An Update on *Clostridiodes difficile* Infection (2019)

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Disclosures

- Advisory Board / Consulting
  - ABEL Therapeutics
  - Biocidium
  - BLC
  - Cepheid
  - NAEJA-RGM
  - Synthetic Biologics
  - Sanofi Pasteur
- Research Support
  - March of Dimes
  - NIH
  - Pfizer
  - EPA

WORD CLOUD!

- When I say *C. difficile*, you think of what?

QUIZ

- *Clostridioides difficile* is part of the normal human gut microbiome (flora)

A. TRUE

B. FALSE

QUIZ

- *Clostridioides difficile* is part of the normal human gut microbiome (flora)

A. TRUE

B. FALSE

Antibiotic-Associated Diarrhea (AAD)

- AAD is Common
  - 5-25% of antibiotic treatment courses
  - 1 dose is sufficient
- ~25% of AAD is due to CDI but nearly all AA **colitis** is CDI
- Disruption of colon microbiome & bile acid physiology are key mechanisms

Clostridioides difficile

Clostridium difficile

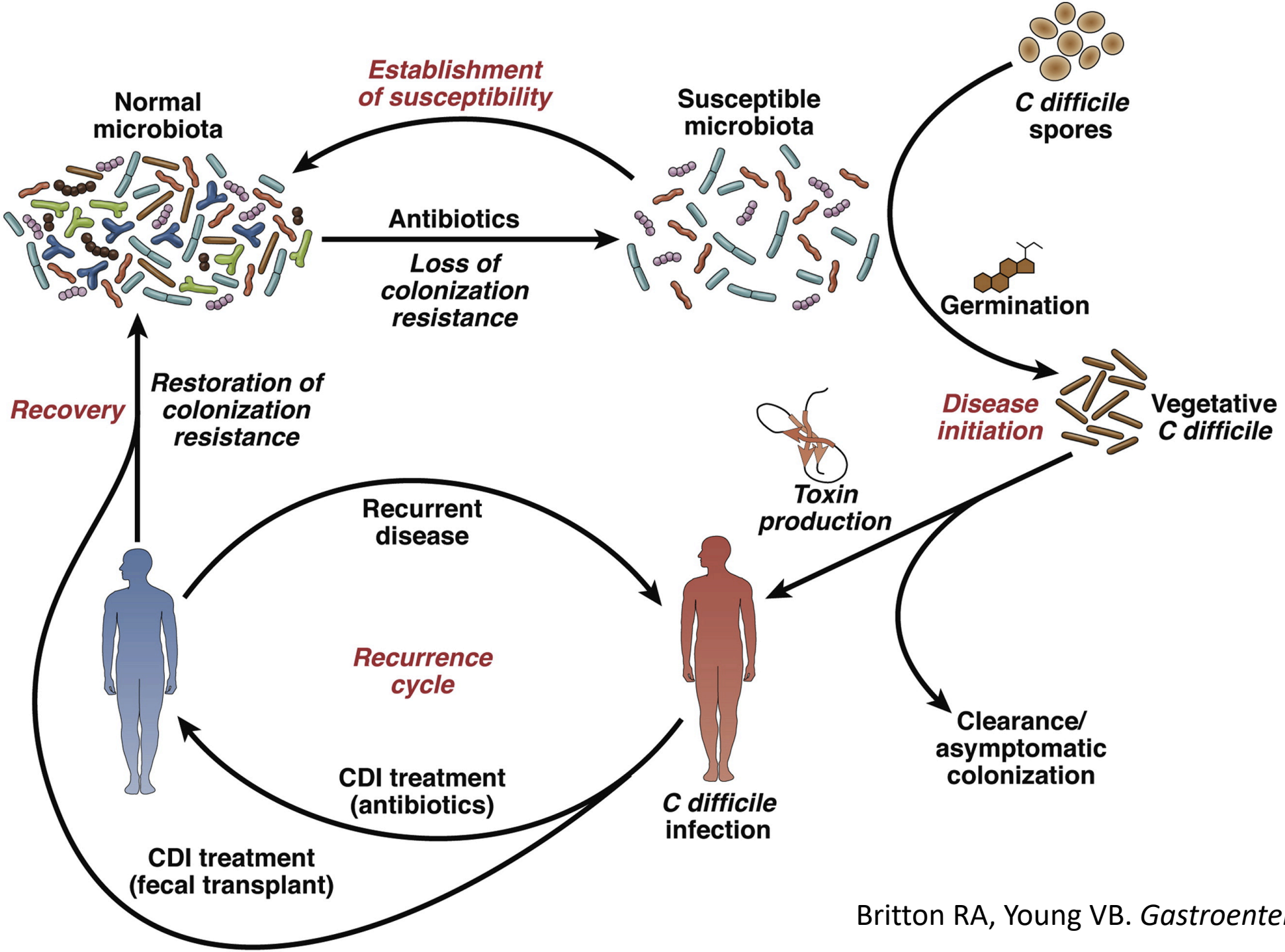
renamed

Clostridioides difficile

in 2016

- Gram positive anaerobic bacillus
- Found in the environment
- Forms stable spores
  - Can survive for years
- Not part of our microbiome

Czepiel J, *et al. Eur J Clin Micro Infect Dis* (2019)

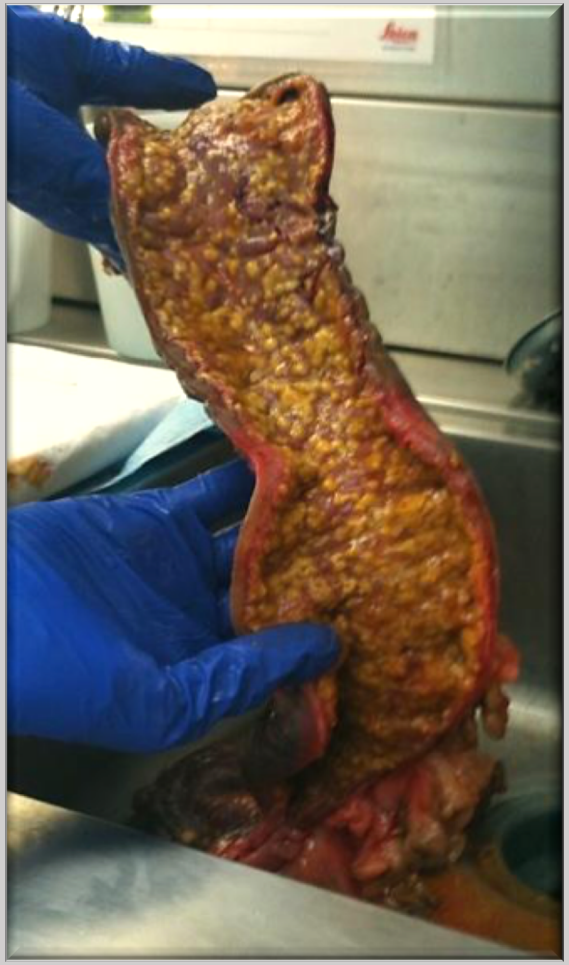


Britton RA, Young VB. *Gastroenterology* (2014)

Clinical Manifestations

- Watery & mucusy diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis
- Nausea
- Anorexia
- Malaise

Complications



- Sepsis ± multiple organ dysfunction
- Megacolon: need for surgical intervention
  - Colectomy
  - Loop iliostomy
- Bowel Perforation
- Lack of treatment response
- Recurrent infection (20%+)
  - Relapse
  - Reinfection

Severity

- Leukocytosis
- AKI
- Sepsis/shock
- Megacolon

Clinical Definition	Supportive Clinical Data
Nonsevere	Leukocytosis with a WBC count of ≤15,000 cells/mL and a serum creatinine level <1.5 mg/dL
Severe	Leukocytosis with a WBC count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

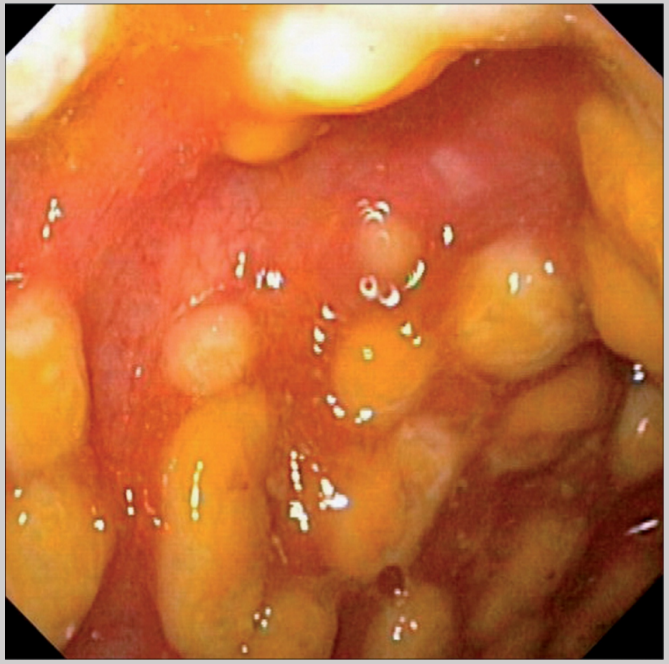
Table from Wilcox M, IDSE (2018)
McDonald LC, *et al. Clin Infect Dis*. (2018)

Risk Factors

- Antibiotic use
- Recent hospitalization or LTCF
- Age > 65 years
- Gastric acid suppression (PPI)
- Abdominal surgeries
- Immunocompromised host

Dubberke E, *et al. Infect Control Hosp Epidemiol* (2011)
Pacheco & Johnson. *Curr Opin Gastroenterol* (2013)
Loo V, *et al. NEJM* (2011)

Epidemiology

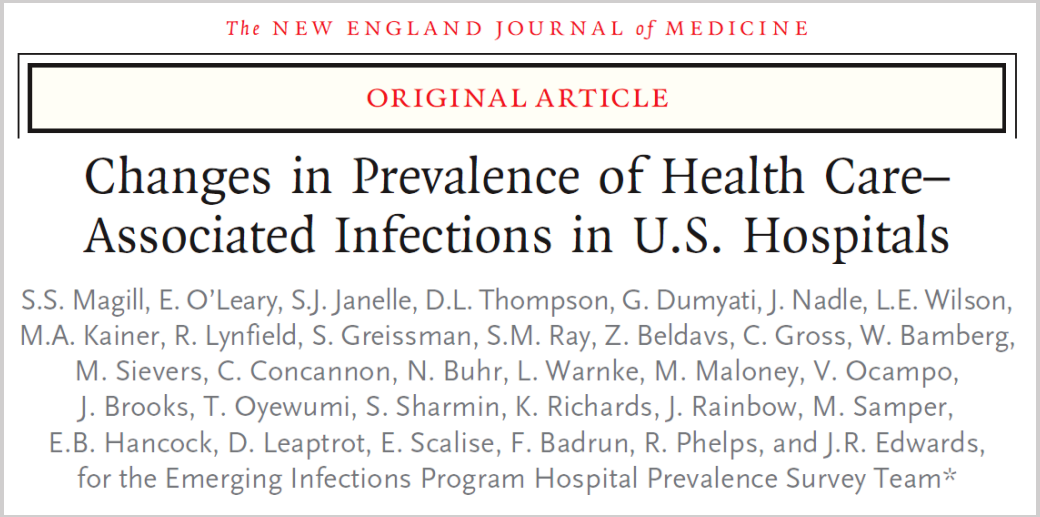


Lancet 371:1486, 2008

- Most common health care-associated infection, USA
- Leading cause of gastroenteritis death in the USA

Ooijevaar RE, *et al. Clin Micro Infect* (2018)
McDonald C, *et al. Clin Infect Dis* (2018)

Epidemiology



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Changes in Prevalence of Health Care–Associated Infections in U.S. Hospitals

S.S. Magill, E. O'Leary, S.J. Janelle, D.L. Thompson, G. Dumyati, J. Nadle, L.E. Wilson, M.A. Kainer, R. Lynfield, S. Greissman, S.M. Ray, Z. Beldavs, C. Gross, W. Bamberg, M. Sievers, C. Concannon, N. Buhr, L. Warnke, M. Maloney, V. Ocampo, J. Brooks, T. Oyewumi, S. Sharmin, K. Richards, J. Rainbow, M. Samper, E.B. Hancock, D. Leaptrot, E. Scalise, F. Badrun, R. Phelps, and J.R. Edwards, for the Emerging Infections Program Hospital Prevalence Survey Team*

C. difficile accounts for 15% of healthcare-associated infections in the United States

Magill S, *et al. NEJM* (2018)

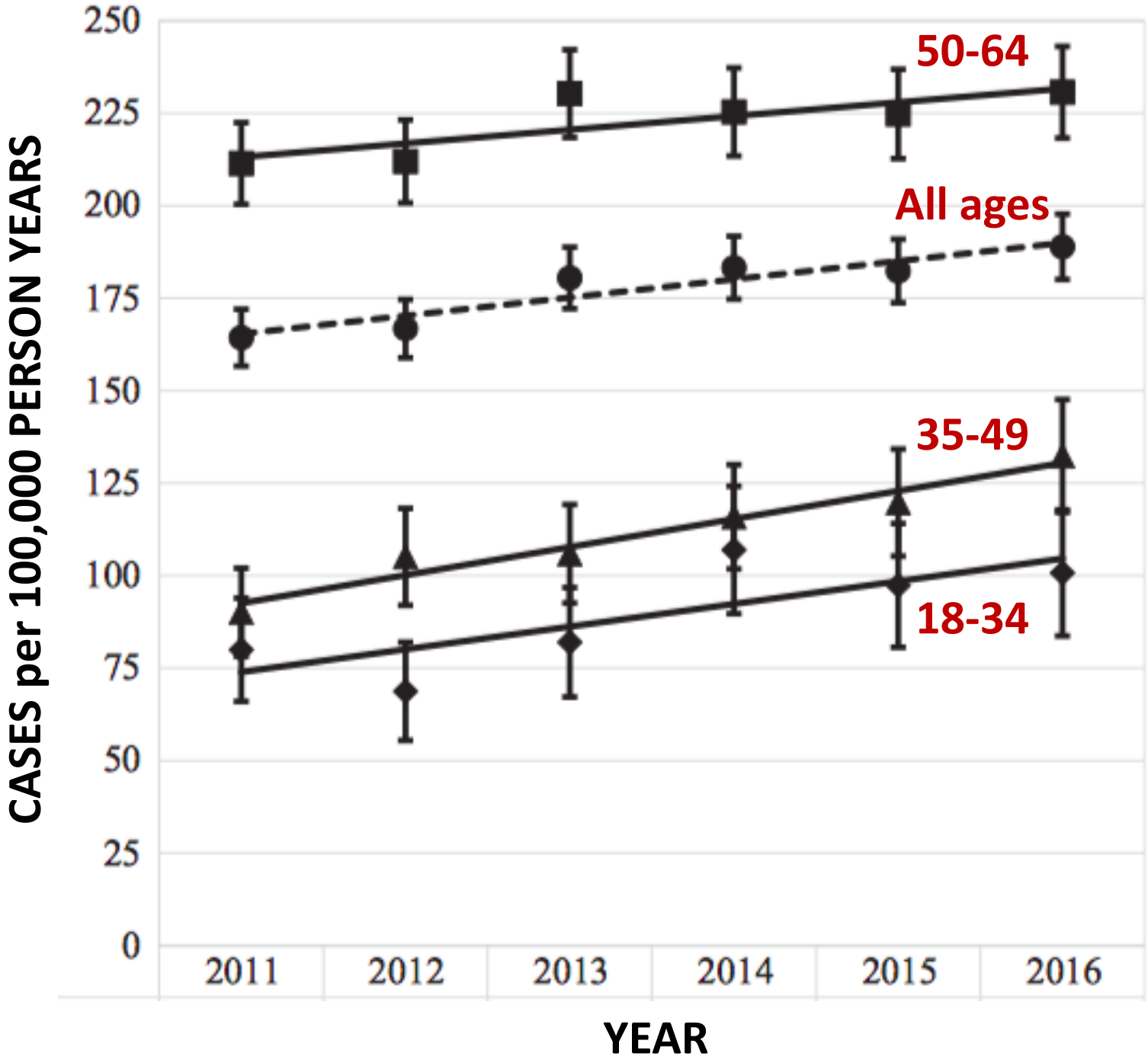
2015

Top Causative Pathogens	% of HAI	Rank
C. difficile	15	1
S. aureus	11	2
E. coli	10	3
***Candida* spp.**	6	4
***Enterococcus* spp**	5	5
***Enterobacter* spp.**	5	6
P. aeruginosa	5	7
K. pneumo/oxytoca	5	8
***Streptococcus* spp.**	5	9
CoNS	4	10

Epidemiology

CDI incidence rising in some populations

These data are from a recent **VA** study of >10,000 CDI patients



Russo EM, *et al. ICHE* (2019)

Case

- 32 year old previously healthy woman c/o diarrhea 4-5 x/day & crampy abdominal pain without fever
- She is an executive at a local bank & has not travelled outside of TN & denies any antibiotic use by her or her family
- An 8 year old child at home has been well
- On exam she is afebrile & mildly uncomfortable with tenderness to lower abdomen

Case

- Is it reasonable to test for *C. difficile*?

A. No. She is healthy & has no antibiotic exposure

B. Yes. Community-associated CDI can occur in healthy persons without antibiotic exposure

Case

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A. No. She is healthy & has no antibiotic exposure

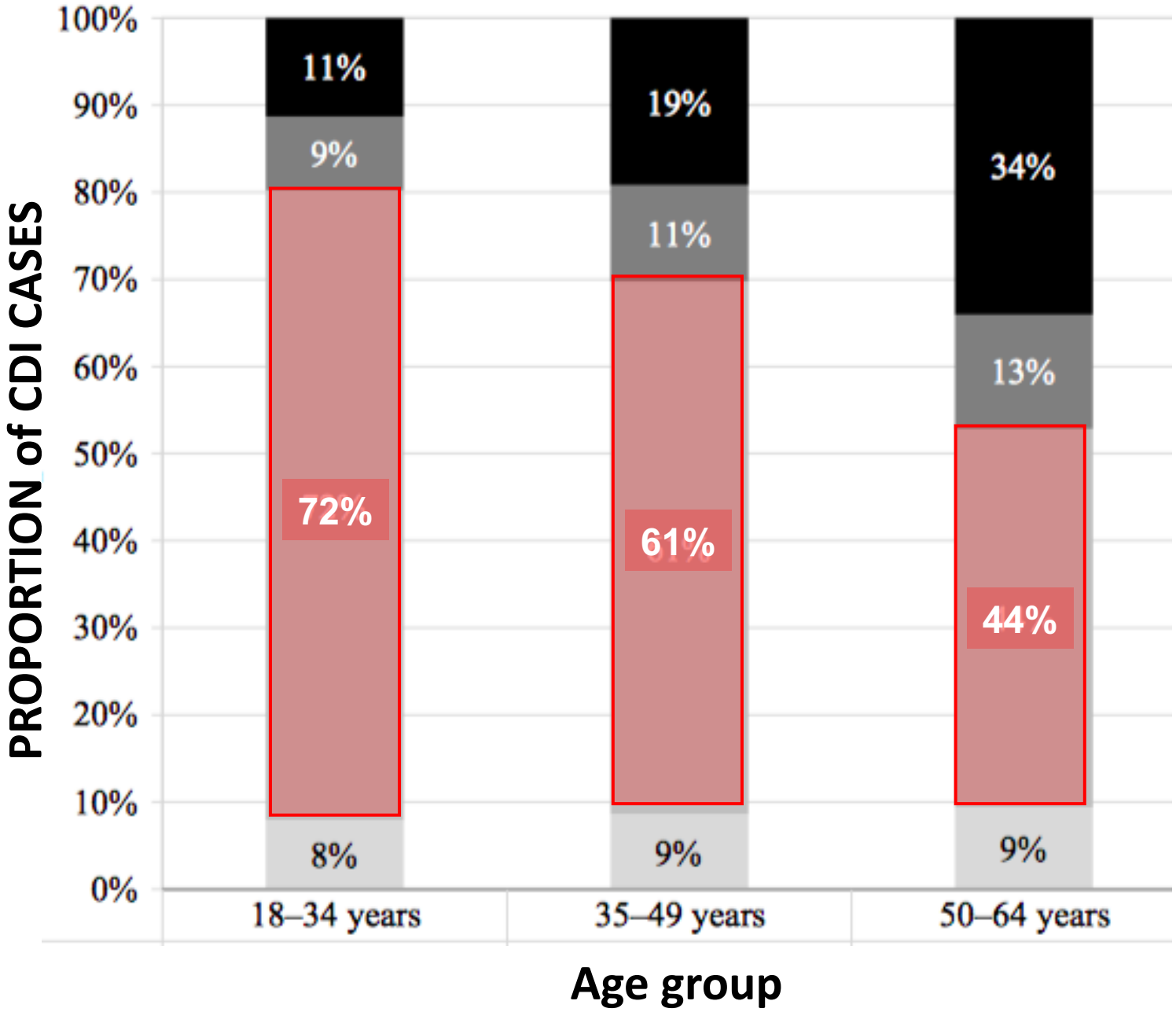
B. Yes. Community-associated CDI can occur in healthy persons without antibiotic exposure

Epidemiology

Community-associated infections are increasingly important

Esp. in young people

- **Healthcare facility onset**
- **Community onset/healthcare facility associated**
- **Community onset**
- **Indeterminant**



Study of >10,000 VA patients

Russo EM, *et al. ICHE* (2019)

Epidemiology

CDI in the community

- Younger patients
- Female slightly more prevalent than male
- 20-50% without antibiotic exposure

Canadian Journal of Infection Control | Summer 2018 | Volume 33 | Issue 2 | 96-101

ORIGINAL ARTICLE

Epidemiology of patients hospitalized with *Clostridium difficile* infection: A comparative analysis of community-associated and healthcare-associated *Clostridium difficile* infections

Maryam Salaripour, MSc, MPH, PhD;[1] Jennie Johnstone, MD, PhD, FRCPC;[2,3,5] Michael Gardam, MSc, MD, CM, MSc, FRCPC[1,4,5]
[1]School of Health Policy and Management, York University, Toronto, ON

"CA-CDI is emerging as an important cause of diarrhea in patients without healthcare exposure; it accounted for **half** of all hospitalized cases of CDI in our study. CA-CDI affects a younger, healthier population and can occur, even **in the absence of the risk factors** traditionally associated with this infection seen in HA-CDI cases."

Salaripour M, *et al. Can J Infec Control* (2018)

Case

- 63 year old woman c/o diarrhea starting 2 weeks after completing a course of amoxicillin-clavulanic acid for sinusitis. ROS (+) crampy abdominal pain, frequent mucusy stools & subjective fever.
- On exam temp. is 100.3^{o}F with mild diffuse abdominal tenderness.
- WBC is 8,200 (normal), creatinine is 0.9 (her baseline) & CMP is normal. FOBT is negative.

Case

- Which of the following is the most appropriate next step in her evaluation & management?

A. Send stool for *C. difficile* testing

B. Prescribe anti-motility agents & probiotics

C. Start empiric metronidazole 500 mg po QID

D. Start empiric vancomycin 125 mg po QID

Case

- Which of the following is the most appropriate next step in her evaluation & management?

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Diagnostic Testing

- Whom to test?
  - Risk factors can be helpful
  - Pt has **diarrhea** or consistent endoscopic findings
  - **No laxatives** within last 48 hrs
- Test diarrheal stools (unless ileus)
  - >3 liquid stools over 24h

McDonald LC, *et al. Clin Infect Dis*. (2018)

Direct Detection of the Bacterium in Stool

1. Antigen test (GDH; glutamate dehydrogenase) by EIA
2. Nucleic acid amplification test (NAAT)
   - PCR testing for *C. difficile* Toxin B

- Both tests are **sensitive** but can detect colonization without disease (overdiagnosis)

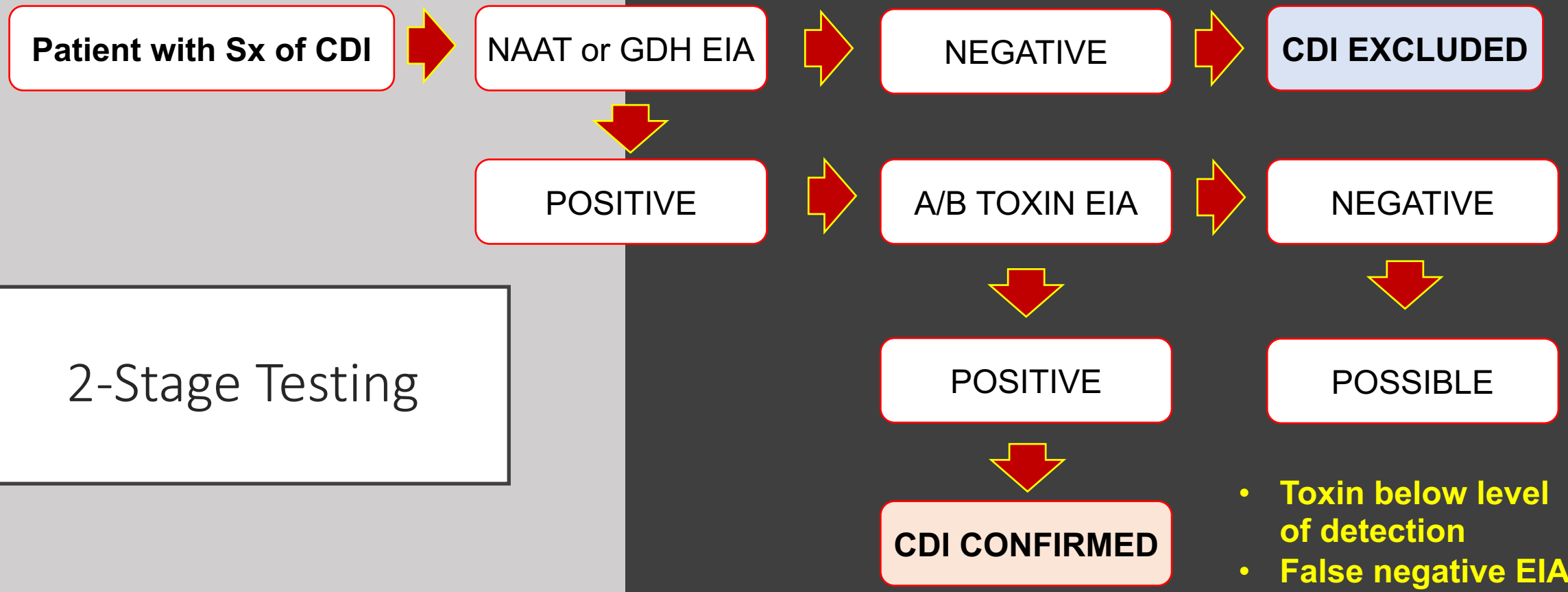
CID. 2018 Mar 19;66(7):987-994
CID 57:1175, 2013
Clin Micro Reviews 26:604, 2013
JAMA 313:398, 2015
JAMA Int Med 175:1792, 2015

Direct Detection of Toxins A/B in Stool

- **Direct detection of toxin A/B** by EIA test in stool
  - Lower sensitivity, high specificity

CID. 2018 Mar 19;66(7):987-994
CID 57:1175, 2013
Clin Micro Reviews 26:604, 2013
JAMA 313:398, 2015
JAMA Int Med 175:1792, 2015

DIRECT PATHOGEN DETECTION



2-Stage Testing

- **Toxin below level of detection**
- **False negative EIA**
- **Colonization**

Czepiel J, et al. Eur J Clin Micro Infect Dis (2019)

Question

- Should **repeat** *C. difficile* testing be performed for test of cure at the end of therapy?

A. YES

B. NO

Question

- Should **repeat** *C. difficile* testing be performed for test of cure at the end of therapy?

A. YES

B. NO

Case

- 67 year old woman develops diarrhea while hospitalized for community acquired pneumonia
- Afebrile, WBC count = 12,000/μl, creatinine = 1.2 mg/dl (baseline 1.0 mg/dl) & she's experiencing 12 small loose stools daily with abdominal cramping
- Stool PCR is positive for *C. difficile* toxin B as is EIA for toxin B

Case

- Which of the following therapies is recommended?
  A. Metronidazole
  B. High dose vancomycin (500 mg)
  C. Normal dose vancomycin (125 mg)
  D. Bezlotoxumab + vancomycin
  E. Fidaxomicin + metronidazole

Case

- Which of the following therapies is recommended?
  A. Metronidazole
  B. High dose vancomycin (500 mg)
  C. Normal dose vancomycin (125 mg)
  D. Bezlotoxumab + vancomycin
  E. Fidaxomicin + metronidazole

Treatment

- Stop unnecessary antibiotics as soon as possible
- Move away from antibiotics with particularly high risk for CDI
  - Fluoroquinolone, cephalosporins, clindamycin
- Avoid anti-paristaltic medications

McDonald LC, *et al. Clin Infect Dis*. 2018

Treatment

VANCOMYCIN 125 mg po QID x 10 d
FIDAXOMICIN 200 mg po BID x 10 d

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days
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.

McDonald LC, *et al. Clin Infect Dis*. 2018

No more metronidazole

Treatment

VANCOMYCIN 125 mg po QID x 10 d
FIDAXOMICIN 200 mg po BID x 10 d

Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis

Tumas Beinortas, Nicholas E Burr*, Mark H Wilcox, Venkataraman Subramanian*

Both antibiotics are better than metronidazole

Vancomycin is less expensive than fidaxomicin

Fidaxomicin is associated with significantly fewer recurrences (more durable cure)

Beinortas T, *et al. Lancet*. 2018

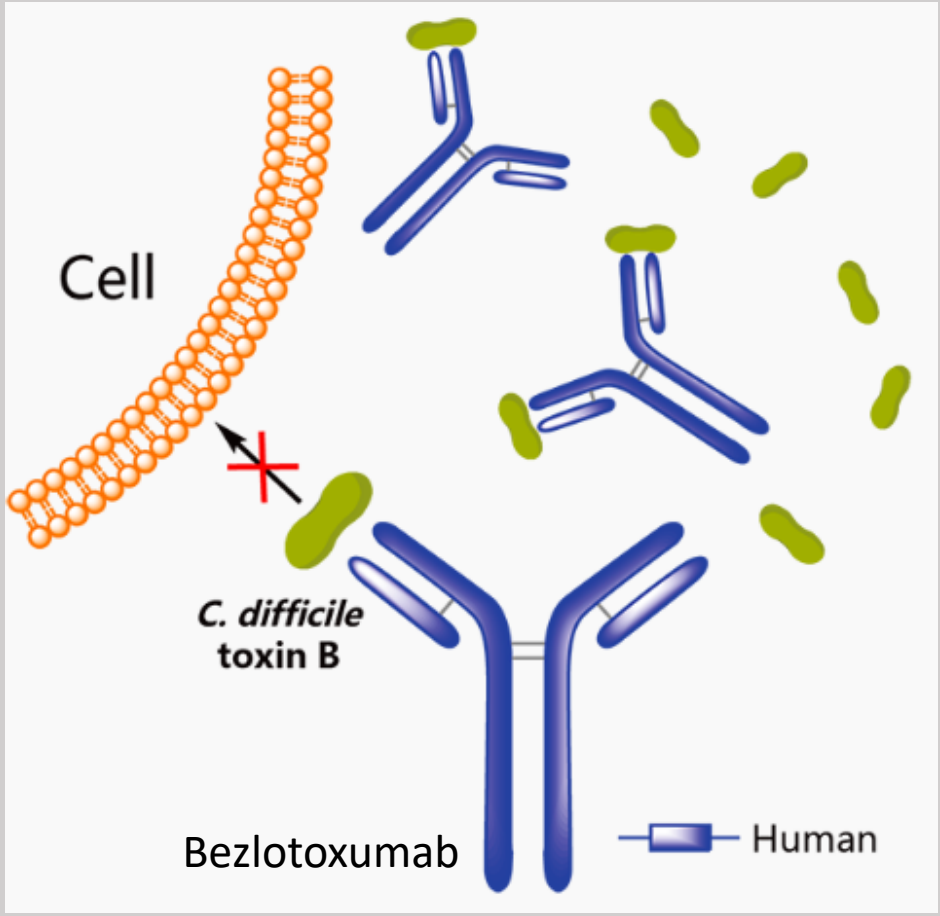
Recurrence

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • 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 • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation[c]

McDonald LC, *et al. Clin Infect Dis*. 2018

Recurrence



McDonald LC, *et al. Clin Infect Dis*. 2018
Figure from http://en.pharmacodia.com/web/drug/1_9806.html

Bezlotoxumab

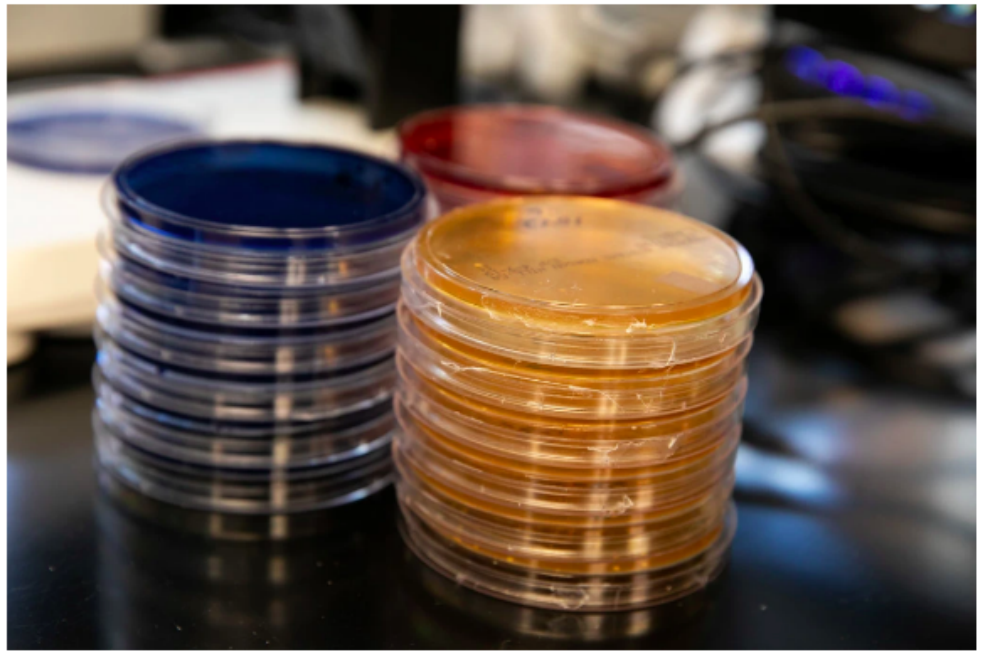
- A monoclonal antibody directed against toxin B
- Approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI & who are at high risk for recurrence
  - Older, frail adults
  - H/o Recurrence

FMT

The New York Times

Fecal Transplant Is Linked to a Patient's Death, the F.D.A. Warns

The agency said two patients received donated stool that had not been screened for drug-resistant germs, leading it to halt clinical trials until researchers prove proper testing procedures are in place.



Petri dishes with fecal bacterial colonies. Kayana Szymczak for The New York Times

Fecal Microbiota Transplant

- Generally reserved for multiple recurrences
- Can be highly effective
- May need > 1 FMT
- Donor screening important, now including MDR organisms

Case

- Your hospital uses toxin B gene PCR to diagnose CDI
- A 73 year old man with coronary disease is transferred from an assisted living center with chest pain & concern for myocardial ischemia. He has not received any antibiotics & was constipated prior to admission.
- He undergoes coronary stenting & on hospital day 3 has 2 unformed bowel movements after receiving laxatives & stool softeners. ROS (+) epigastric pain. He is afebrile. WBC count is 9,200.

Case

- A concerned nurse sends stool for *C. difficile* testing, which comes back **positive**. You place the patient on contact precautions. The next best step is:

A. Start metronidazole

B. Hold laxatives, isolate & observe

C. Start fidaxomicin

D. Start vancomycin

Case

- A concerned nurse sends stool for *C. difficile* testing, which comes back **positive**. You place the patient on contact precautions. The next best step is:

A. Start metronidazole

B. Hold laxatives, isolate & observe

C. Start fidaxomicin

D. Start vancomycin

Case EXPLANATION

- PCR detects the toxin-encoding gene, confirming the presence of a toxin-producing strain, but **it does not necessarily mean the strain is making any toxins at the moment**
- Thus, PCR cannot readily distinguish **colonization** from **infection**

Czepiel J, *et al. Eur J Clin Micro Infect Dis* (2019)
Carter KA & Malani AN. *Am J Infect Control* (2019)

Case EXPLANATION

- Laxative use is a common cause of hospital-associated diarrhea
- *C. difficile* testing should be limited to persons with 3 or more unformed stools in ≤24 h, not on laxatives

Carter KA & Malani AN. *Am J Infect Control* (2019)

Case EXPLANATION

- Asymptomatic colonization with *C. difficile* occurs in <5% of healthy adults in the community but between 3%-51% of hospitalized adults
- Only 25–30% of asymptomatic colonized patients develop diarrhea

Czepiel J, *et al. Eur J Clin Micro Infect Dis* (2019)
Carter KA & Malani AN. *Am J Infect Control* (2019)

Prevention

- Contact precautions for patient care
  - Gloves, gowns while diarrhea persists
- Single rooms
- Handwashing with SOAP & WATER
  - Alcohol gel rubs do not kill *Cd* spores
- Sporocidal solutions for hospital cleaning
  - Eg. hypochlorite solutions
- Antibiotic restriction policies
  - Antimicrobial stewardship programs

Lancet ID 17:194, 2017 Scotland
Lancet ID 17:411, 2017 England

TAKE AWAYS

- Epidemiology
  - Most CDI is health-care associated
- Diagnosis
  - Need to demonstrate toxin B in stool with NAATS, EIA
  - Send only unformed stools when diarrhea meets CDC definition

TAKE AWAYS

- Treatment: Primary or Recurrent CDI
  - Vancomycin & fidaxomicin > Metronidazole
  - Bezlotoxumab & fidaxomicin associated with lower risk for recurrent CDI
  - Consider FMT for second or more recurrence
- Prevention
  - Hand wash as alcohol gels ineffective
  - Bleach
  - Antimicrobial Stewardship Programs

QUIZ

- In adults & children prescribed antibiotics, is co-administration of a probiotic associated with a **lower risk** of symptomatic CDI without an increase in adverse events?

A. TRUE

B. FALSE

C. MAYBE

QUIZ

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A. TRUE

B. FALSE

C. MAYBE

QUIZ EXPLANATION

- Among 31 studies comparing antibiotics & probiotics *vs* placebo or no treatment for preventing CDI in patients receiving antibiotics, probiotics were associated w/ a lower risk of CDI, adverse events, & antibiotic-associated diarrhea
  - **NNT = 40**

Goldenberg JZ, *et al. JAMA* (2018)

QUIZ EXPLANATION

- **HOWEVER**: the benefit seems to be limited to people with >5% risk of getting CDI, which is not most US hospitalized patients
- Further research is needed to identify high-risk populations that may benefit most from addition of probiotics to antibiotic treatment
  - Those colonized w/ *C. difficile*
  - Patients w/ a history of CDI

Goldenberg JZ, *et al. JAMA* (2018)

QUIZ EXPLANATION

- **Several recent studies** (of relatively small number & retrospective) suggest no benefit
- So: **if there is a benefit**, it is probably small & we do not know the best probiotic, the best target population or those who might get hurt

Box MJ, *et al. Open Forum Infect Dis* (2018)

THANK YOU

Feel free to contact me at

d.aronoff@vumc.org

Follow me on Twitter @DMAronoff

Case

- A 57 yo male with leukemia is undergoing chemotherapy and taking prophylactic ciprofloxacin for neutropenia
- He presents with abdominal pain, diarrhea, & fever. ROS (+) nausea, vomiting, & abdominal distension.

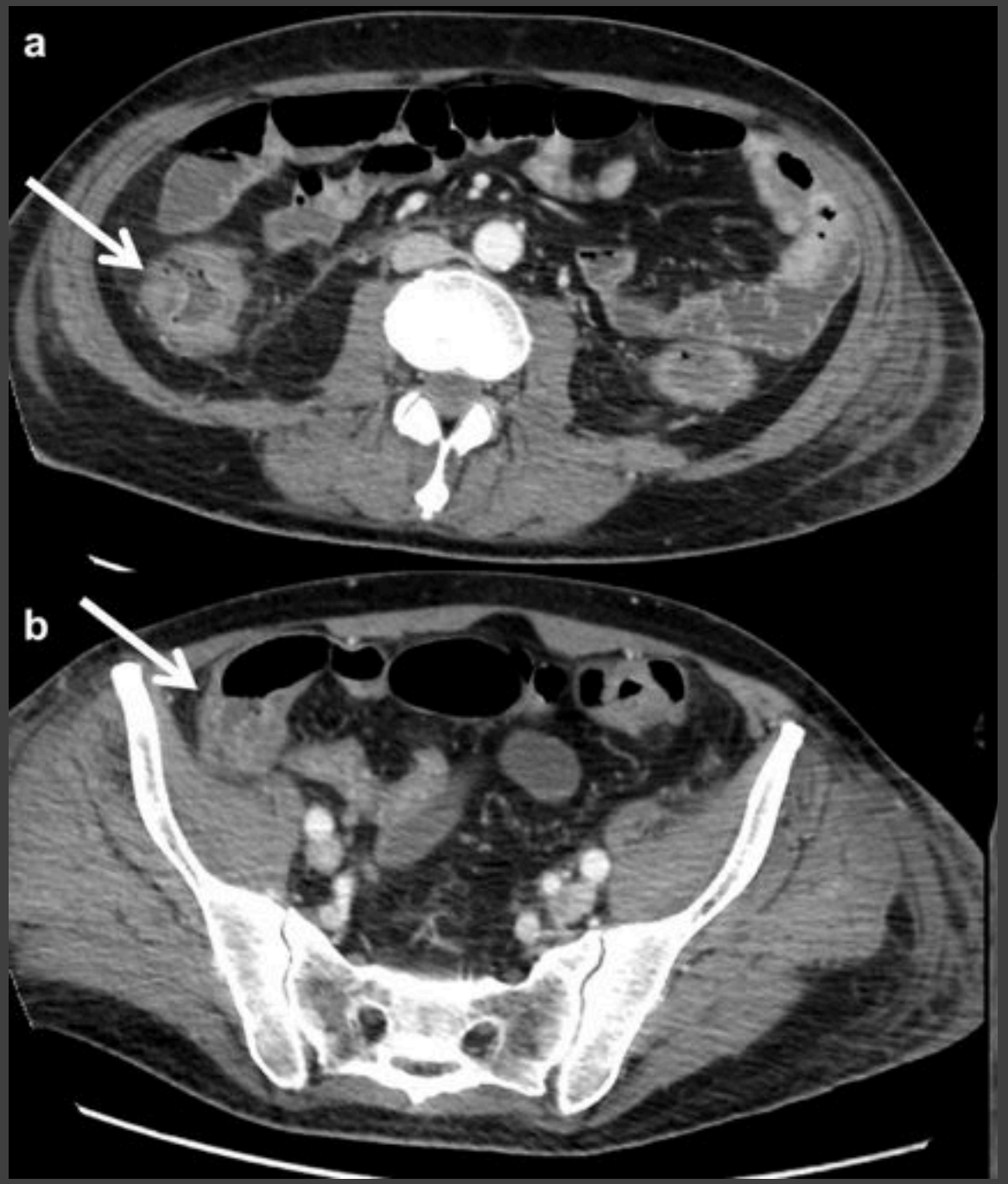
Guerri S, *et al*. *La radiologia medica* (2019)
Rodrigues FG, *et al. World J Gastroenterol* (2017)

Case

- On physical exam he is febrile and appears uncomfortable. Abdomen is tender, especially in the RLQ. Labs reveal WBC count of 323 (ANC ~200) & normal renal function.
- CT scan shows moderate wall thickening of the cecum & terminal ileum. *C. difficile* testing by PCR is **negative**.

Guerri S, *et al*. *La radiologia medica* (2019)
Rodrigues FG, *et al. World J Gastroenterol* (2017)

Case



Guerri S, *et al*. *La radiologia medica* (2019)

Case

- What is the most likely diagnosis?

A. Colitis caused by toxin-negative *C. difficile*
B. CDI with a false negative PCR test
C. Ischemic colitis
D. Neutropenic enterocolitis (typhlitis)
E. *Yersinia* pseudotuberculosis

Guerri S, *et al*. *La radiologia medica* (2019)
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Guerri S, *et al*. *La radiologia medica* (2019)
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Case Explanation

- Neutropenic colitis (**typhlitis**) is a severe condition usually affecting immunocompromised patients
- The pathogenesis is not completely understood
- The main elements in disease onset appear to be intestinal mucosal injury with neutropenia
- These initial conditions lead to intestinal edema, engorged vessels, and a disrupted mucosal surface, which becomes more vulnerable to bacterial intramural invasion

Rodrigues FG, *et al. World J Gastroenterol* (2017)