# *Clostridium difficile* Infection Update

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# Introduction

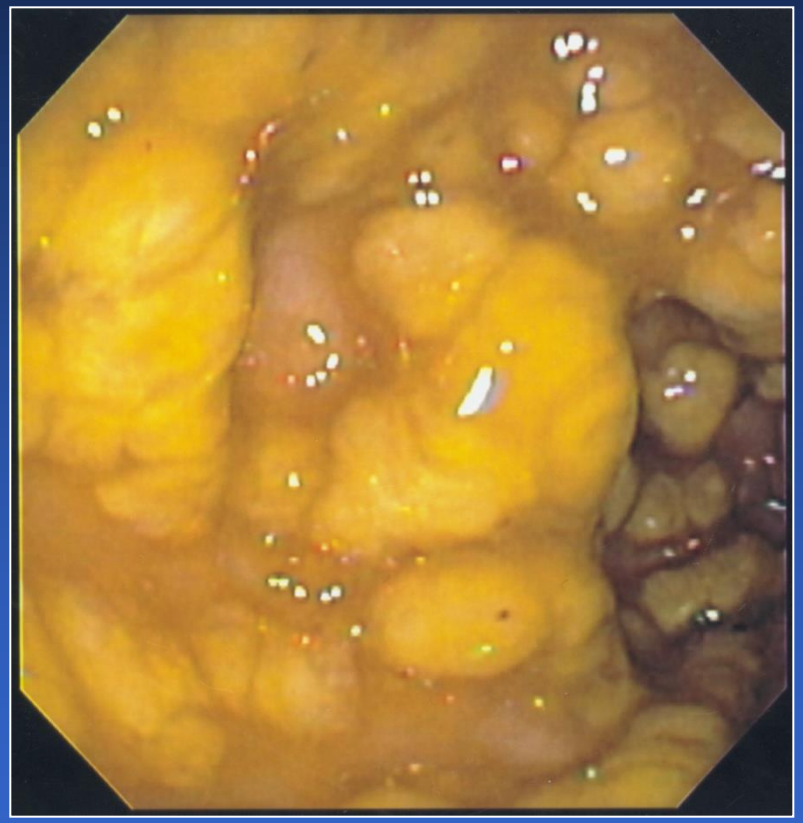
- Clostridium difficile infection (CDI) is a significant healthcare-associated infection with considerable economic impact.
- In the US, CDI causes approximately 453,000 infections and 29,000 deaths every year, with an annual economic burden ranging from $436 million to $3 billion dollars.
- There has also been an increase in the prevalence of fulminant C. difficile colitis in the past several decades. This is due in part to newly recognized hypervirulent strains such as the C. difficile BI/NAP1/027 clone

# Case Definition CDI

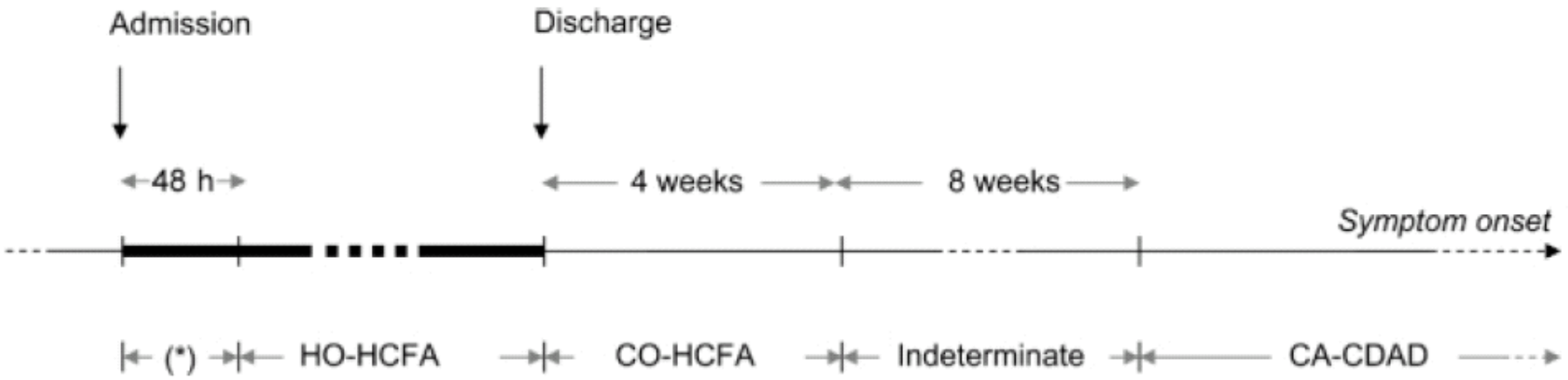
- The presence of diarrhea
  - 3 or more unformed stools in 24 or fewer consecutive hours
- A stool test result positive for the presence of toxigenic *C. difficile or* its toxins; or
- Colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.

Cohen, et al. Infect Control Hosp Epidemiol 2010; 31(5): 431-55.

# Case Images: Colon

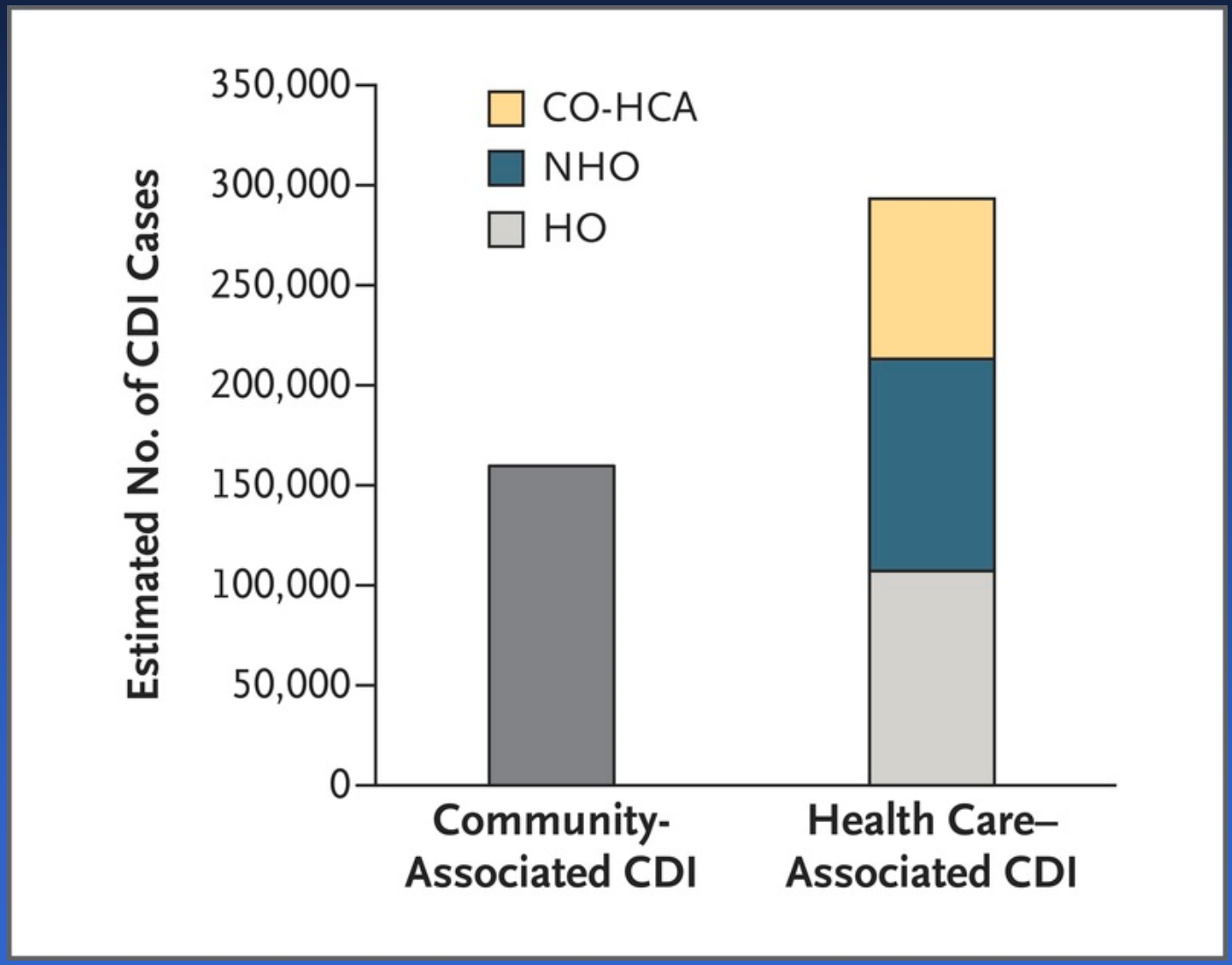


# Time line for definitions of *Clostridium* difficile–associated disease (CDAD)




McDonald, et al. Infect Control Hosp Epidemiol 2007; 28:140-145

# Estimated Burden of *Clostridium difficile* Infection (CDI), 2011




Lessa, et al. N Engl J Med 2015; 372:825-834

# Pathogenesis of CDI

**Antibiotic therapy**

↓

**Alteration of colonic microflora**

↓

***C. difficile* exposure and colonization**

↓

**Release of toxin A and toxin B**

↓

**Colonic mucosal injury and inflammation**

Reprinted from Kelly CP, et al. *Annu Rev Med*. 1998;49:375-390.

# Risk Factors for CDI

| | |
|---|---|
| Admission(s) in previous 60 days | 2.1 (1.7–2.6) |
| Age | |
| <45 years | Reference |
| 45–59 years | 1.9 (1.3–2.7) |
| 60–74 years | 2.4 (1.7–3.4) |
| >74 years | 3.5 (2.4–5.0) |
| CDAD pressure | |
| <0.3 | Reference |
| 0.3–1.4 | 2.9 (2.1–4.2) |
| >1.4 | 4.0 (2.9–5.6) |
| Albumin level | |
| Normal (>3.5 g/dL) | Reference |
| Low (2.5–3.5 g/dL) | 1.4 (1.1–1.8) |
| Very low (<2.5 g/dL) | 1.8 (1.2–2.5) |
| Leukemia/lymphoma | 2.3 (1.6–3.2) |
| Mechanical ventilation | 1.9 (1.4–2.6) |
| Medication(s) | |
| Histamine-2 blocker | 2.0 (1.6–2.5) |
| Proton pump inhibitor | 1.6 (1.3–2.1) |
| Antimotility agent | 1.3 (1.1–1.7) |

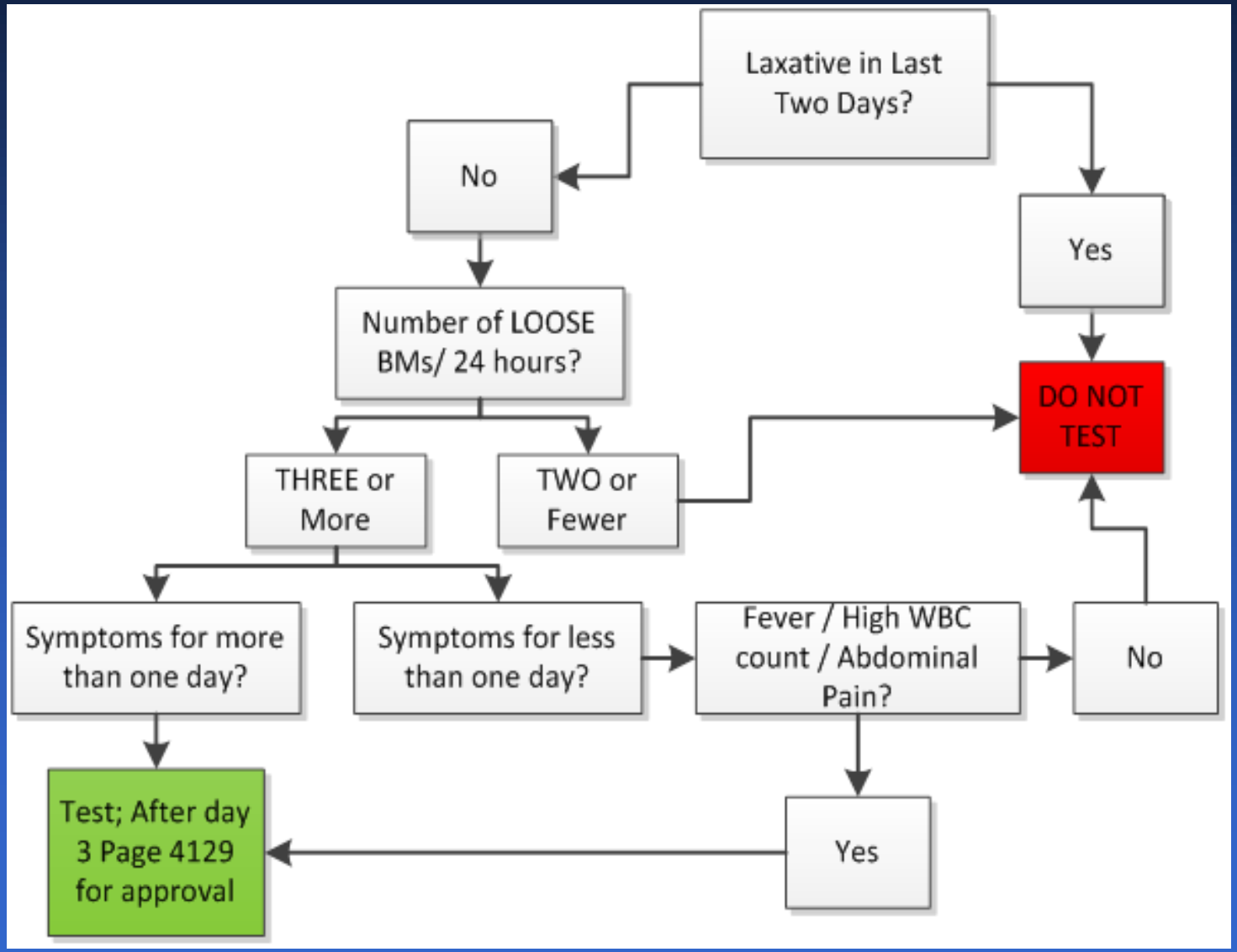
Dubberke, et al. Clinical Infectious Diseases 2007; 45

# Who Should Get Tested?

- Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI *(weak recommendation, very low quality of evidence).*

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# *C. difficile* Testing Algorithm at RUMC



# CDI Testing Issues

- Inappropriate *C. difficile* testing is common[1,2] and nucleic acid amplification testing may lead to overdiagnosis of CDI in patients who have asymptomatic colonization[3]
- Currently, NHSN requires that hospitals report laboratory-identified CDI as the sole means of surveillance. HO-CDI cases determine facility-specific SIR, which is a publically reported safety measure and is used for VBP.
- The 2017 IDSA *C. difficile* guidelines recommend the use of NAAT alone for detection of *C. difficile* infection (CDI) if appropriate stool specimens are collected (e.g., patients not receiving laxatives and ≥3 unformed stools in 24 hours)

1. Dubberke ER et al. JCM. 2011 Jun 22:JCM-00891.
2. Buckel WR et al. ICHE 36.2 (2015): 217-221.
3. McDonald LC, et al. Clin Infect Dis. 2018: 987-994.

# Advantages and Disadvantages of *Clostridium difficile* Assays

| Assay | Method/target | Advantages | Disadvantages |
|---|---|---|---|
| Culture | Organism | High sensitivity ("gold standard") | •Turn-around time >7 days<br>•Labor intensive<br>•Lacks specificity |
| Cell cytotoxicity | Functional assay for C. difficile toxin B | •Moderate-to-high sensitivity<br>•High specificity | •48-72 h turn-around<br>•Subjective interpretation<br>•Labor intensive |
| Enzyme immunoassays (EIA), | Toxin A/B detection | •Easy to perform<br>•Rapid turn-around<br>•Inexpensive<br>•High specificity | Lower sensitivity |
| EIA, glutamate dehydrogenase | Common antigen detection | •High sensitivity<br>•Good screening test | Low specificity. Positive specimens must be further tested |
| Nucleic acid amplification tests | Toxin gene(s) detection | High sensitivity | Expensive. Doesn't distinguish colonization and infection |

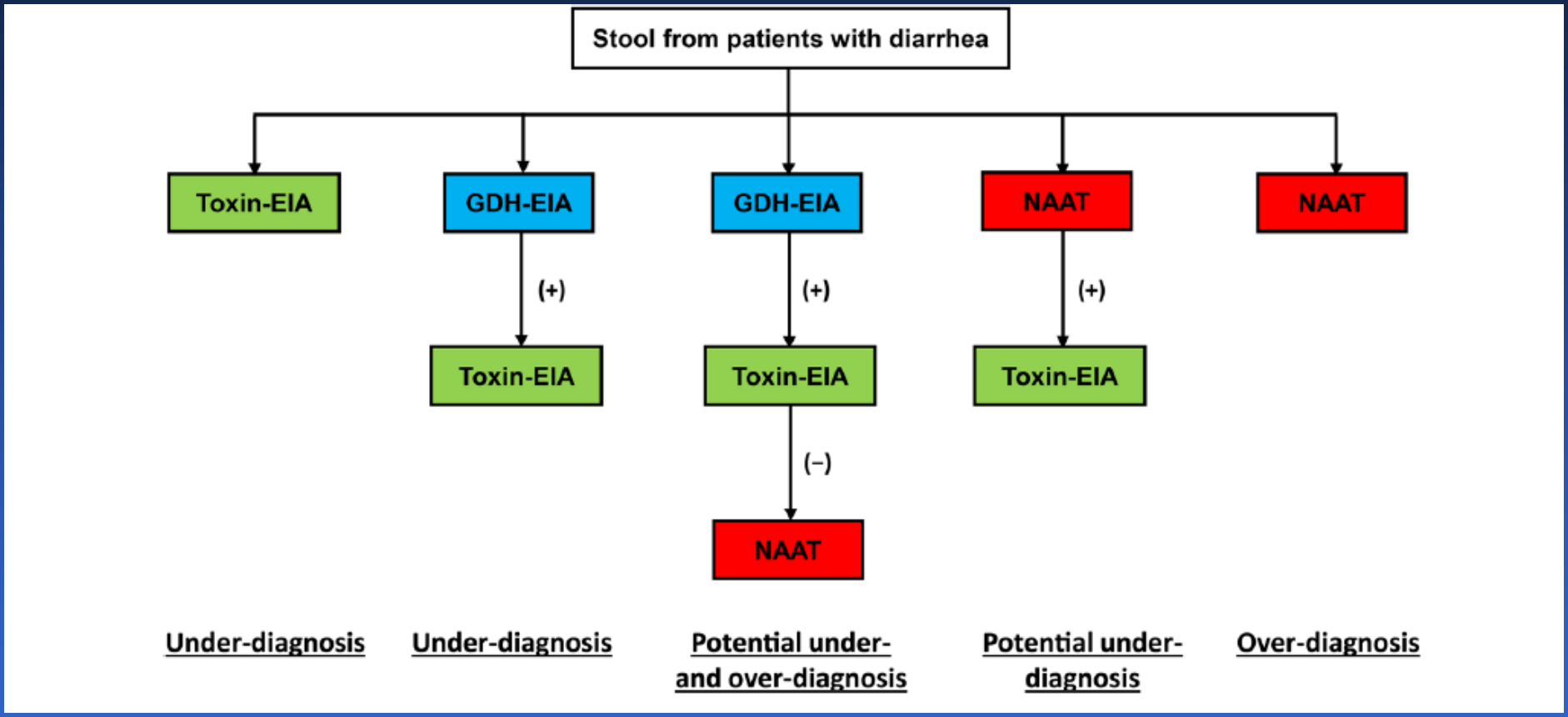
Cohen, et al. Infect Control Hosp Epidemiol 2010; 31(5): 431-55.

# What is the best testing strategy to diagnose CDI ?

- Use a stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission *(weak recommendation, low quality of evidence).*

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# Test Algorithms for the Diagnosis of Clostridium difficile Infection.




Peng et al. Emerging Microbes & Infections (2018) 7:15

Original Investigation

# Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era

Christopher R. Polage, MD, MAS; Clare E. Gyorke, BS; Michael A. Kennedy, BS; Jhansi L. Leslie, BS; David L. Chin, PhD; Susan Wang, BS; Hien H. Nguyen, MD, MAS; Bin Huang, MD, PhD; Yi-Wei Tang, MD, PhD; Lenora W. Lee, MD; Kyoungmi Kim, PhD; Sandra Taylor, PhD; Patrick S. Romano, MD, MPH; Edward A. Panacek, MD, MPH; Parker B. Goodell, BS, MPH; Jay V. Solnick, MD, PhD; Stuart H. Cohen, MD

JAMA Intern Med. doi:10.1001/jamainternmed.2015.4114
Published online September 8, 2015.

# Findings

- No CDI-related complications occurred in Tox−/PCR+ patients vs 10 complications in Tox+/PCR+ patients (0% vs 7.6%, P < .001).
- One Tox−/PCR+ patient had recurrent CDI as a contributing factor to death within 30 days vs 11 CDI-related deaths in Tox+/PCR+ patients (0.6%vs 8.4%, P = .001).

JAMA Intern Med. doi:10.1001/jamainternmed.2015.4114
Published online September 8, 2015.

# Conclusions

- Among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay test results.
- Patients with a positive molecular test result and a negative toxin immunoassay test result had outcomes that were comparable to patients without C difficile by either method.
- Exclusive reliance on molecular tests for CDI diagnosis without tests for toxins or host response is likely to result in overdiagnosis, overtreatment, and increased health care costs.

JAMA Intern Med. doi:10.1001/jamainternmed.2015.4114
Published online September 8, 2015.

# What is the Role of Repeat Testing?

- Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies *(strong recommendation, moderate quality of evidence).*
- Do not repeat testing as a test of cure.

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# CDI Prevention

- Place patients with CDI in a private room with a dedicated toilet.
- If there is a limited number of private single rooms, prioritize patients with stool incontinence for placement in private rooms (*strong recommendation, moderate quality of evidence*).

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# CDI Prevention

- Patients with suspected CDI should be placed on contact precautions pending the C. difficile test results (*strong recommendation, moderate quality of evidence*).
- Continue contact precautions for at least 48 hours after diarrhea has resolved (*weak recommendation, low quality of evidence*).
- Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI (*weak recommendation, low quality of evidence*).

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# CDI Prevention

- In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand hygiene product *(strong recommendation, moderate quality of evidence)*.
- In CDI outbreaks or hyperendemic (sustained high rates) settings, perform hand hygiene with soap and water preferentially instead of alcohol-based hand hygiene products before and after caring for a patient with CDI given the increased efficacy of spore removal with soap and water *(weak recommendation, low quality of evidence).*

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# CDI Prevention

- Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk (*strong recommendation, moderate quality of evidence*).
- Implement an antibiotic stewardship program (good practice recommendation).
- Antibiotics to be targeted should be based on the local epidemiology and the C. difficile strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered (*strong recommendation, moderate quality of evidence*).

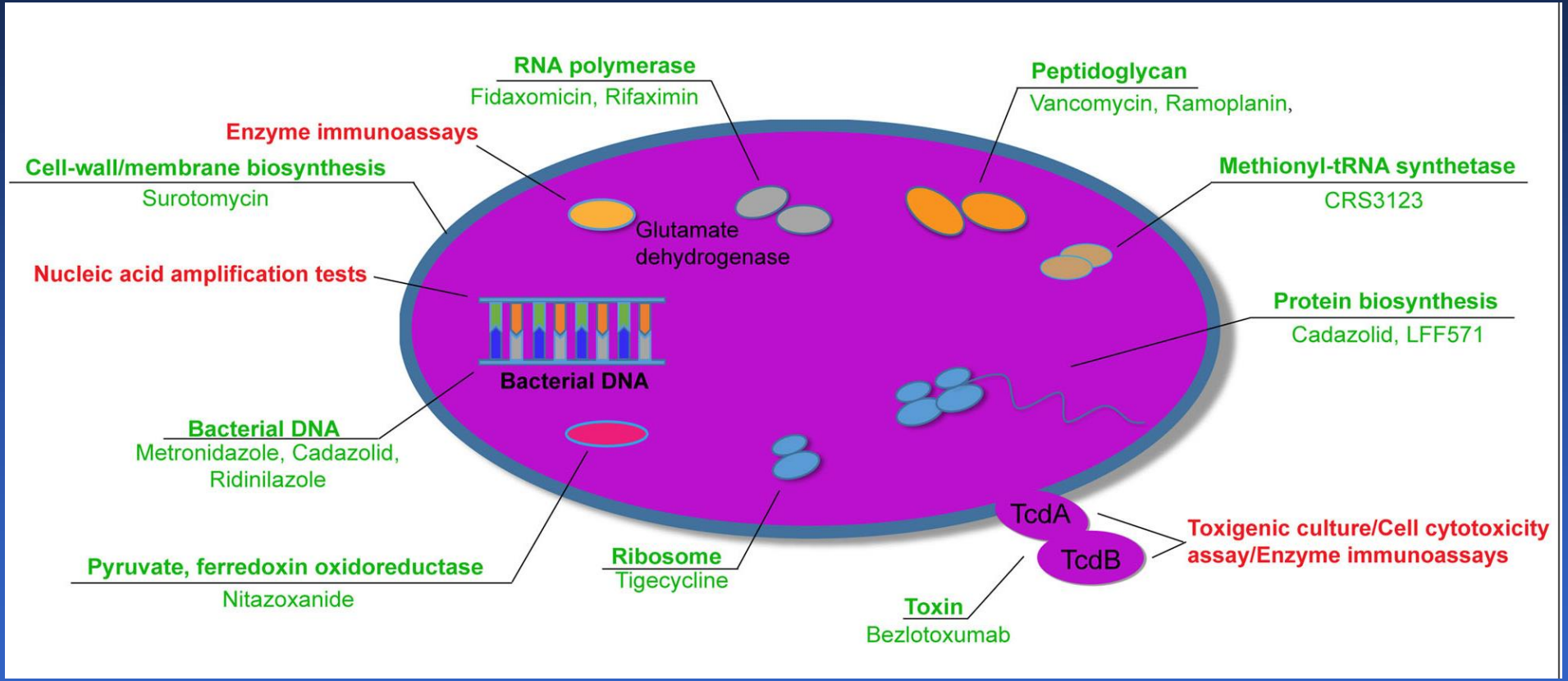
McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# Risk Factors for CDI: Antibiotics

| | |
|---|---|
| First-generation cephalosporin | |
| 0 days | Reference |
| >0 to 7 days | 0.7 (0.5–0.9) |
| >7 days | 5.6 (3.8–8.4) |
| Third-generation cephalosporin | |
| 0 days | Reference |
| >0 to 7 days | 0.9 (0.6–1.3) |
| >7 days | 9.2 (5.9–14.5) |
| Fourth-generation cephalosporin | |
| 0 days | Reference |
| >0 to 7 days | 2.2 (1.6–3.0) |
| >7 days | 3.3 (2.3–4.8) |
| Fluoroquinolone | |
| 0 days | Reference |
| >0 to 7 days | 0.7 (0.5–0.9) |
| >7 days | 2.5 (1.8–3.5) |
| Vancomycin (intravenous) | |
| 0 days | Reference |
| >0 to 7 days | 1.1 (0.8–1.5) |
| >7 days | 1.9 (1.3–2.7) |
| Metronidazole | 0.5 (0.3–0.6) |

Dubberke, et al. Clinical Infectious Diseases 2007; 45

# Bacterial Targets for CDI Therapeutics




Peng et al. Emerging Microbes & Infections (2018) 7:15

# Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

| Clinical Definition | Supportive Clinical Data | Recommended Treatment[a] | Strength of Recommendation/ Quality of Evidence |
|---|---|---|---|
| Initial episode, non-severe | Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL | • VAN 125 mg given 4 times daily for 10 days, OR<br>• FDX 200 mg given twice daily for 10 days<br>• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days | Strong/High<br>Strong/High<br>Weak/High |
| Initial episode, severe[b] | Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL | • VAN, 125 mg 4 times per day by mouth for 10 days, OR<br>• FDX 200 mg given twice daily for 10 days | Strong/High<br>Strong/High |
| Initial episode, fulminant | Hypotension or shock, ileus, megacolon | • VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present. | Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole) |

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

| | | | |
|---|---|---|---|
| First recurrence | … | • VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR | Weak/Low |
| | | • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR | Weak/Low |
| | | • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode | Weak/Moderate |
| Second or subsequent recurrence | … | • VAN in a tapered and pulsed regimen, OR | Weak/Low |
| | | • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR | Weak/Low |
| | | • FDX 200 mg given twice daily for 10 days, OR | Weak/Low |
| | | • Fecal microbiota transplantation[c] | Strong/Moderate |

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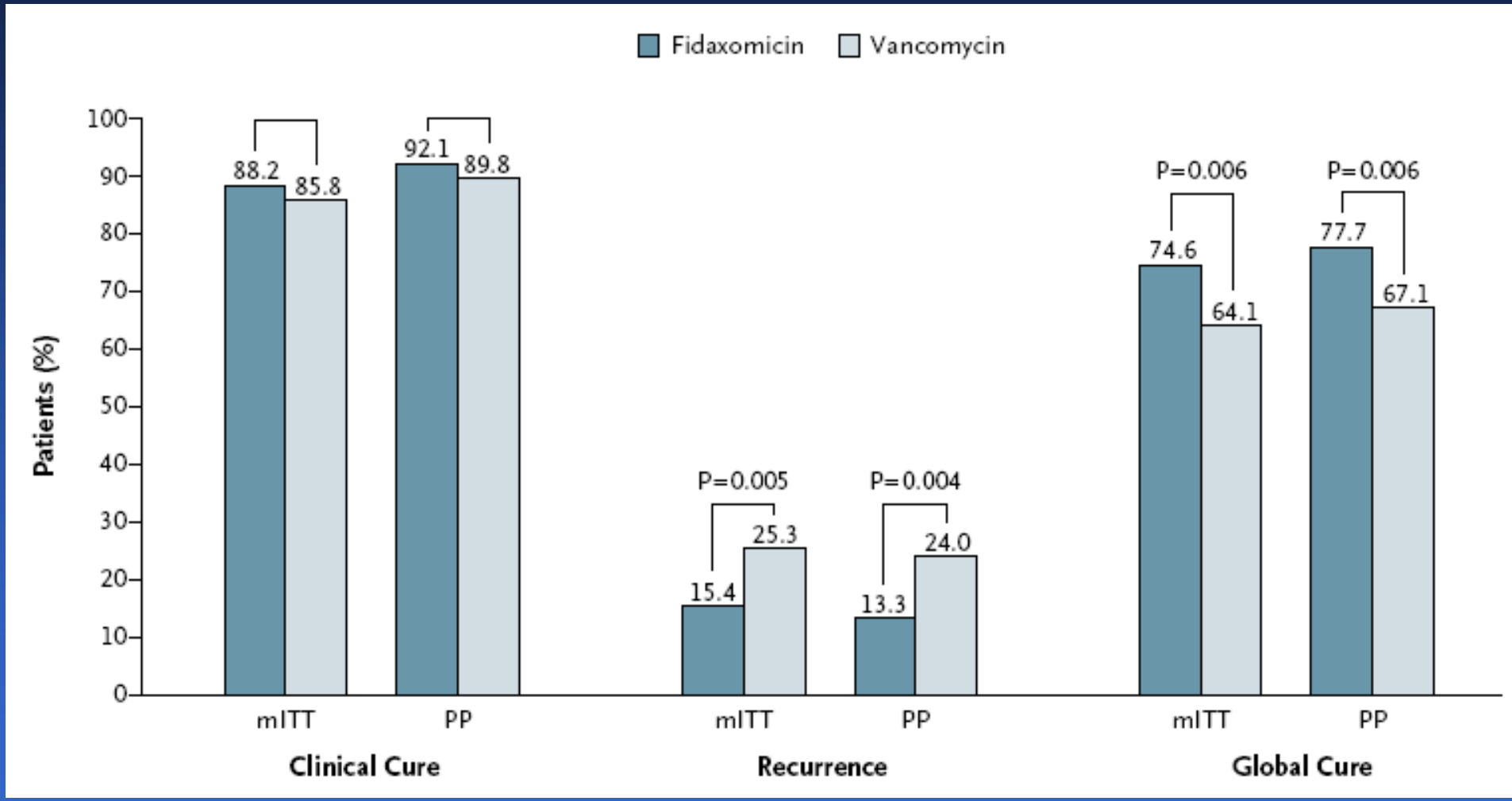
# Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection




Louie, et al. N Engl J Med 2011;364:422-31.

# Rates of Recurrence of *C. difficile* Infection

| Subgroup | Modified Intention-to-Treat Population | | | Per-Protocol Population | | |
|---|---|---|---|---|---|---|
| | Fidaxomicin | Vancomycin | P Value | Fidaxomicin | Vancomycin | P Value |
| | *no./total no. (%)* | | | *no./total no. (%)* | | |
| Severity of disease at baseline | | | | | | |
| Mild | 7/59 (11.9) | 20/68 (29.4) | 0.02 | 4/44 (9.1) | 13/55 (23.6) | 0.06 |
| Moderate | 20/102 (19.6) | 18/88 (20.5) | 0.89 | 15/90 (16.7) | 18/71 (25.4) | 0.18 |
| Severe | 12/92 (13.0) | 29/109 (26.6) | 0.02 | 9/77 (11.7) | 22/95 (23.2) | 0.05 |
| Strain type | | | | | | |
| NAP1/BI/027 | 16/59 (27.1) | 14/67 (20.9) | 0.42 | 11/45 (24.4) | 13/55 (23.6) | 0.93 |
| Non–NAP1/BI/027 | 12/117 (10.3) | 34/121 (28.1) | <0.001 | 8/103 (7.8) | 27/106 (25.5) | <0.001 |
| Concomitant systemic antimicrobial therapy | | | | | | |
| Yes | 14/81 (17.3) | 25/90 (27.8) | 0.10 | 8/56 (14.3) | 20/65 (30.8) | 0.03 |
| No | 25/172 (14.5) | 42/175 (24.0) | 0.03 | 20/155 (12.9) | 33/156 (21.2) | 0.05 |

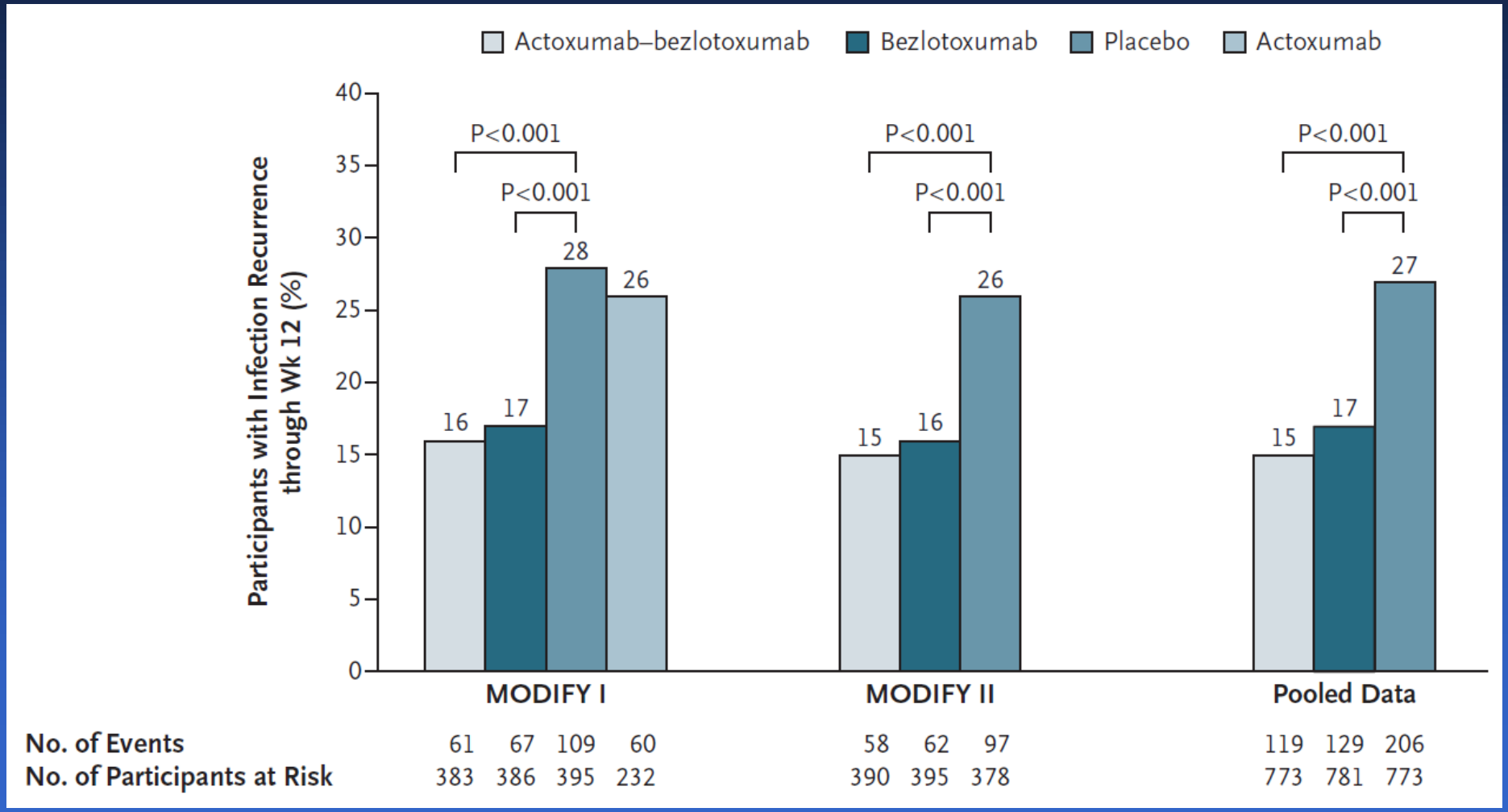
Louie, et al. N Engl J Med 2011;364:422-31.

# Role of Bezlotoxumab

- Two double-blind studies done. Both were randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection.
- Participants received an infusion of bezlotoxumab, actoxumab plus bezlotoxumab, or placebo.
- The primary end point was recurrent infection within 12 weeks after infusion in the modified intention-to-treat population.
- In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo

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

# Role of Bezlotoxumab




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

# Fecal Microbial Transplantation (FMT)—Suggested Tests for Donors

**Table 1** Common serologic and stool tests for FMT donors [11, 16•, 17]

| Serologic Test |
|---|
| Bacterial serology |
| *Treponema palladium* |
| Viral serology |
| Hepatitis A virus IgM |
| Hepatitis B surface antigen |
| Hepatitis C antibody |
| HIB |
| Cytomegalovirus |
| Epstein-Barr virus |
| Parasite serology |
| *Strongyloides stercoralis* |
| *Entamoeba histolytica* |
| Blood tests |
| Complete blood count |
| Complete metabolic panel |
| Liver tests (AST, ALT, alkaline phosphatase, total bilirubin) |
| ESR |
| CRP |
| Stool Studies |
| Stool *Clostridium difficile* studies |
| Toxin PCR |
| Enzyme-linked immunoassay (ELISA) |
| Toxigenic culture |
| Bacterial stool studies |
| *Salmonella*, *Shigella*, *Campylobacter* cultures |
| *E. coli* O157 culture |
| *H. pylori* immunoassay |
| Vancomycin-resistant *Enterococcus* culture |
| Viral stool studies |
| Adenovirus ELISA |
| Norovirus ELISA or quantitative PCR |
| Rotavirus ELISA |
| Parasite stool studies |
| Ova and parasite microscopy |
| *Microsporidia* microscopy |
| *Giardia* fecal antigen ELISA |
| *Cryptosporidium* ELISA |
| *Isospora* and *Cyclospora* microscopy |

Bhutiani, et al. Curr Gastroenterol Rep (2018) 20: 30

# Efficacy of Methods of FMT Administration

| Method | Success rate (%) |
|---|---|
| Route | |
| "Southern" (colonoscopy, enema) | 86 |
| FMT delivered to cecum | 63 |
| FMT delivered to rectum | 90 |
| "Northern" (upper endoscopy, nasoenteric tube) | 74 |
| Number of FMT | |
| First FMT | 62 |
| Second FMT | 83 |
| Novel formulations | |
| Sterile fecal filtrate | 83–100 |
| Lyophilized powder | 85–88 |

Bhutiani, et al. Curr Gastroenterol Rep (2018) 20: 30

# Emerging Therapies: Nontoxigenic C diff

- Among patients with CDI who clinically recovered following treatment with metronidazole or vancomycin, oral administration of spores of NTCD-M3 was well tolerated and appeared to be safe.
- Nontoxigenic C difficile strain M3 colonized the gastrointestinal tract and significantly reduced CDI recurrence. (30% of placebo patients and (11%) of NTCD-M3 patients ( [OR], 0.28; 95%CI, 0.11-0.69; *P* = .006)

Gerding, et al. JAMA. 2015;313(17):1719-1727.

# Environmental Cleaning and Disinfection

- Terminal and daily room cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room *(weak recommendation, low quality of evidence)*.
- There are limited data to recommend use of automated, terminal disinfection using a sporicidal method for CDI prevention *(no recommendation)*.

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# Use of Probiotics

- There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials (*no recommendation*).

McDonald LC, et al. Clin Infect Dis. 2018: 987-994

# Summary

- The incidence and severity of *C. difficile* infection appears to be increasing
- Antibiotic use is strongly associated with the development of CDI
- Decreased use of antibiotics may lead to a decrease in the rates of CDI
- Environmental and hand hygiene are important in controlling the spread of *C. difficile*
- Optimal management of recurrent CDI is still unclear