Guideline updates for *C. difficile* infection

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Conflicts of interest

- I have no significant financial disclosures related to the content of this presentation

Objectives

- Compare and contrast recent Infectious Diseases Society of America (IDSA) and American College of Gastroenterology (ACG) guideline updates for *C. difficile* infection
- Provide recommendations for management of *C. difficile* infection

Epidemiology

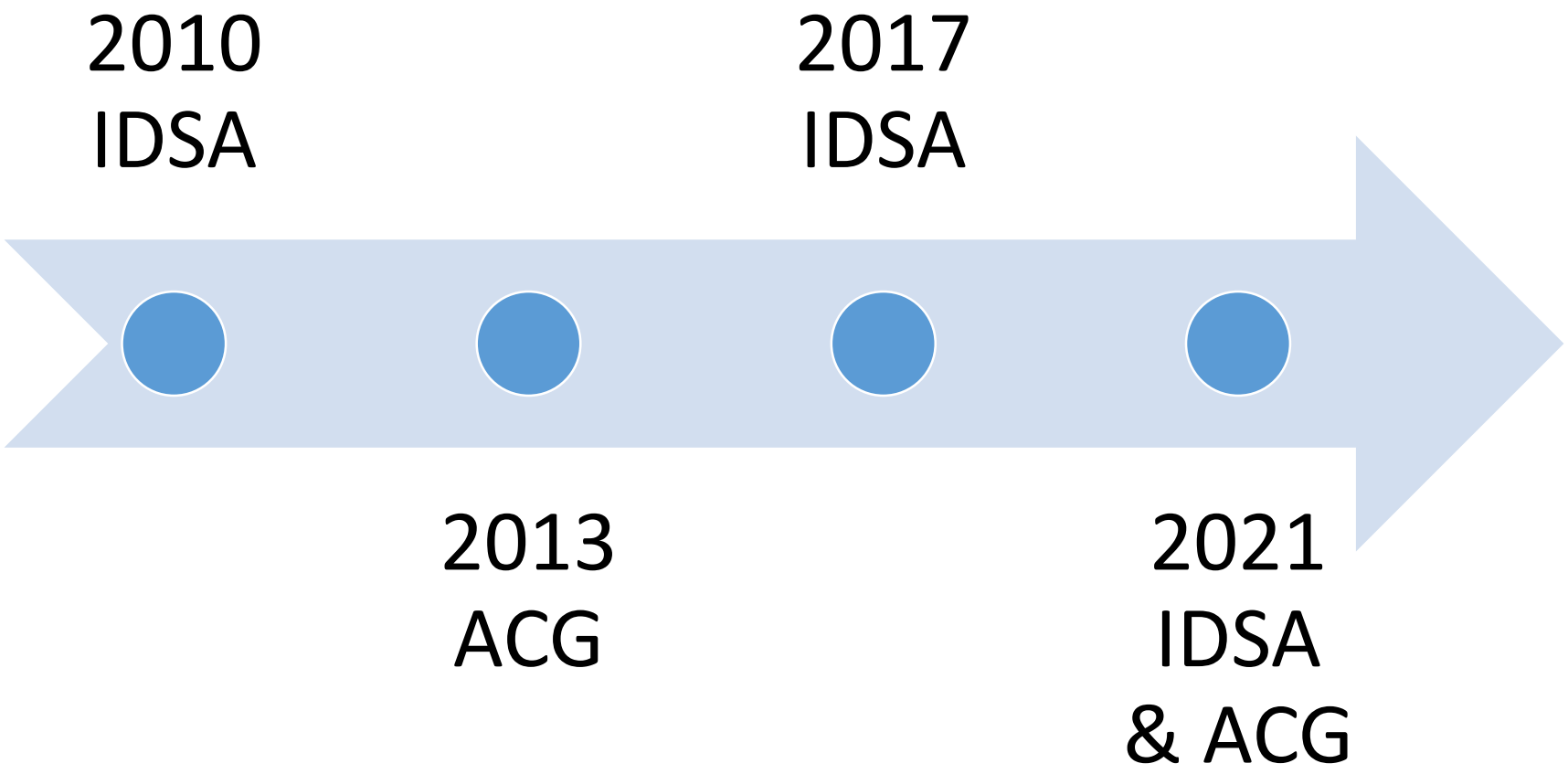
CDC. Antibiotic Resistance Threats in the United States, 2019.

Recurrent *C. Difficile* infection (CDI)

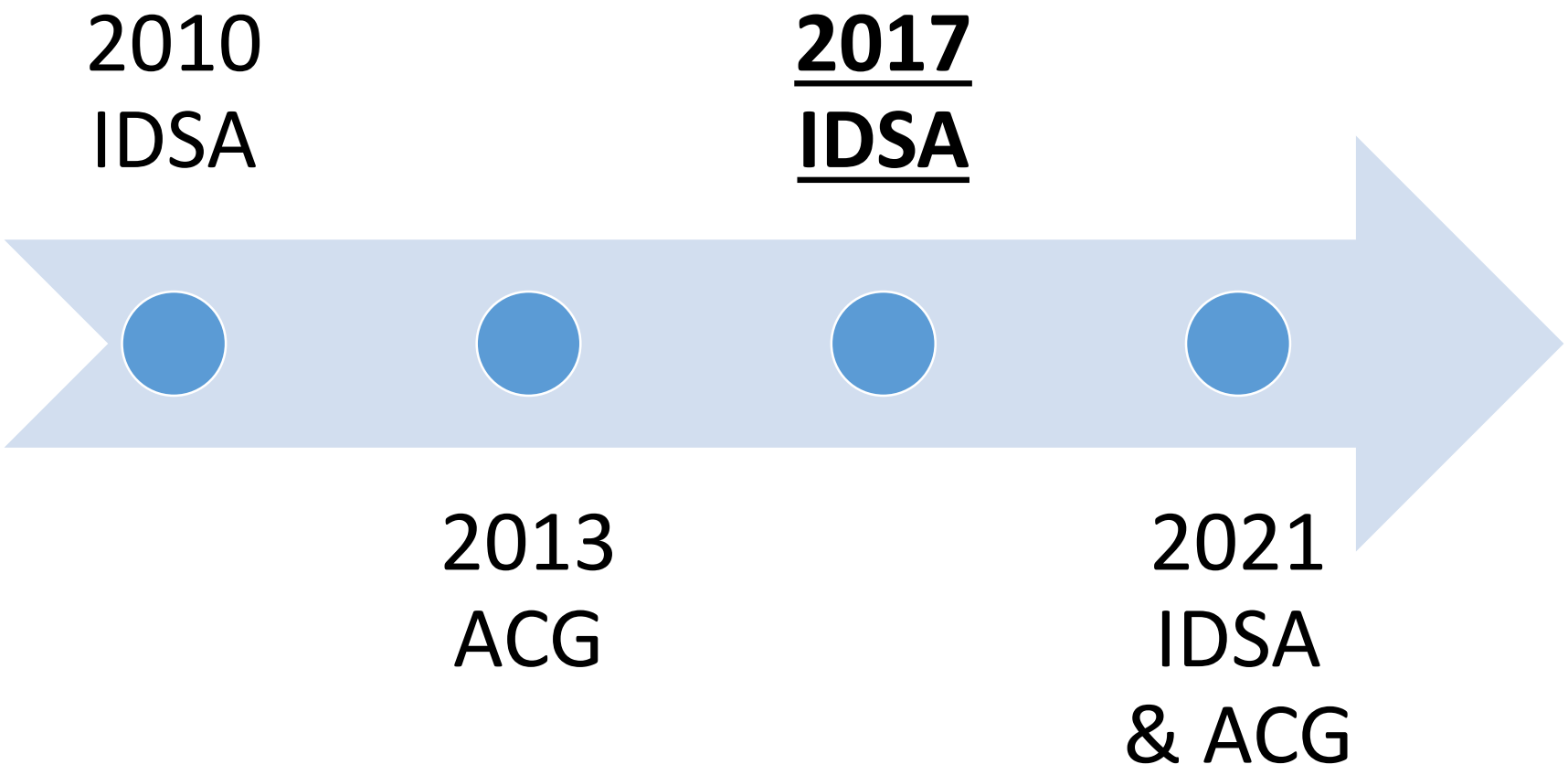
- Up to 25% of patients will have recurrent disease
- Risk factors for recurrence:
  - History of CDI
  - Antimicrobial use
  - Increasing age
  - Prolonged health-care exposure
  - Severity of underlying illness
  - Immunosuppression
  - Infection with B1/NAP1/027 strain

Gerding DN, Young VB, Donskey CJ. 9th ed. Elsevier, 2020: 2933-2947.e4

Guideline Recommendations



Guideline Recommendations



2017 IDSA Guidelines

- Selection based on occurrence and severity
  - Severe
    - WBC ≥ 15, 000 cells/mL OR
    - SCr > 1.5 mg/dL
- 1st episode severe and non-severe disease
  - Vancomycin 125 mg PO QID x 10 days OR
  - Fidaxomicin 200 mg BID x 10 days OR
  - Metronidazole 500 mg PO TID x 10 days (only if non-severe)
- No recommendation for bezlotoxumab

McDonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Vancomycin vs. Fidaxomicin Trial 1 & 2

- Prospective, multicenter, double-blind, randomized controlled trial
- Non-inferiority design
- Inclusion
  - ≥ 16 years of age
  - *C. difficile infection* (CDI)
    - Toxin A, B, or both in stool specimen within 48 hours of randomization
- Exclusion
  - > 4 doses of metronidazole of vancomycin in 24 hours prior to randomization
  - Received other CDI medication (e.g. PO bacitracin, fusidic acid, or rifaximin)
  - Fulminant or life threatening CDI
  - Toxic megacolon
  - Previously exposed to fidaxomicin
  - History of Ulcerative colitis or Crohn's disease
  - > 1 CDI within 3 months prior

Louie TJ, Miller MA, Mullane KM, et al. *N Engl J Med* 2011; 364:422-31
Cornely OA, Crook DW, Esposito R, et al.. *Lancet Infect Dis*. 2012;12(4):281-289.

Vancomycin vs. Fidaxomicin Trial 1 & 2

- Interventions
  - Vancomycin 125 mg PO q6h
  - Fidaxomicin 200 mg q12h with placebo for q6h regimen
- Outcomes
  - 1°: Clinical cure measured 2 days after end of therapy (day 12)
  - 2°: Recurrence within 4 weeks after end of therapy
  - 2°: Global cure or sustained clinical response at 4 weeks after end of therapy
- 10% margin of non-inferiority

Louie TJ, Miller MA, Mullane KM, et al. *N Engl J Med* 2011; 364:422-31
Cornely OA, Crook DW, Esposito R, et al.. *Lancet Infect Dis*. 2012;12(4):281-289.

Patients	Characteristics (mITT*)	Results (mITT*)
52 sites in USA 15 sites in Canada **596 mITT *** 287 fidaxomicin, 309 vancomycin **548 per protocol** 265 fidaxomicin, 283 vancomycin	Groups well balanced **Age:** 61.6 ± 16.9 **Female:** 55.9% **Inpatient:** 59.4% **Previous CDI:** 39.1% **B1/NAP1/027:** 38.1%	**Clinical cure:** 88.2% fidaxomicin, 85.5% vancomycin (95% CI lower bound: - 3.1%) **Recurrence:** 15.5% fidaxomicin, 25.3% vancomycin -9.9%; 95% CI -16.6 to -2.9 **Global cure:** 74.6% fidaxomicin, 64.1% vancomycin 10.5%; 95% CI 3.1 to 17.7
45 sites in Europe 41 sites in USA & Canada **509 mITT** 252 fidaxomicin 257 vancomycin **451 per protocol** 216 fidaxomicin 235 vancomycin	Groups well balanced **Age:** 63.4 ± 18.1 **Female:** 60.9% **Inpatient:** 68.2% **Previous CDI:** 14.9% **B1/NAP1/027:** 33.2%	**Clinical cure:** 87.7% fidaxomicin, 86.8% vancomycin (95% CI lower bound: - 4.9%) **Recurrence:** 12.7% fidaxomicin, 26.9% vancomycin -14.2%; 95% CI -21.4 to -6.8 **Sustained response:** 76.6% fidaxomicin, 63.4% vancomycin 13.2%; 95% CI 5.3 to 21.0

*modified intention to treat

Louie TJ, Miller MA, Mullane KM, et al. *N Engl J Med* 2011; 364:422-31
Cornely OA, Crook DW, Esposito R, et al.. *Lancet Infect Dis*. 2012;12(4):281-289.

Main Takeaways

- Diagnosis included detection of toxin
- No difference in initial clinical cure
- Reduced recurrence with fidaxomicin
  - Mean ages in early 60's
  - No fulminant disease
  - Mostly 1st episode
  - ~ 30% - 40% outpatients
- High risk antibiotics nullify benefit of fidaxomicin
  - 23.91% vs. 29.41%, recurrence in fidaxomicin and vancomycin, respectively

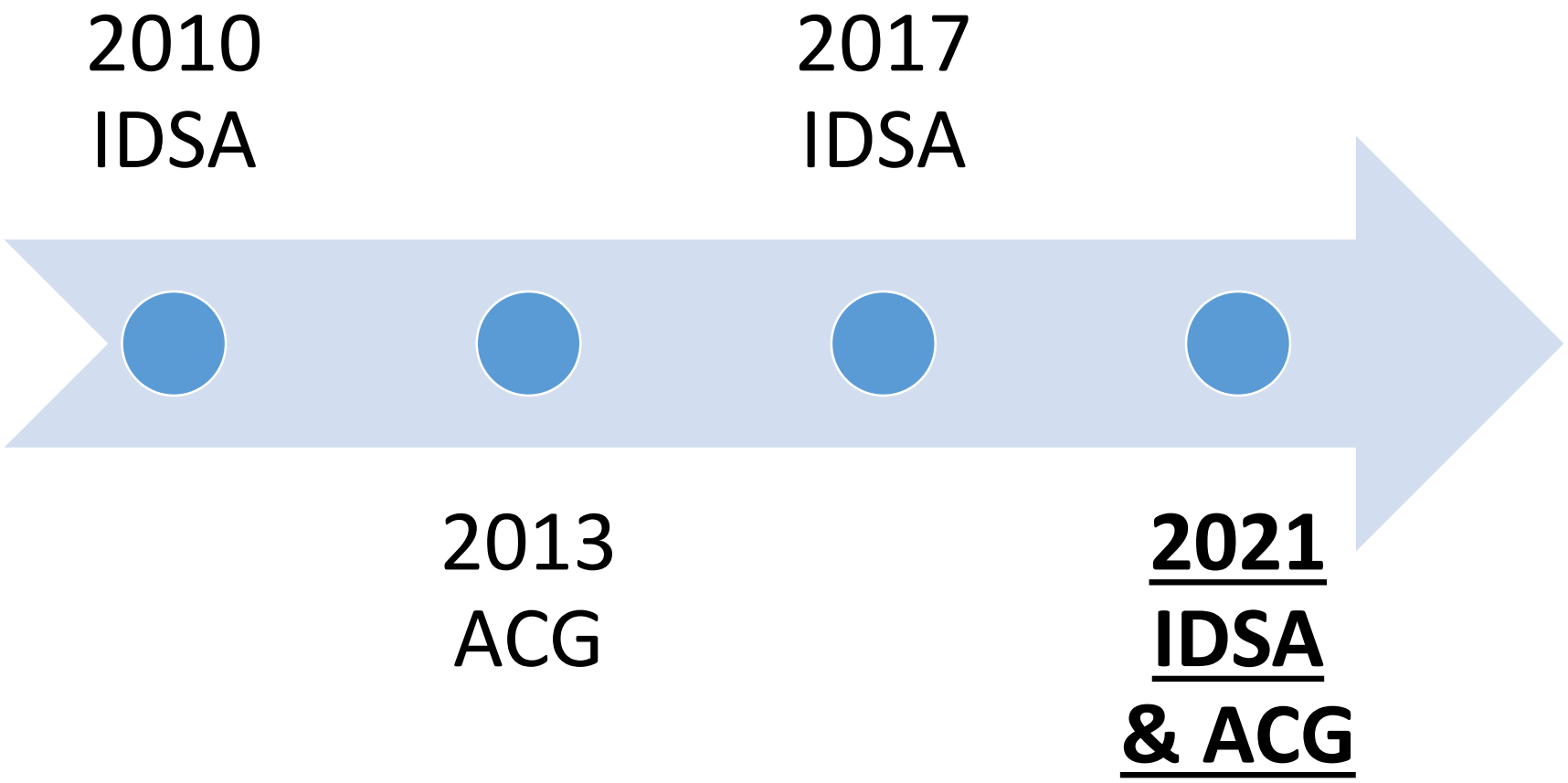
Mullane KM, Miller MA, Weiss K, et al. *Clin Infect Dis*. 2011;53(5):440-447.

2017 IDSA Guideline

- "**Consensus on optimal treatment of CDI is evolving** with the availability of new data on established agents and introduction of a new, FDA-approved drug, fidaxomicin."
- "Based on these 2 large clinical trials meta-analysis, **fidaxomicin should be considered along with vancomycin** as the drug of choice for an initial episode of CDI."

McDonald LC, Gerding DN, Johnson S, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Guideline Recommendations



New guideline recommendations

2021 IDSA	2021 ACG
1st episode severe and non-severe **<u>Preferred: Fidaxomicin 200 mg BID x 10 days</u>** Implementations depends upon available resources Alternative: Vancomycin 125 mg PO QID x 10 days* Alternative: metronidazole 500 mg PO TID x 10 – 14 days (non-severe) In patients with recurrent CDI within last 6 months, bezlotoxumab suggested as co-intervention with standard of care antibiotics.¥	1st episode severe and non-severe Vancomycin 125 mg PO QID x 10 days OR Fidaxomicin 200 mg BID x 10 days OR Metronidazole 500 mg PO TID (non-severe, low risk only) Bezlotoxumab suggested for prevention of CDI in patients who are at high risk for recurrence

*Remains an acceptable alternative

¥ If logistics allow can use in first episode in patients at high risk

Johnson S, Lavergne V, Skinner AM, et al. *Clin Infect Dis.* 2021;73(5):e1029-e1044.
Kelly CR, Fischer M, Allegretti JR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147.

Vancomycin vs. Fidaxomicin Trial 3

- Prospective, multicenter, double-blind, randomized controlled trials
- Non-inferiority design
- Inclusion
  - **Inpatient**
  - **≥ 20** years of age
  - *C. difficile* infection (CDI)
    - Toxin A, B, or both in stool specimen within 48 hours of randomization
  - No treatment yet for CDI (eligible if clinical failure after ≥ 3 days of metronidazole)
- Exclusion
  - Fulminant CDI
  - Toxic megacolon or paralytic ileus
  - Previously exposed to fidaxomicin
  - History of Ulcerative colitis or Crohn's disease
  - > 1 CDI within 3 months prior

Mikamo H, Tateda K, Yanagihara K, et al.. *J Infect Chemother*. 2018;24(9):744-752.

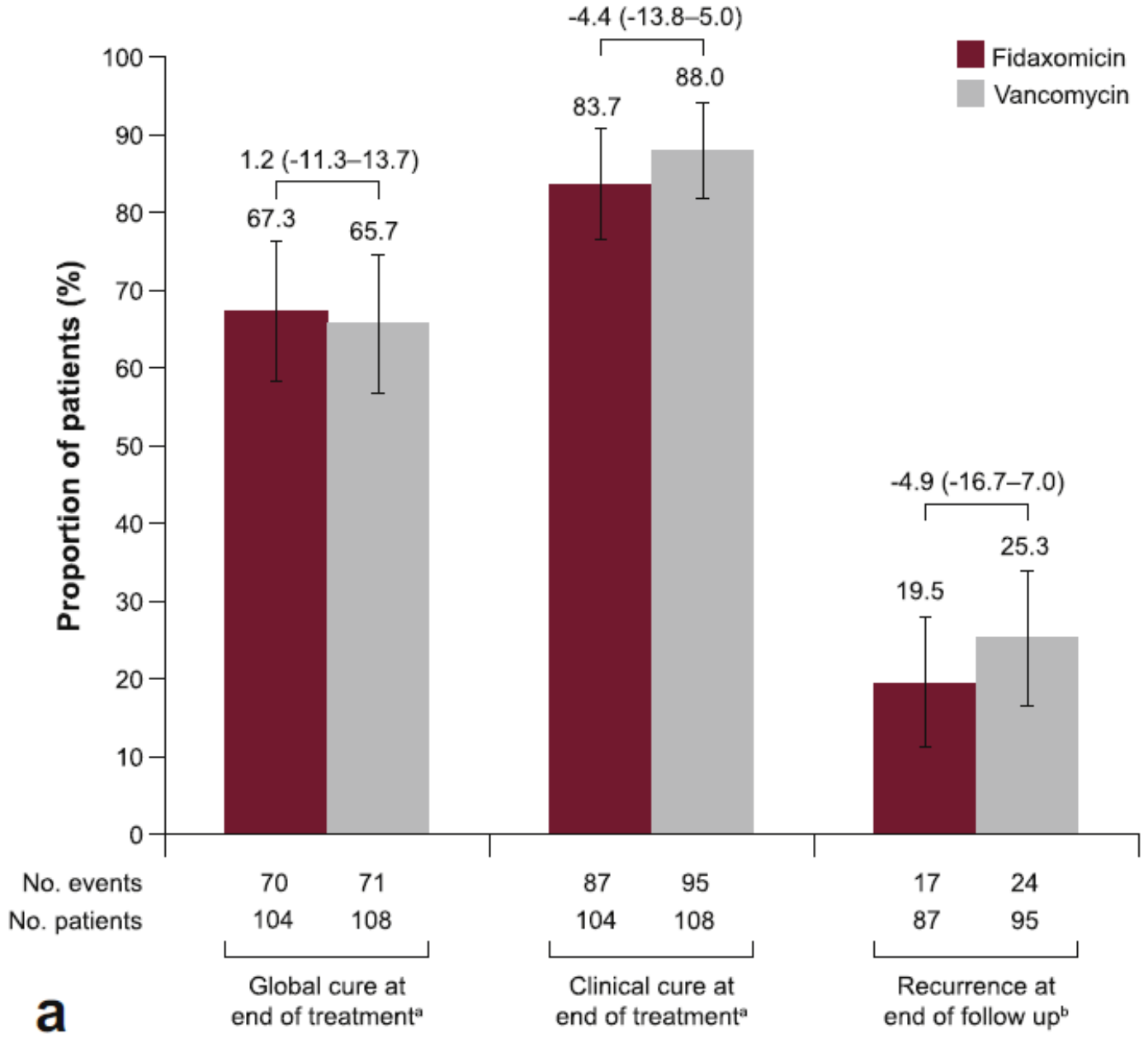
Vancomycin vs. Fidaxomicin Trial 3

- Interventions
  - Vancomycin 125 mg PO q6h
  - Fidaxomicin 200 mg q12h with placebo for q6h regimen
- Outcomes
  - **1°: Global cure** within 4 weeks after end of treatment
  - 2°: Clinical cure rate at end of treatment
  - 2°: Recurrence rate within 4 weeks after end of treatment
- 10% margin of non-inferiority
- 210 patients (105 per treatment group) needed for 90% power

Mikamo H, Tateda K, Yanagihara K, et al.. *J Infect Chemother*. 2018;24(9):744-752.

Patients	Characteristics (FAS*)
82 sites in Japan **212 FAS*** 104 fidaxomicin, 108 vancomycin **180 per protocol** 85 fidaxomicin, 95 vancomycin	Groups well balanced **Age:** 74 - 75 **Female:** 51.9% **Inpatient:** ALL **Previous CDI:** 14.5% **B1/NAP1/027:** 1

*FAS – full analysis set



Mikamo H, Tateda K, Yanagihara K, et al.. *J Infect Chemother*. 2018;24(9):744-752.

Vancomycin vs. Fidaxomicin Trial 4 – EXTEND trial

- Prospective, multicenter, **open-label**, randomized controlled trials
- **Superiority** design
- Inclusion
  - **Inpatient**
  - **≥ 60** years of age
  - *C. difficile* infection (CDI)
    - Toxin A, B, or both in stool specimen within 48 hours of randomization
- Exclusion
  - Received other CDI active antibiotics or non-study vancomycin or fidaxomicin
  - > 1 day of CDI therapy in the last 48 hours
  - Concomitant FMT
  - Toxic megacolon
  - **> 2 CDI within 3 months prior**
  - Diagnosis of IBD

Guery B, Menichetti F, Anttila VJ, et al. *Lancet Infect Dis*. 2018;18(3):296-307.

Vancomycin vs. Fidaxomicin Trial 4 – EXTEND trial

- Interventions
  - Vancomycin 125 mg PO q6h x 10 days
  - Fidaxomicin 200 mg q12h x 5 days followed by 200 mg q48h x 20 days
- Outcomes
  - 1°: Sustained cure 30 days after end of treatment
    - Day 40 vancomycin, day 55 fidaxomicin
  - 2°: Clinical response 2 days after end of treatment
    - Day 12 vancomycin, Day 27 fidaxomicin
  - 2°: Recurrence rate at day 40, 55, and 90
  - 2°: Sustain clinical cure at day 40, 55, and 90

Guery B, Menichetti F, Anttila VJ, et al. *Lancet Infect Dis*. 2018;18(3):296-307.

Patients	Characteristics (mFAS*)
86 sites in Europe, Russia, and Turkey **356 mFAS*** 177 fidaxomicin, 179 vancomycin **252 per protocol** 127 fidaxomicin, 125 vancomycin	Groups well balanced **Age:** 75 **Female:** 58% **Inpatient:** ALL **Previous CDI** **1:** 15% - 16% **2:** 6% **B1/NAP1/027:** 13%

*mFAS – modified full analysis set

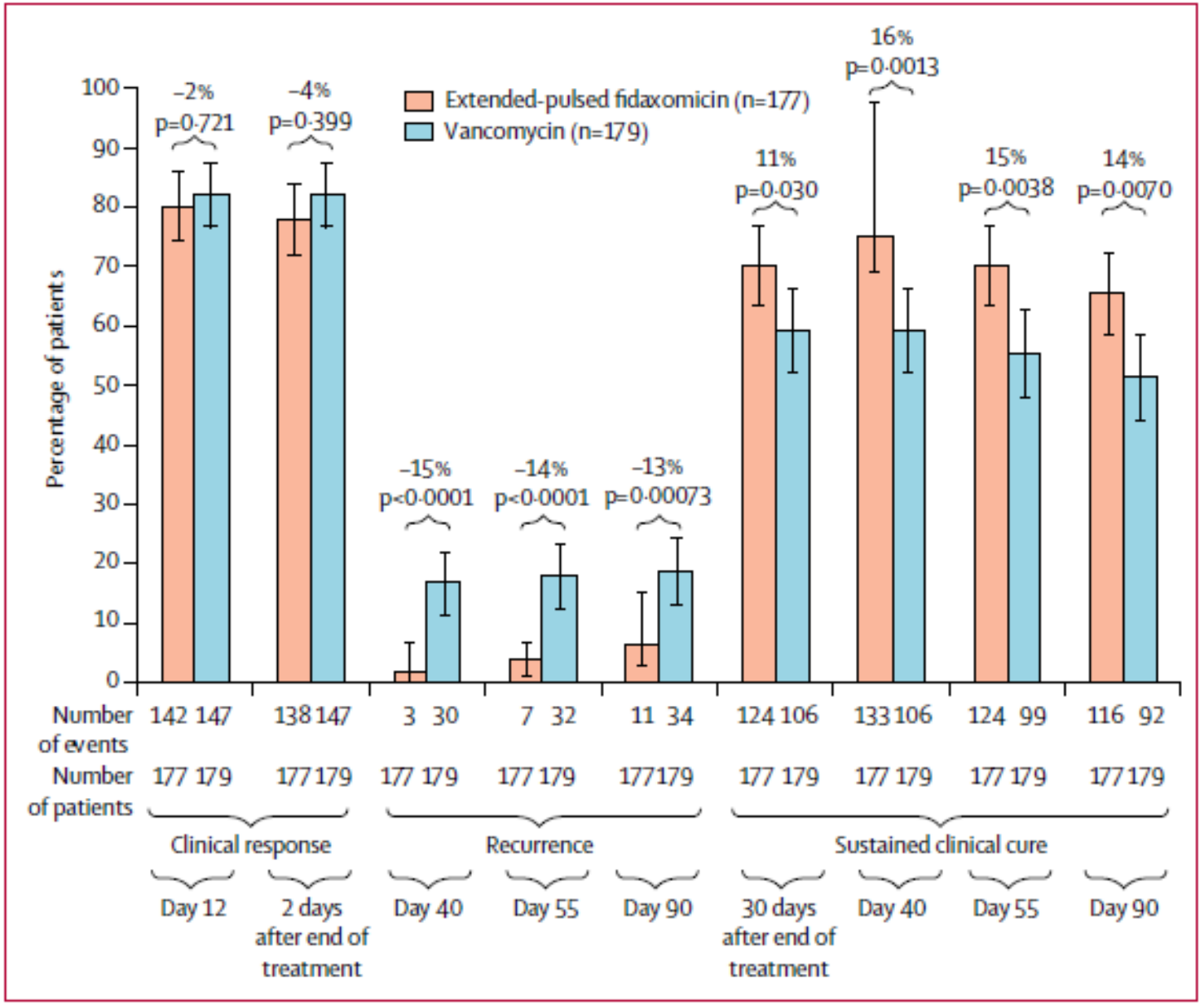


***Figure 2:* Selected clinical outcomes**
Bars show 95% CI. Percentage increase or decrease for extended-pulsed fidaxomicin compared with vancomycin is shown above each pair of bars.

Guery B, Menichetti F, Anttila VJ, et al. *Lancet Infect Dis*. 2018;18(3):296-307.

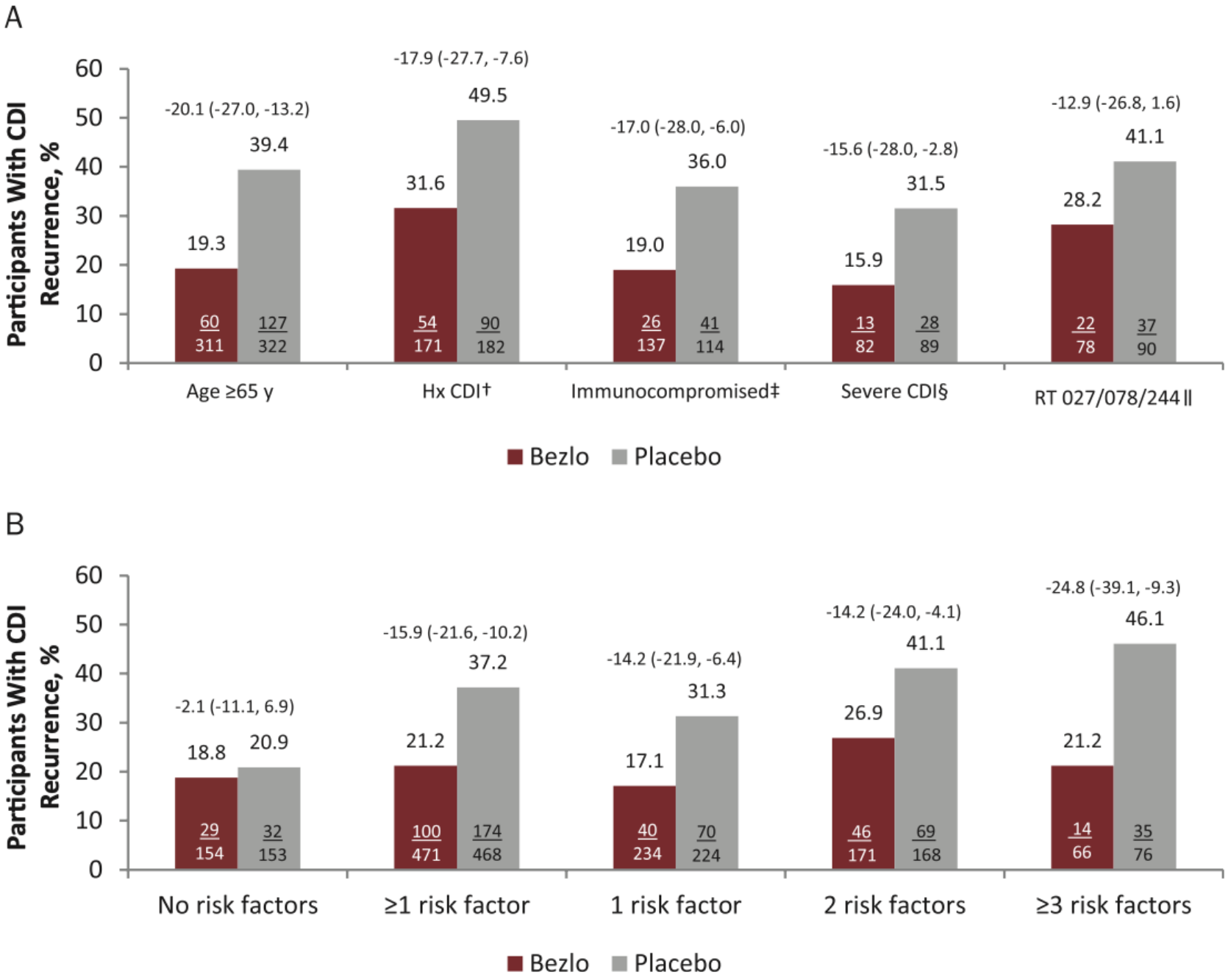
Main Takeaways

- No difference in initial clinical cure between fidaxomicin or vancomycin
- No difference in recurrence or global cure in Trial 3
  - Older patients
  - Only inpatients
- Fidaxomicin pulse dosing superior to standard dosing vancomycin
  - Open-label
  - Appropriate comparison?
    - Fidaxomicin better or longer duration better?
- TAPER-V trial ongoing comparing vancomycin taper to 14-day vancomycin
  - ClinicalTrials.gov Identifier: NCT04138706

Bezlotoxumab

- Two double blind, randomized, placebo-controlled trials
  - Standard of care (SOC) + bezlotoxumab ± actoxumab vs. SOC + placebo
  - SOC: metronidazole (46.7%), vancomycin (47.7%), fidaxomicin (3.6%)
- 2559 in modified intention to treat
- 27.5% with ≥ 1 occurrence in past **6 months**
  - 14.2% with ≥ 2 occurrences in the past **6 months**
- No difference in initial clinical cure
- Higher sustained cure at 12 weeks with bezlotoxumab ± actoxumab
  - Pooled analysis: 64% bezlotoxumab vs 54% placebo

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



Gerding DN, Kelly CP, Rahav G, et al. *Clin Infect Dis*. 2018;67(5):649-656.

2021 Guidelines

- Bezlotoxumab suggested by IDSA & ACG
- Individual results of Japanese study not discussed by IDSA
- IDSA recommendation primarily made on pooled effects of four trials
  - Sustained response of CDI 4 weeks after end of therapy
    - RR: 1.16; 95% CI 1.09 to 1.24
  - Heterogeneity
    - Inpatient vs outpatient
    - Dosing/duration
- ACG notes no preference with fidaxomicin or vancomycin
- IDSA: “Implementation depends upon available resources. Vancomycin remains an acceptable alternative”

Resource Considerations – Norton

- Inpatient
  - No difference in clinical cure
    - Hospital length of stay not expected to change
  - Fidaxomicin - $192.45 per day
  - Vancomycin - $1.15 per day
- Transitions of care/outpatient
  - Negligible vancomycin PO costs with meds to beds
  - Fidaxomicin typically not preferred or prior authorization required
    - Co-pay cards
    - Patient assistance program
  - Bezlotoxumab at infusion center
- Transitions of care pharmacists not at all adult inpatient hospitals

Norton Formulary

- April 2022 P&T update – Fidaxomicin restricted to recurrent disease
  - No benefit with initial clinical cure
    - No clear role in refractory disease
  - Lack of consensus among major society guidelines (IDSA & ACG)
  - Unclear recurrence benefit in inpatients
  - Fidaxomicin ~200 times more expensive than PO vancomycin
- Bezlotoxumab restricted to outpatient use

Recommendation for Practice

- 2022 Norton CDI guideline – 1st episode severe and non severe
  - Vancomycin PO 125 mg q6h x 10 days
  - Vancomycin taper with bezlotoxumab in high risk patients may be considered
    - Immunocompromised
    - Age ≥ 65
    - Severe disease
  - Fidaxomicin may be considered
    - Requires non-formulary non-stock request
    - Strongly recommend confirm outpatient script approval

Case Patient

YM is a 70 year old male who presents to the hospital with fever, shortness of air, productive cough with green sputum, and chest pain. A chest x-ray reveals a right lung infiltrate. YM is diagnosed with pneumonia and started on ceftriaxone and azithromycin. On hospital day 4 he develops frequent loose stools, and his WBC increases from 8,000 from the day prior to 16,000. A stool sample returns positive for *C. difficile* by polymerase chain reaction and toxin by enzyme immunoassay.

The provider engages you and asks you for the latest national guideline recommendations. What do you reply with?

- A: metronidazole 500 mg PO TID x 10 days
- B: IDSA & ACG guidelines both recommend fidaxomicin 200 mg BID or vancomycin 125 mg PO Q6H but IDSA notes a preference for fidaxomicin while ACG does not
- C: tigecycline 100 mg once followed by 50 mg BID
- D: intravenous immune globulin

The provider engages you and asks you for the latest national guideline recommendations. What do you reply with?

- A: metronidazole 500 mg PO TID x 10 days
- **B: IDSA & ACG guidelines both recommend fidaxomicin 200 mg BID or vancomycin 125 mg PO Q6H but IDSA notes a preference for fidaxomicin while ACG does not**
- C: tigecycline 100 mg once followed by 50 mg BID
- D: intravenous immune globulin

The provider wants to finish 7 days of treatment for pneumonia and asks for your recommendation for CDI treatment. Which of the following would you recommend?

- A. fidaxomicin 200 mg BID x 10 days
- B. metronidazole 500 mg TID x 10 days
- C. vancomycin 125 mg PO Q6H x 10 days
- D. vancomycin taper with outpatient bezlotoxumab

The provider wants to finish 7 days of treatment for pneumonia and asks for your recommendation for CDI treatment. Which of the following would you recommend?

- **D. vancomycin taper with outpatient bezlotoxumab**
- **C. vancomycin 125 mg PO Q6H x 10 days**
- **A. fidaxomicin 200 mg BID x 10 days**
- B. metronidazole 500 mg TID x 10 days

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