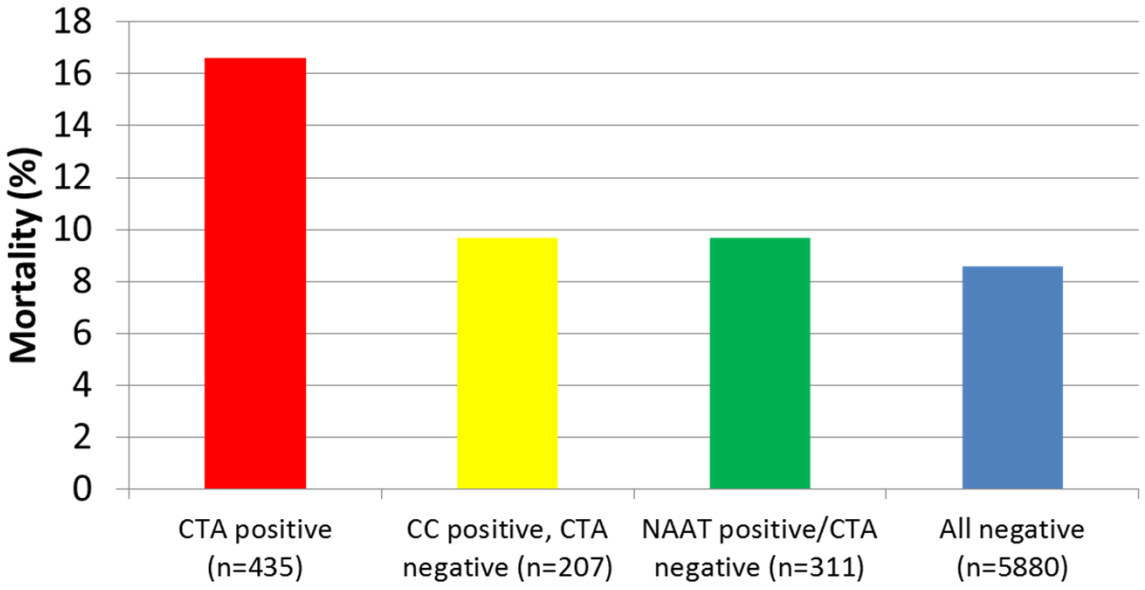

Planche TD et al. *Lancet Infect Dis*. 2013;13(11):936-945.

Mortality increased significantly in CTA-positive patients (OR 1.61, 95% CI 1.12–2.31)

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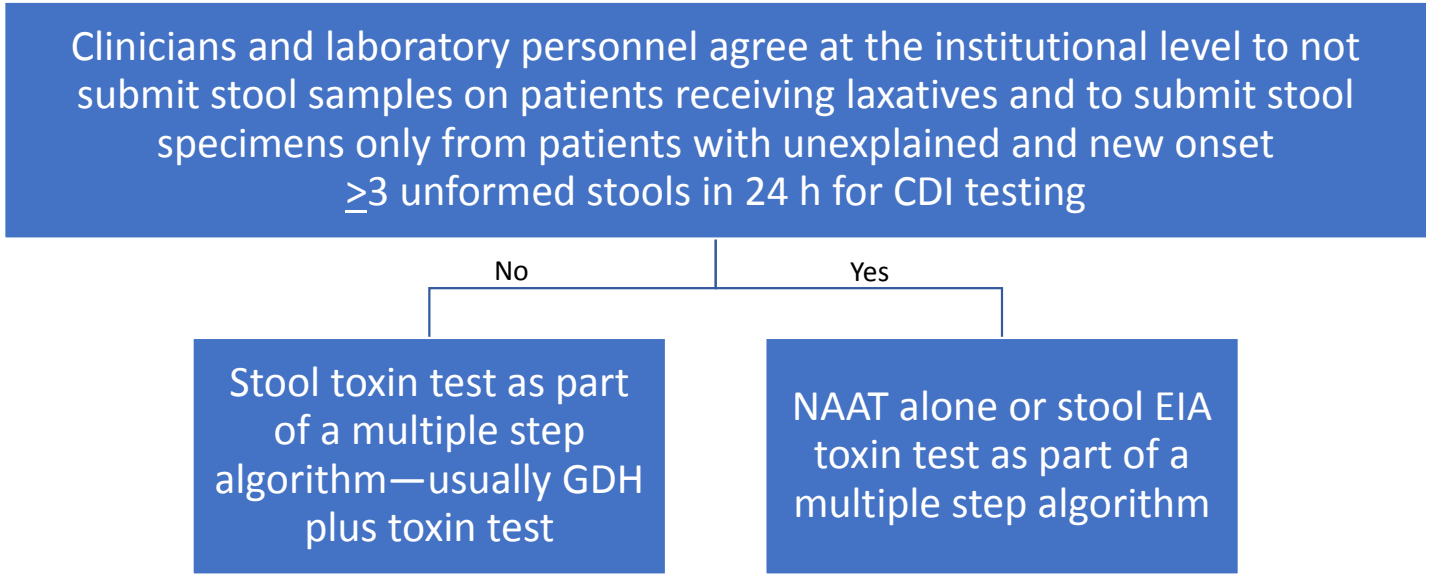
CDI Laboratory Test Recommendations



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

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Why Is Metronidazole No Longer Considered a Drug of Choice for CDI?

- In 2009, a small case series of patients treated with metronidazole showed only a 50% response rate
- A few years later, a randomized, controlled trial compared oral vancomycin with metronidazole, stratified by disease severity
  - In patients with severe CDI, oral vancomycin performed better; changed the 2010 guidelines
- For severe *C. diff*, use oral vancomycin; for mild to moderate, use metronidazole

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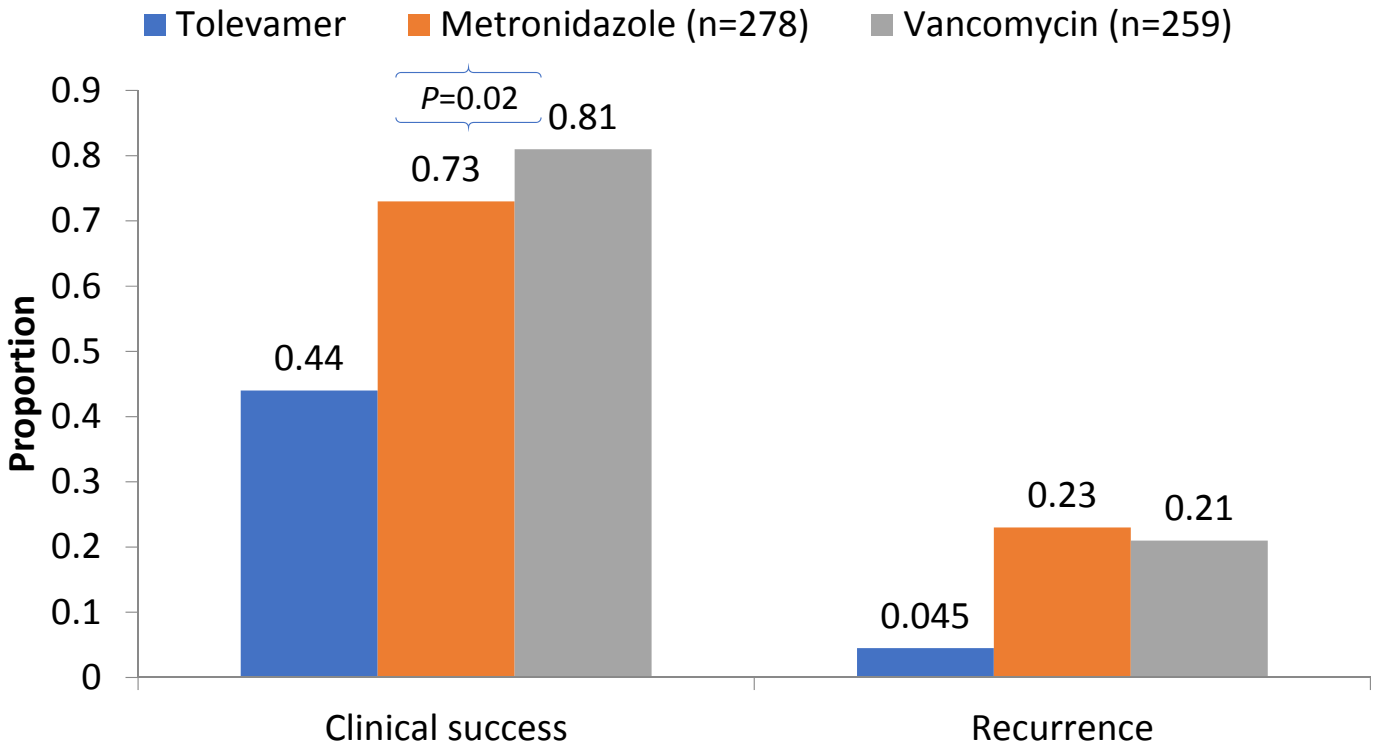
Metronidazole Shown to Be Globally Inferior to Vancomycin (Tolevamer Phase III RCT)



Johnson S et al. *Clin Infect Dis*. 2014;59(3):345-354.

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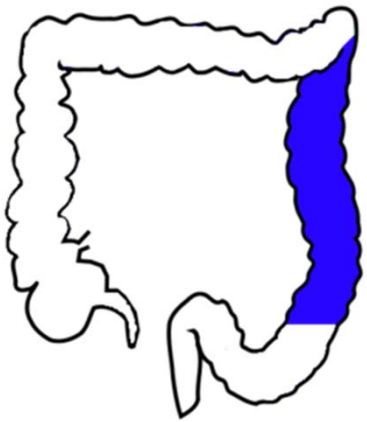
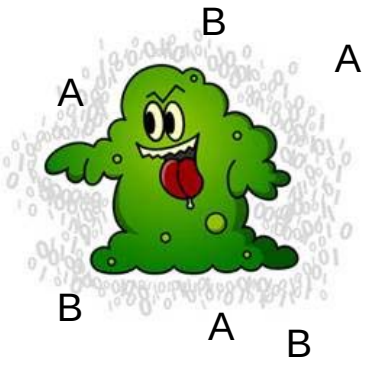
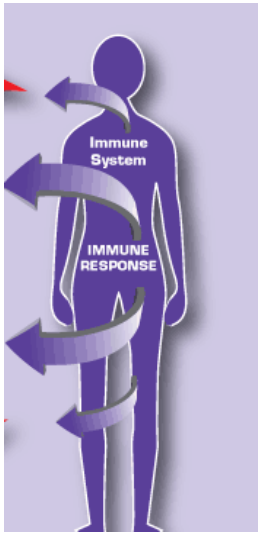
Treatment Possibilities for CDI



Probiotics
FMT
Narrow-spectrum antibiotics



Metronidazole
Vancomycin
Fidaxomicin



IVIG
Monoclonal antibodies vs. *C. diff* toxins

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Recommendations 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 hours if ileus present

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

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

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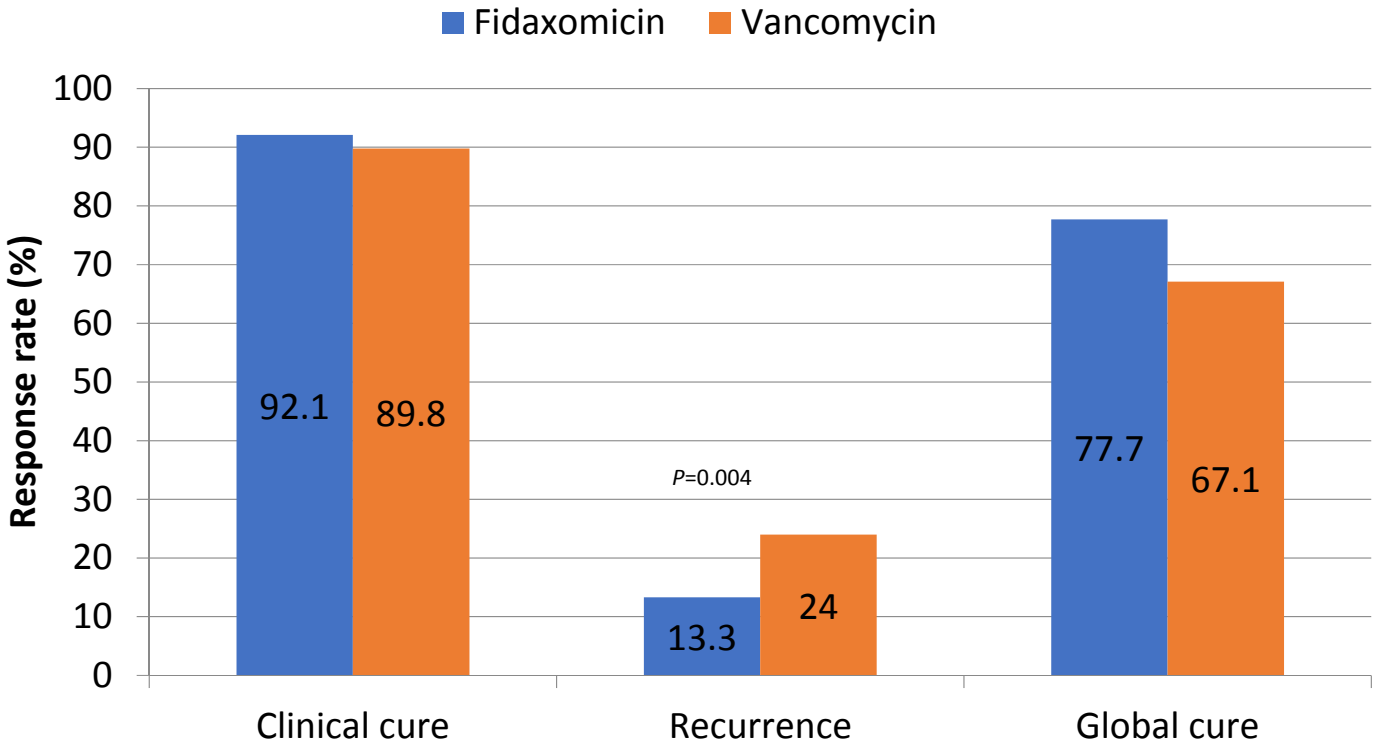
Fidaxomicin: Equal Efficacy at Vancomycin to Cure Patients and Lessens the Risk of Recurrence



Louie TJ et al. *N Engl J Med*. 2011;364(5):422-431.

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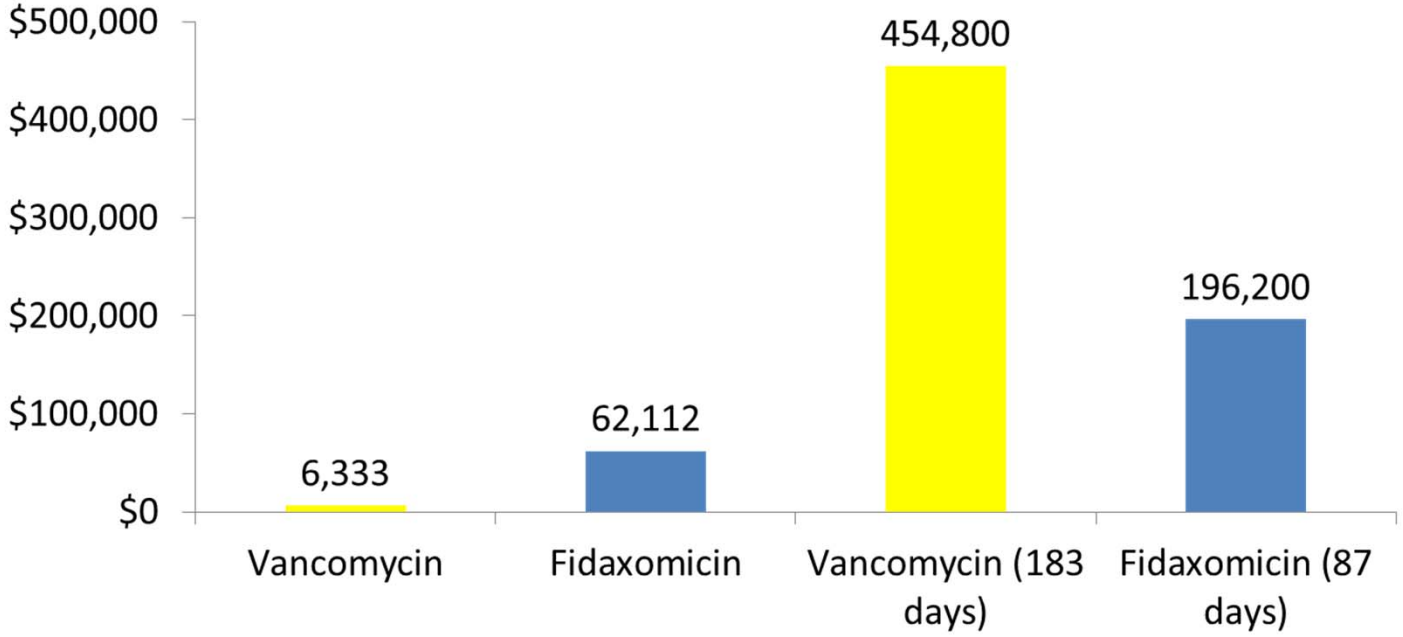
Any Evidence That Fidaxomicin May Reduce Costs?

Patients 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

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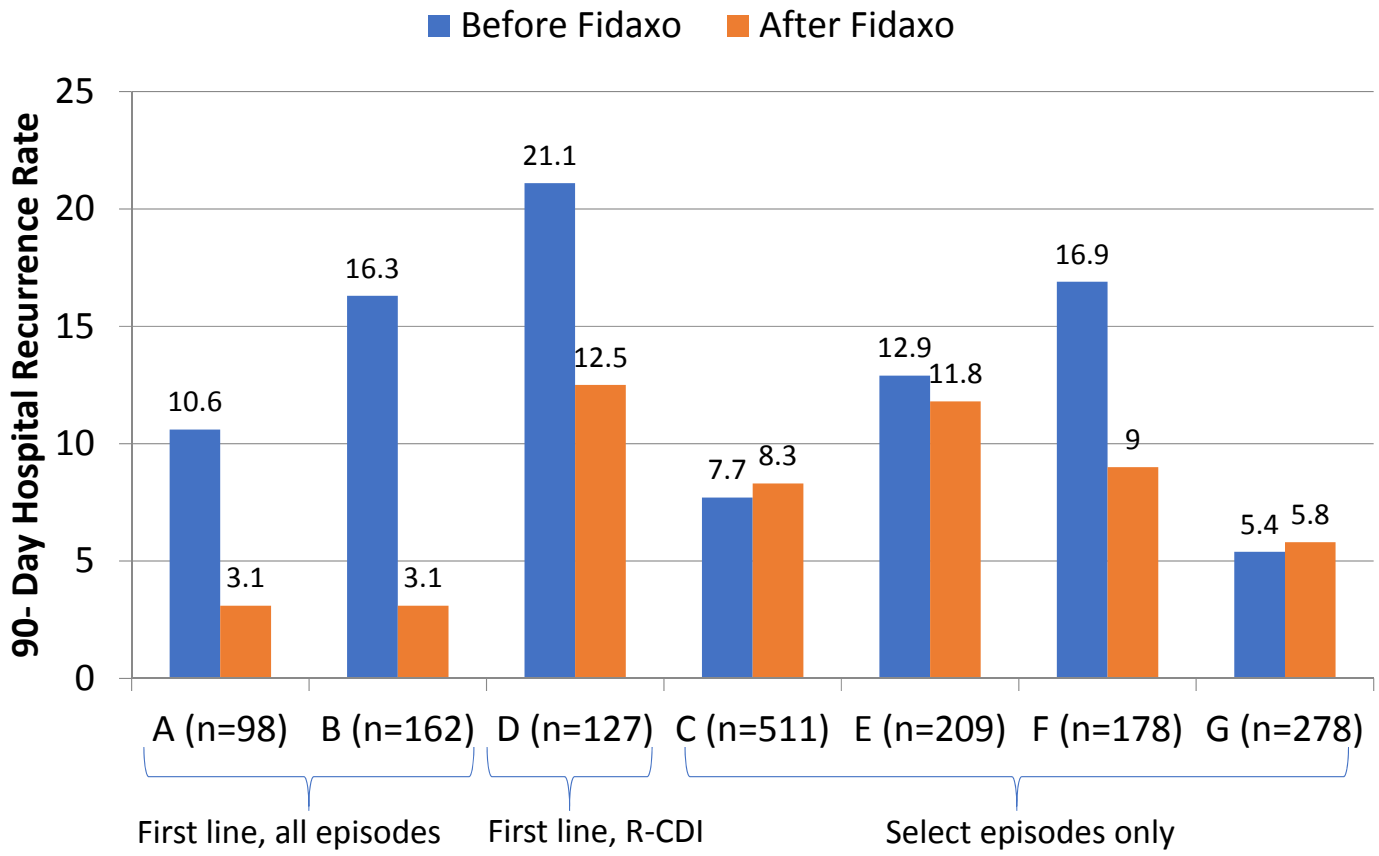
Real-World Evidence That Fidaxomicin May Reduce Costs?

UK, 2012-13: 7 hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals.



Goldenberg SD et al. *Eur J Clin Microbiol Infect Dis*. 2016;35(2):251-259.

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Recommendations for Recurrence of CDI in Adults

Clinical Definition	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 first 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(7):987-994.

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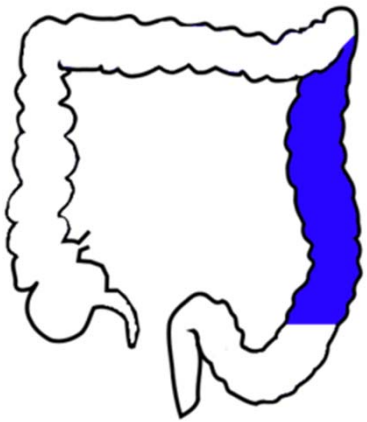
Treatment Possibilities for CDI



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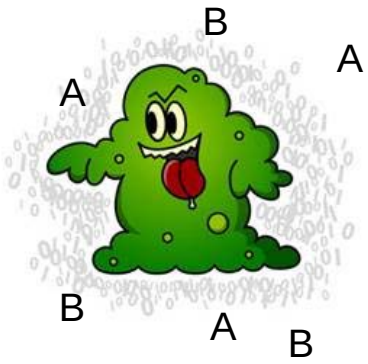
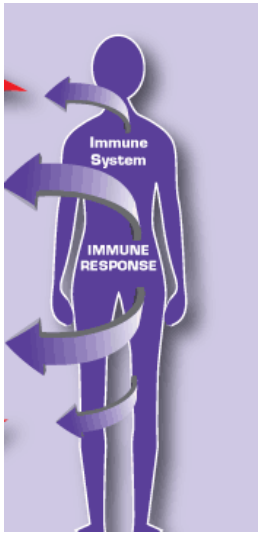
FMT
Narrow-spectrum antibiotics



Metronidazole
Vancomycin
Fidaxomicin



IVIG
Monoclonal antibodies vs. *C. diff* toxins

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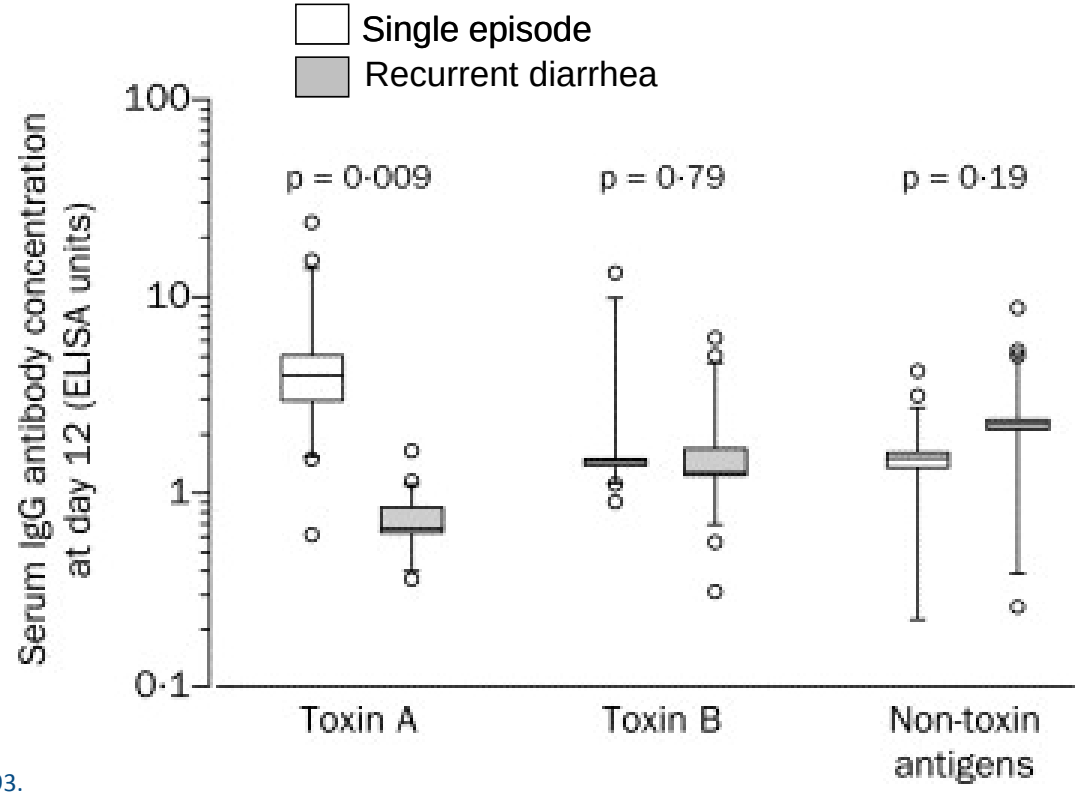
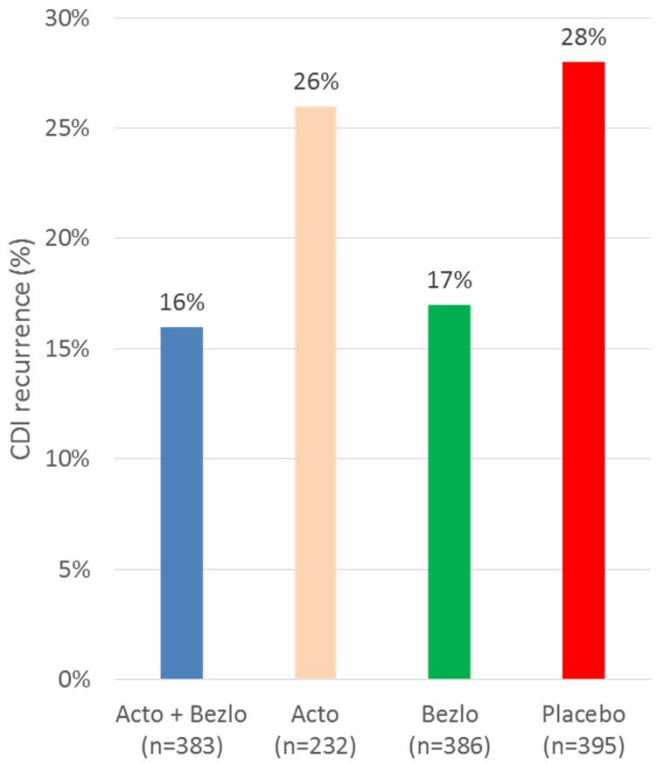
Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens

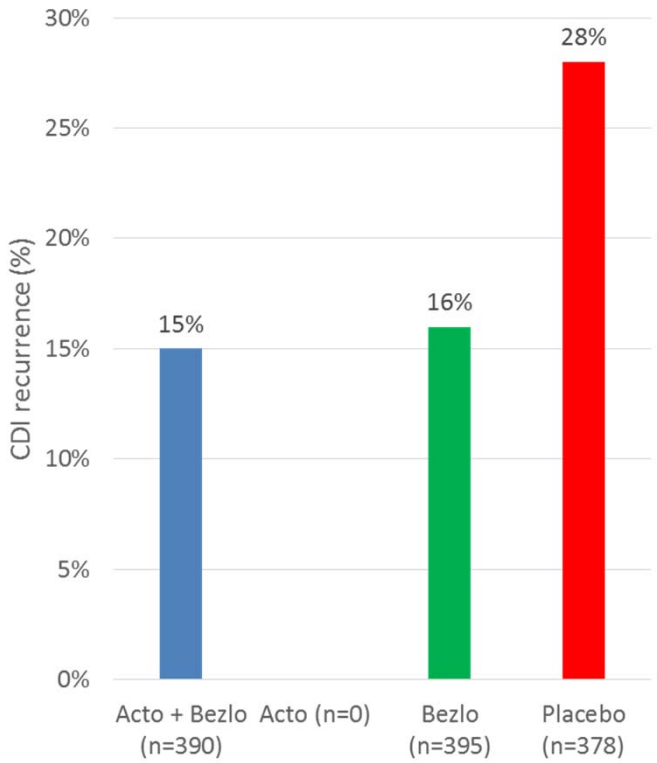


Kyne L et al. *Lancet*. 2001;357(9251):189-193.

Phase III Studies of Bezlotoxumab (Bezlo): Overall



Modify I



Modify II

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

Actoxumab (acto) is another monoclonal antibody originally studied for the prevention of recurrent CDI

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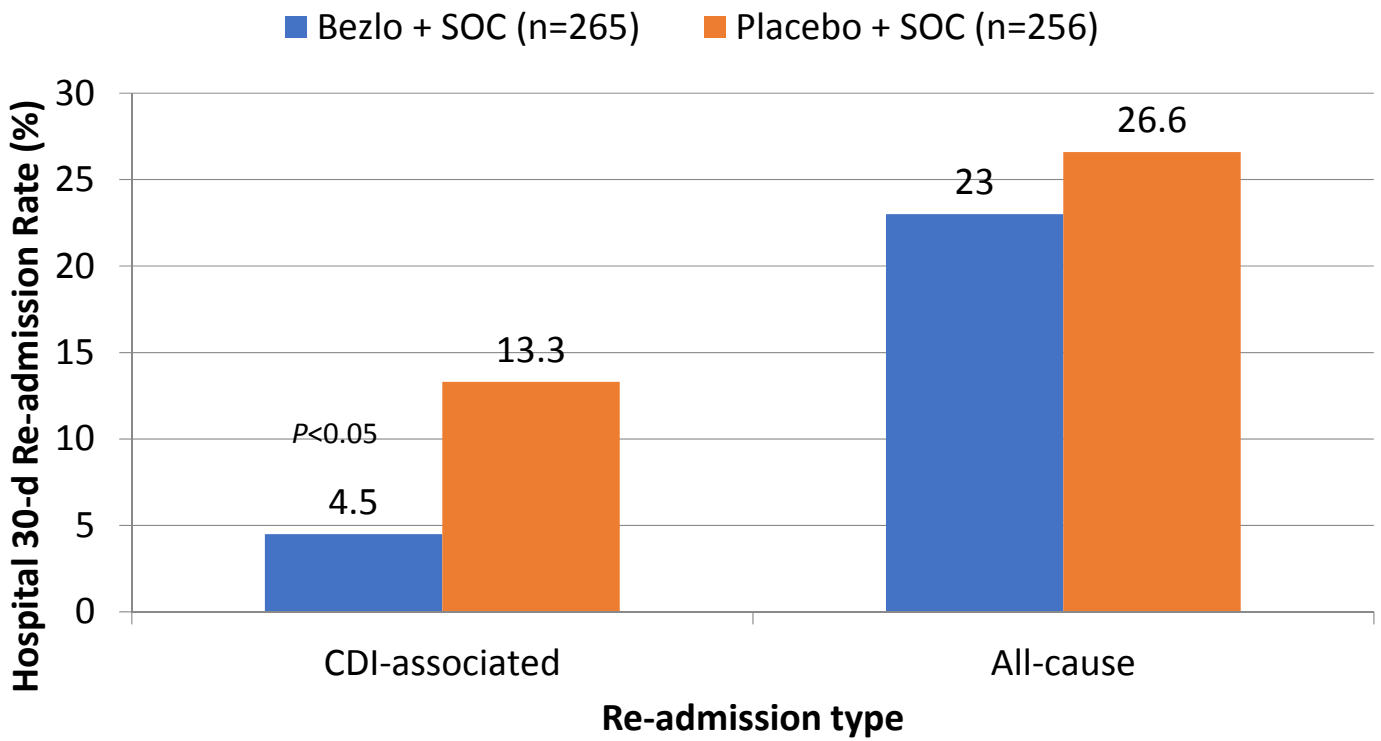
BEZLO was Shown to Reduce Hospital Re-admissions (European Population)



Prabhu VS, Dubberke ER, et al. *Clin Infect Dis*. 2017 Oct;65(7):1218–1221.

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Incremental Cost-Effectiveness Ratio (ICER)

- Cost effectiveness of bezlotoxumab vs. placebo
- ICER represents the average incremental cost per quality-adjusted life-years gained associated with an intervention
- Bezlotoxumab was found to be a cost-effective measure for preventing recurrent CDI, with an ICER of $19,824 per quality-adjusted life-year gained
- Better ICER for patients at increased risk for recurrence
  - ~$15,000 for patients ≥65 years of age
  - ~$13,000 for immunocompromised patients
  - ~$5,000 for immunocompromised patients with a history of CDI in the past 6 months
  - ~ $3,500 for patients ≥65 years of age with a history of CDI in the past 6 months

Prabhu VS et al. *Clin Infect Dis*. 2018;66(3):355-362.

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Conclusions

- *C. diff* remains a significant clinical challenge
- 2017 guidelines had major changes compared with 2010 guidelines
  - Additional guidance for diagnosis of CDI
  - Treatment guidelines
    - Metronidazole no longer is a first-line treatment for CDI
    - Fidaxomicin as a first-line treatment for a first or second episode of CDI or first episode and first recurrence of CDI; not mentioned in 2010 guidelines, not available until 2011
    - Bezlotoxumab is cost-effective and prevents recurrent CDI; will also improve patient outcomes
- Appropriate treatment of *C. diff* is "a team sport"
  - Key role of antimicrobial stewardship team to prevent overuse of antibiotics and develop treatment algorithms
  - Interprofessional team members should collaborate to provide optimal care