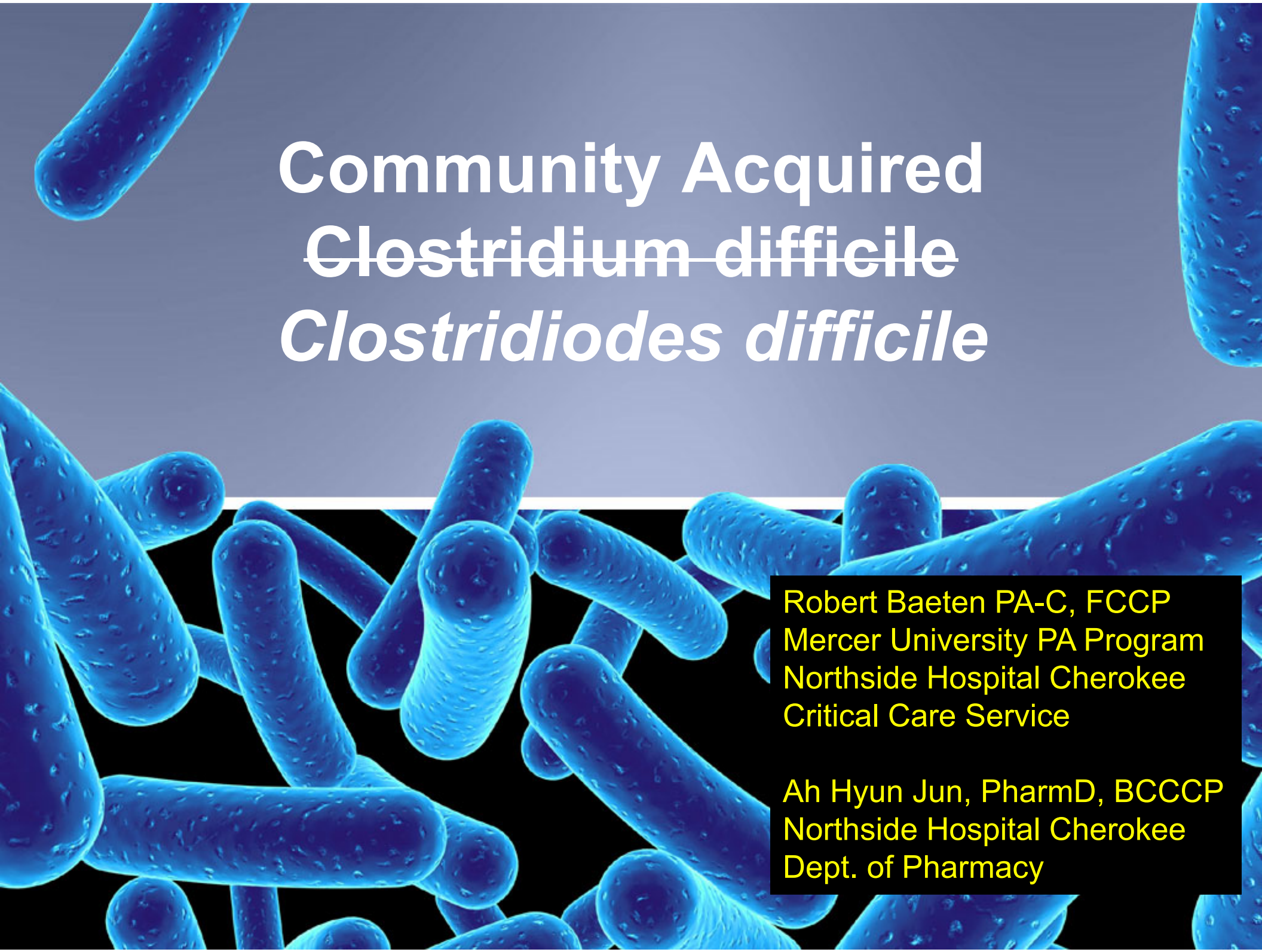


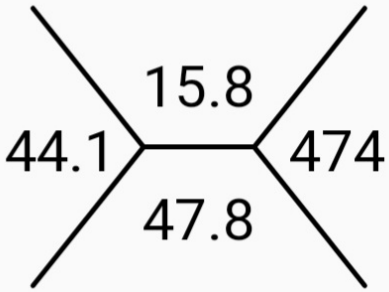
Community Acquired ~~*Clostridium difficile*~~ *Clostridiodes difficile*

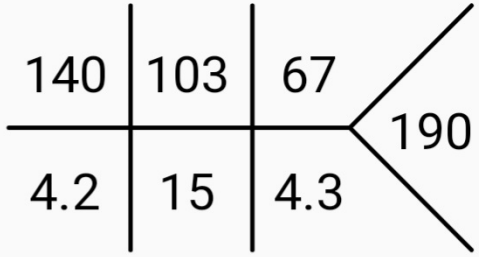
Robert Baeten PA-C, FCCP
Mercer University PA Program
Northside Hospital Cherokee
Critical Care Service

Ah Hyun Jun, PharmD, BCCCP
Northside Hospital Cherokee
Dept. of Pharmacy

Case

- 71 M w/pmh of HTN admit w/~4 days of non-blood diarrhea and weakness. Hypotensive w/abd pain on exam.
- No recent abx or healthcare exposure
- Required norepi to keep MAP 65 despite initial 3L crystalloid

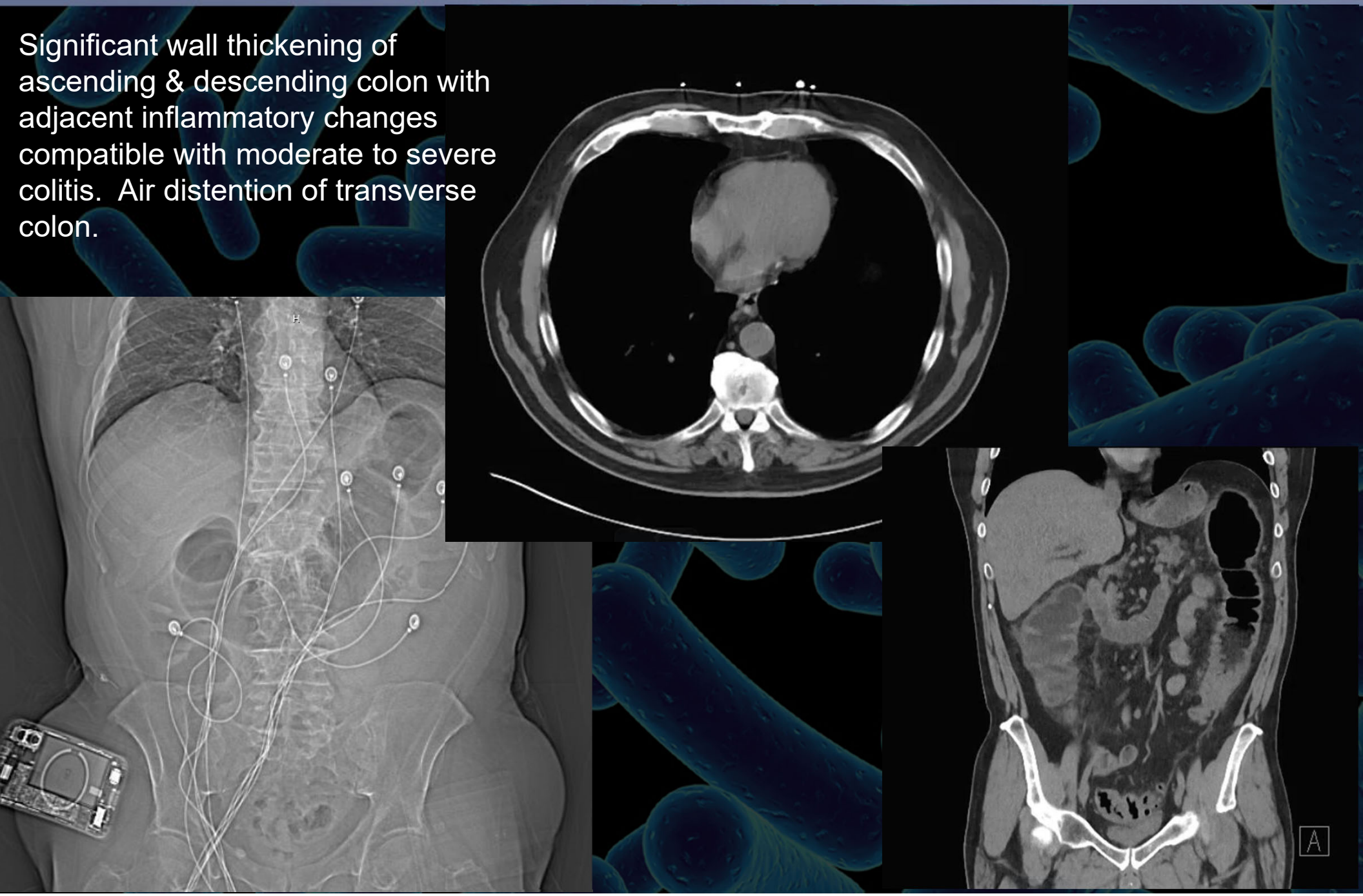




Mg++:	2.4	T.Bili:	1.5	Lactate:	7.07
Phos:	5.0	Albumin:	3.5	Trop:	0.01
Ca++:	9.3	Lipase:	4		
AST:	19	INR:	1.2		
ALT:	25	PT:	16.1		
AlkPhos:	86	PTT:	30.4		

CT Abd/Pelvis wo Contrast

Significant wall thickening of ascending & descending colon with adjacent inflammatory changes compatible with moderate to severe colitis. Air distention of transverse colon.



Consultants

- Day of Admission
  - **General Surgery**
  - **Infectious Disease**
  - **Nephrology**
- Day 2 of Admission
  - **Gastroenterology**

C. Diff Colitis

- C. diff lab resulted later on the day of admission
- Initial Abx:
  - **IV Meropenem, metronidazole (2p, 1p)**
  - **PO Vanco (4p)**

- Later received Bezlotoxumab (afternoon of admission)
  - **Monoclonal Ab binds to Toxin B**
    - C. diff produces toxin A & toxin B

<48 hours after admit

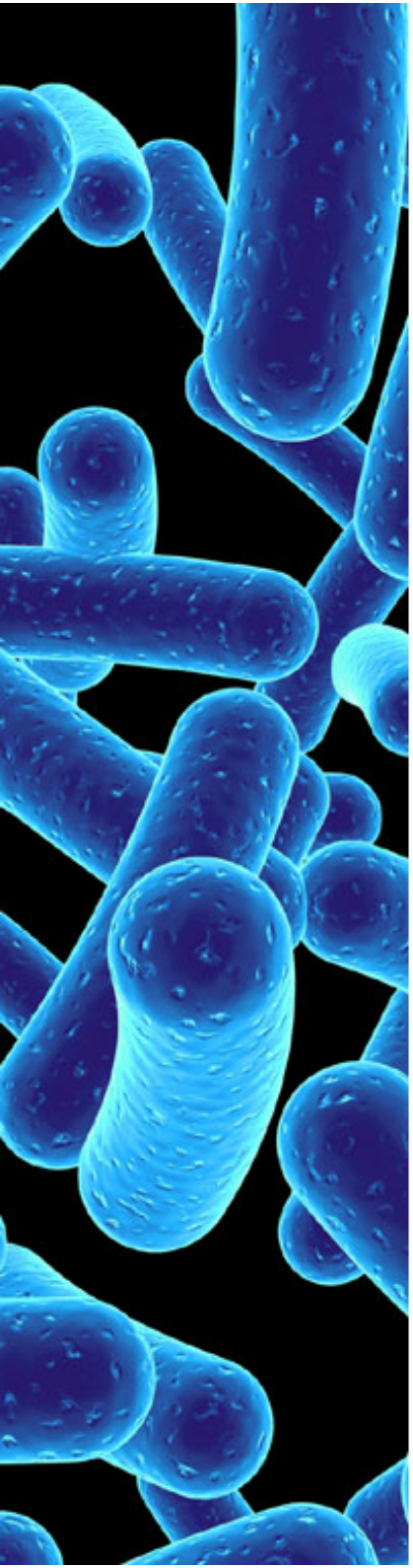
- Progressive decline
  - **Multipressor shock**
  - **Intubated**
  - **CRRT initiated**
  - **Ex Lap, Total Abd Colectomy/ileostomy**

End of week 1

- Severe resp fx w/high fio2 req and iNO
- DIC – blood products
- DNR

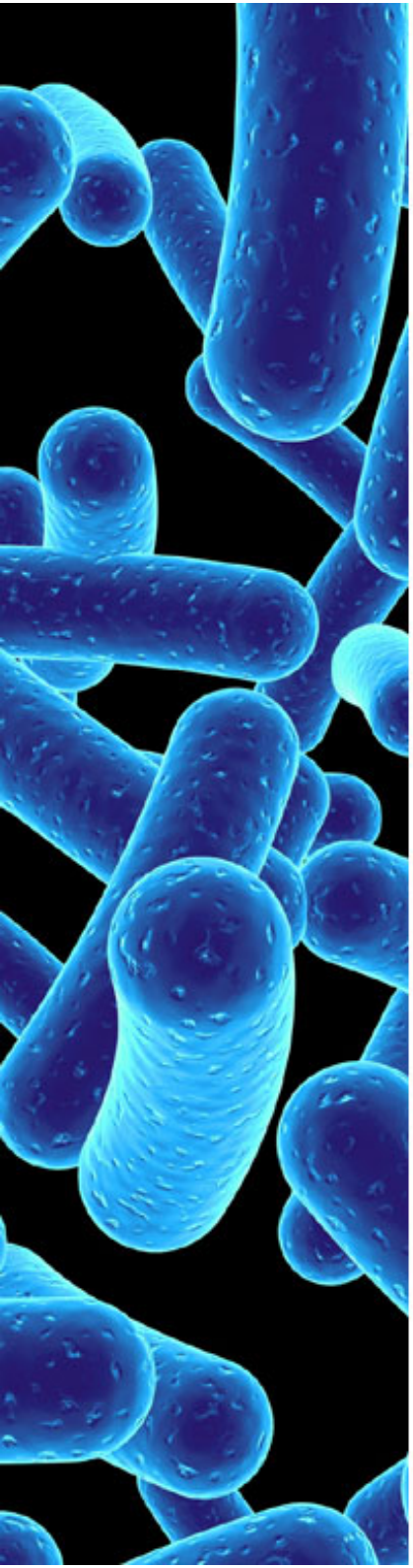
End of week 2

- Brief improvement at end of week one then…..
- Clinical decline
  - **Hepatic & Splenic infarcts w/possible gastric wall ischemia**
  - **Worsening shock**
- Expired day 18



Community Acquired C. diff

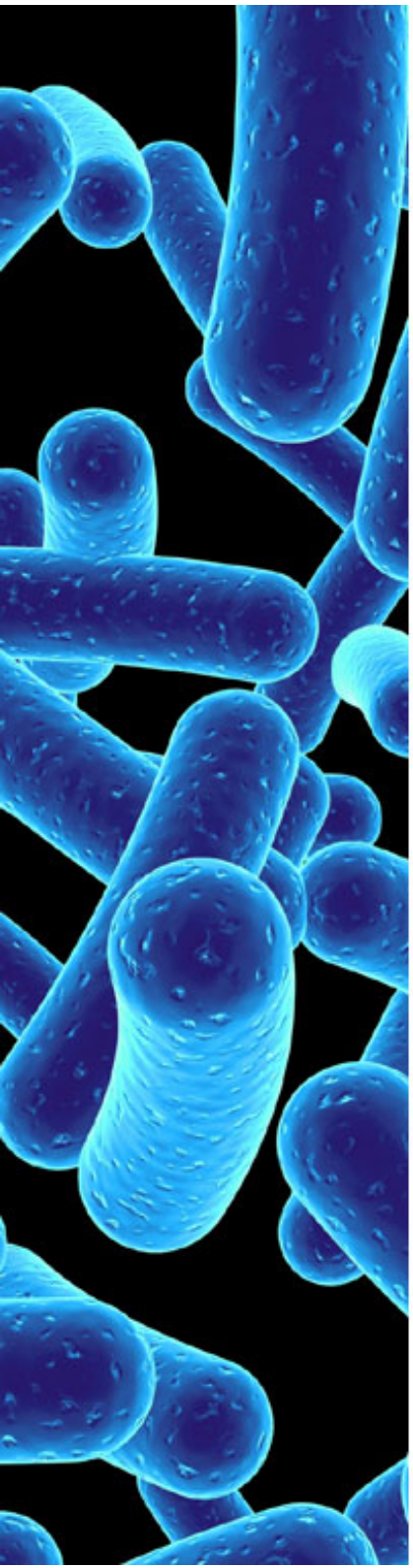
- What is C. diff
- Prevalence
- Manifestation/Diagnosis
- Management



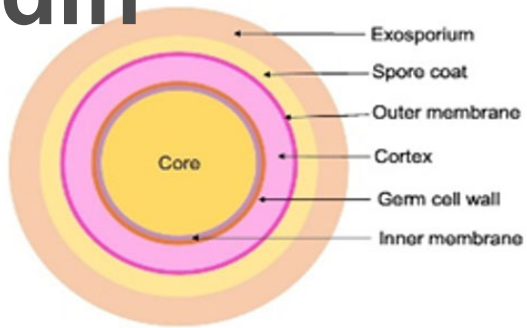
Community Acquired C. diff

- *Clostridium difficile* changed to *Clostridiodes difficile* in 2016
  - Genetically in family Peptostreptococcaceae
    - Initially suggested to be in new genus: Peptoclostridium
    - Ultimately this would be too confusing and cumbersome as C. diff is very familiar both clinically and commercially and would lead to significant financial burden with relabeling etc.
    - Needed to keep genus starting with the letter "C" →Clostridioides
    - Similar to prior 2007 Comment in *The Lancet Infectious Diseases*
      - "the purpose of scientific names of organisms is unambiguous communication" [1]

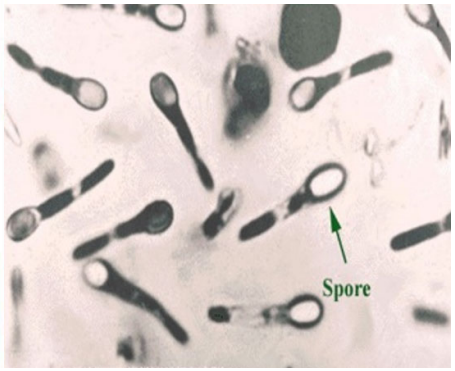
- Gram positive rod, obligate anaerobe, spore forming

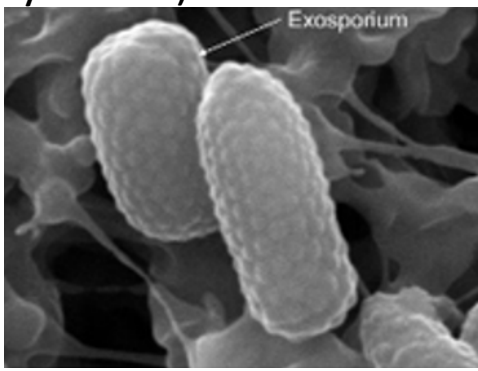


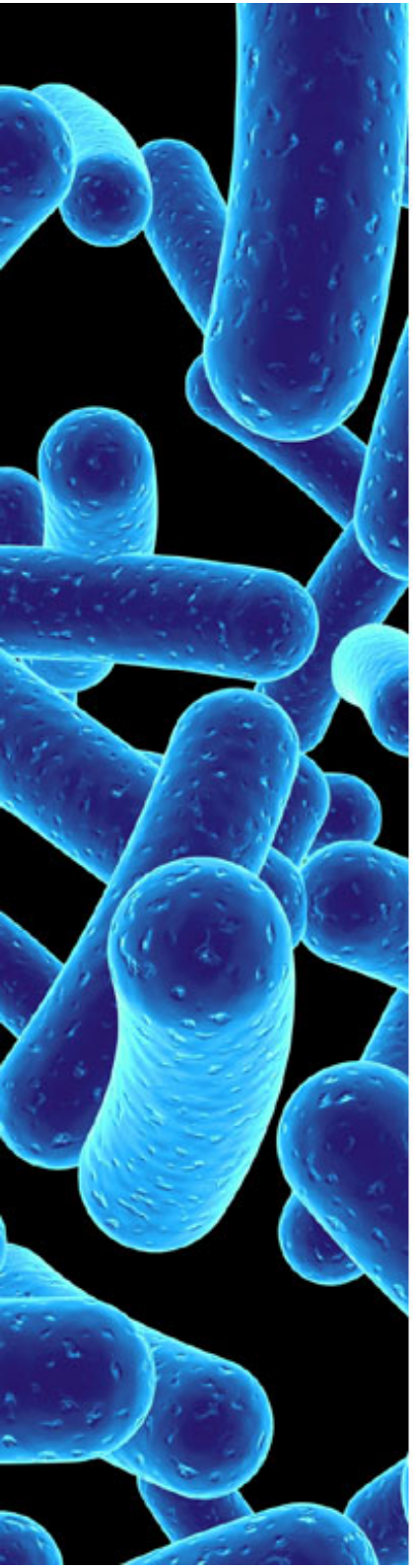
Community Acquired C. diff



- Spore formation is crucial for:
  - survival in an aerobic atmosphere→ aerotolerant
  - Resistance to extreme environmental conditions
  - Dissemination and persistence of C. diff infections
- Spore germination to colonize the host
  - Spores reactivated by specific environmental signals
    - Designed to not grow until it is in the small intestine
      - Involves primary bile acids and secondary bile salts
      - Normal gut microbiota also metabolize these bile moities
        - (flora…misnomer as flora refers to plants)
        - Decreased normal gut organisms (dysbiosis)reduces competitive inhibition [2]

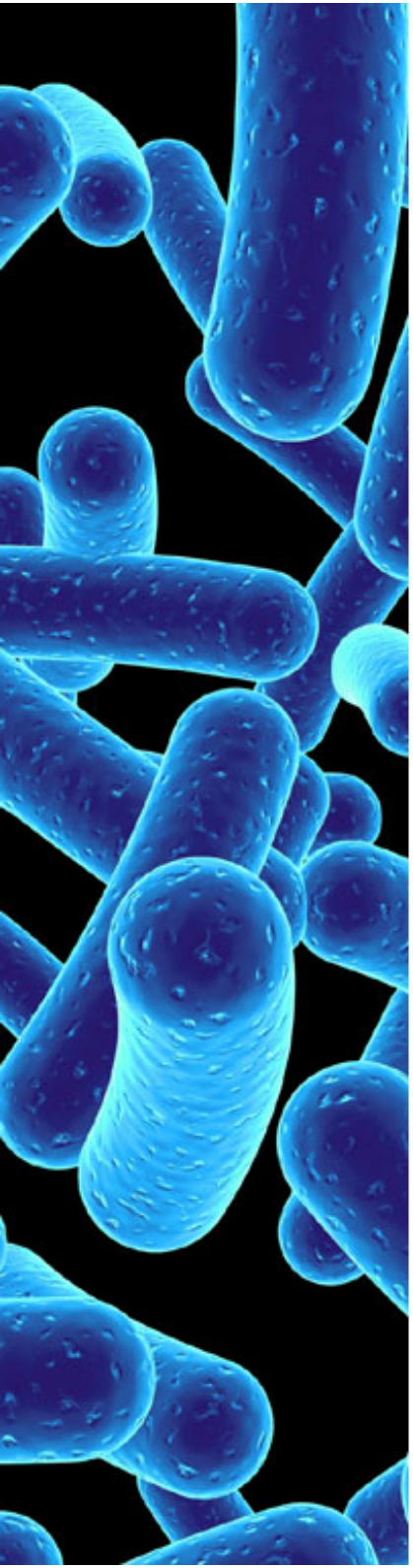






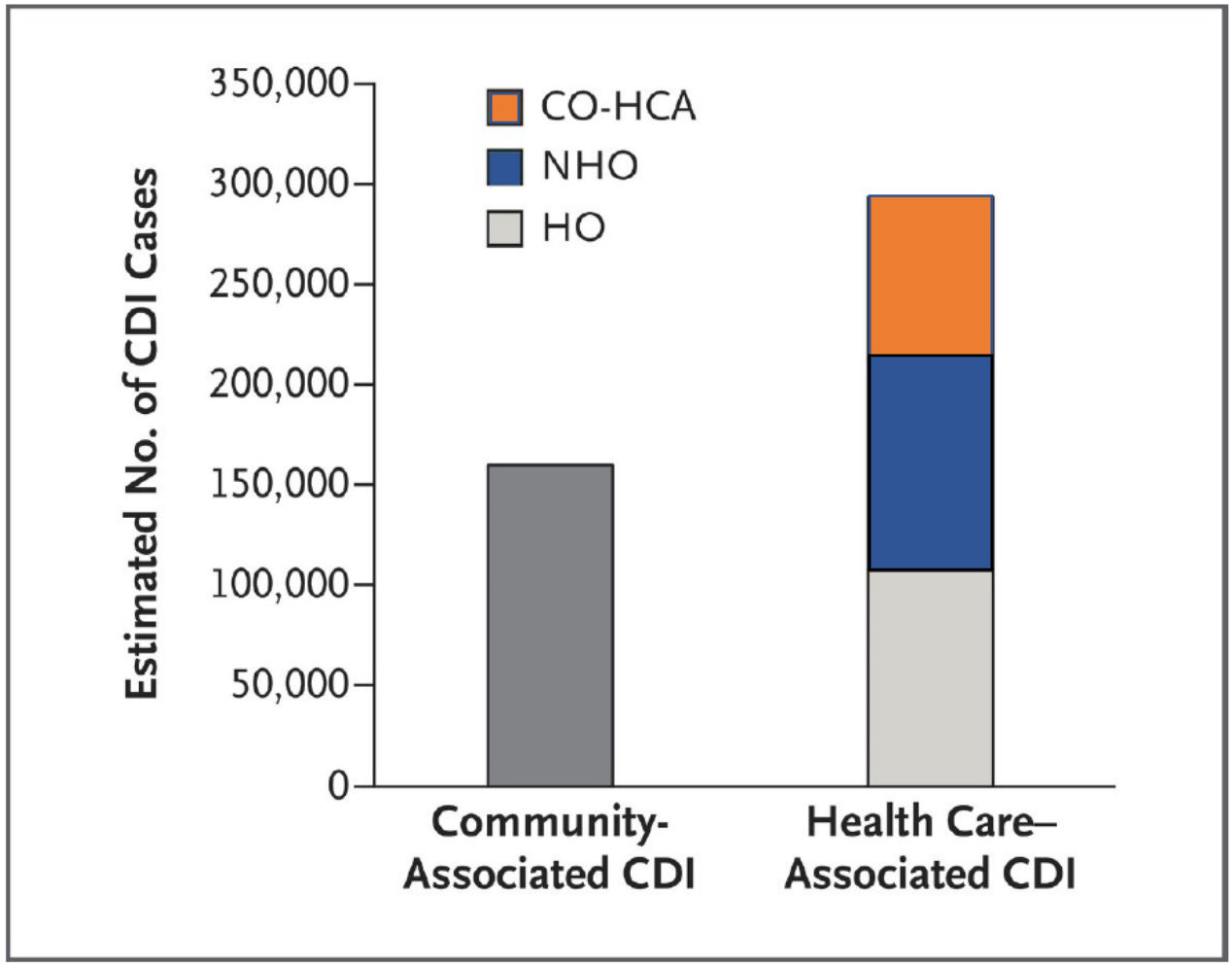
Community Acquired C. diff

- Epidemiology-Prevalence
  - **Community acquired**
    - – symptom onset ≤48hrs from admission without contact with health facility in last previous 3 months
  - **CA CDI steadily increasing (1991-2015)** [3]
  - **Exact number of C. diff infection difficult to know**
    - Underdiagnosis
      - European studies found ~24% of diarrhea hospitalizations are undiagnosed [4,5]
      - False negative rate 17%
      - Absence of clinical suspicion [5]

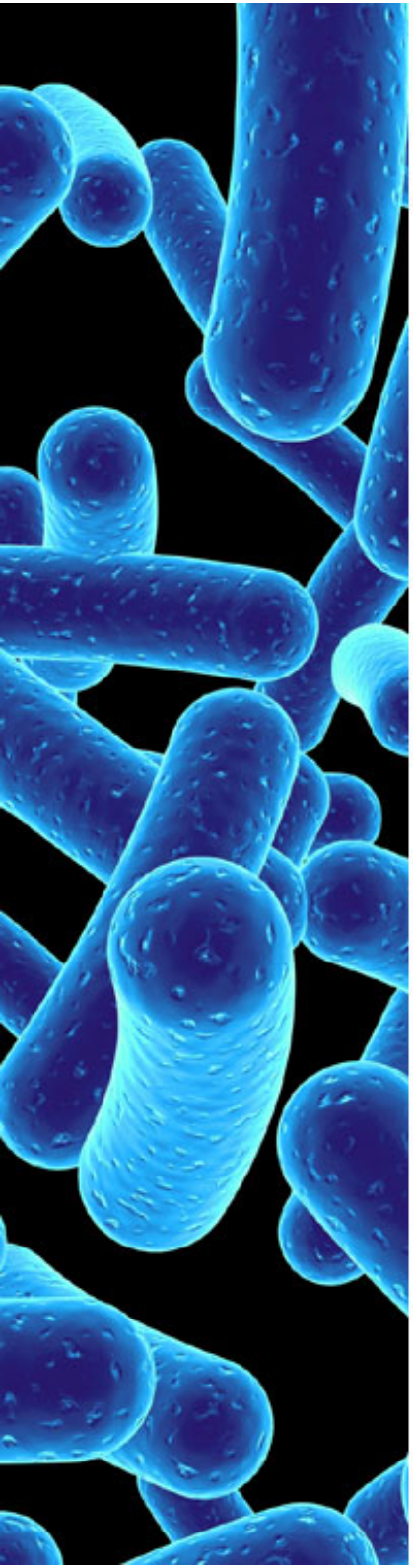


Community Acquired C. diff

- Prevalence
  - **Estimated U.S. Burden of C. diff Infection** [6]



Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

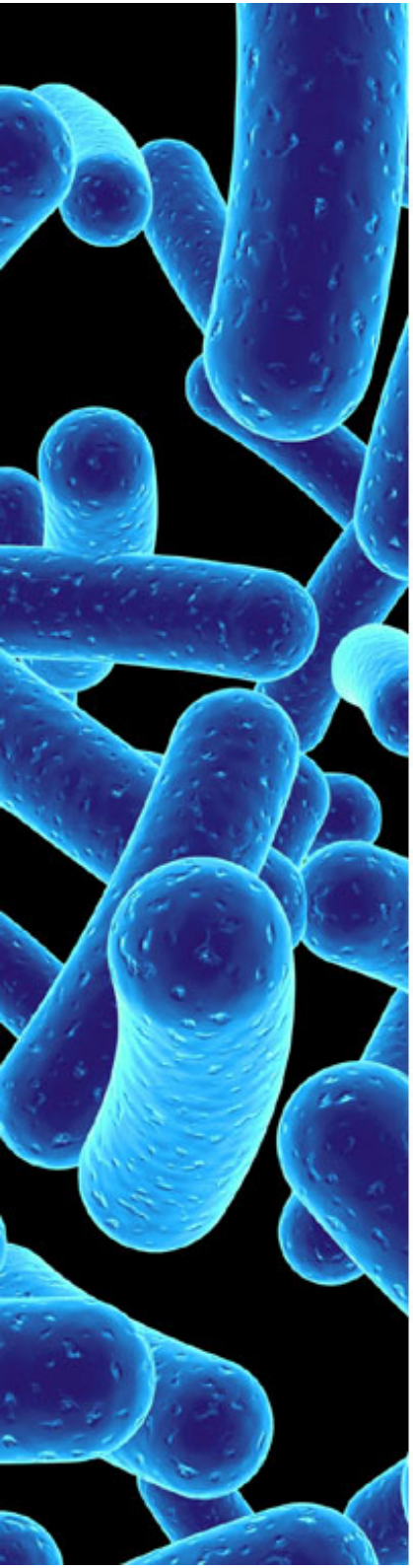


Community Acquired C. diff

- CDC surveillance program
  - **Measure burden in population**
  - **10 sites across U.S.**
    - 3 epidemiologic categories
      - Healthcare facility-onset (HCFO)
        - » Stool + >3 days after admission
      - Community-onset healthcare facility-associated (CO-HCFA)
        - » Stool + within 12 weeks of a healthcare facility stay
      - Community-associated (CA)
        - » Stool + no recent heathcare exposure (>12 weeks)

Areas Under Surveillance	Population
San Francisco County, CA	883,305
Adams, Arapahoe, Denver, Douglas and Jefferson Counties, CO	2,802,584
New Haven County, CT	857,620
Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton and Rockdale Counties, GA	4,126,399
Caroline, Cecil, Dorchester, Frederick, Kent, Somerset, Talbot, Queen Anne's, Washington, Wicomico and Worcester Counties, MD	861,997
Benton, Morrison, Olmsted*, Stearns and Todd Counties, MN	413,829
Bernalillo County, NM	678,701
Monroe County, NY	742,474
Klamath County, OR**	67,653
Davidson County, TN	692,587
Total	**12,127,149**

*Surveillance in Olmsted County began July 2012
**Deschutes County, OR participated in CDI surveillance during 2012-2013.

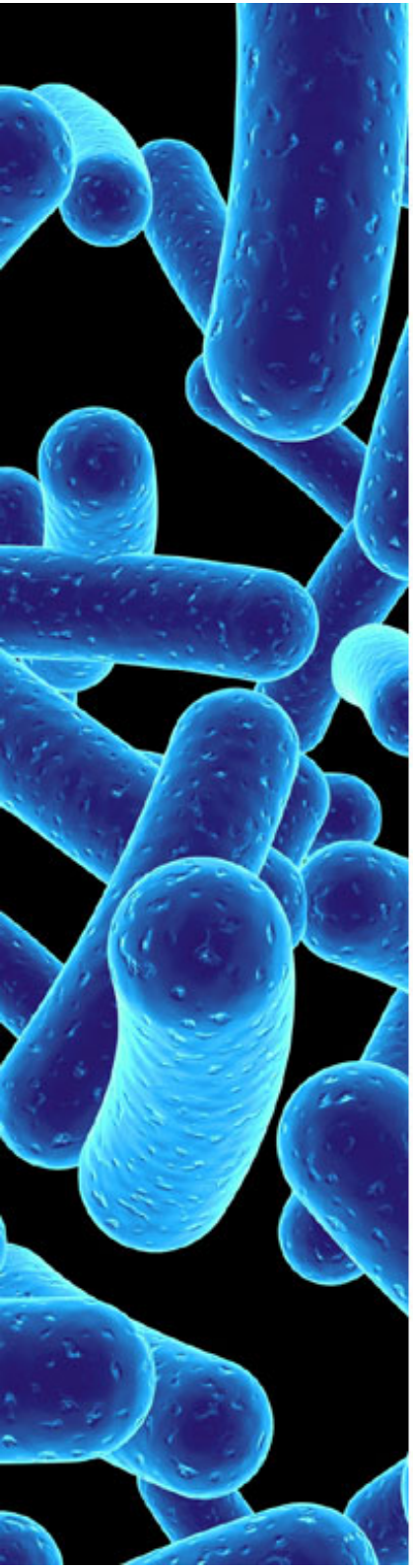


Community Acquired C. diff

- 2011-2017 Data
  - **15,512 cases in 2017**
    - 7973 health care-associated
    - 7539 community-associated
- CA increased
- Healthcare assoc decreased
- Total unchanged with trend lower incidence

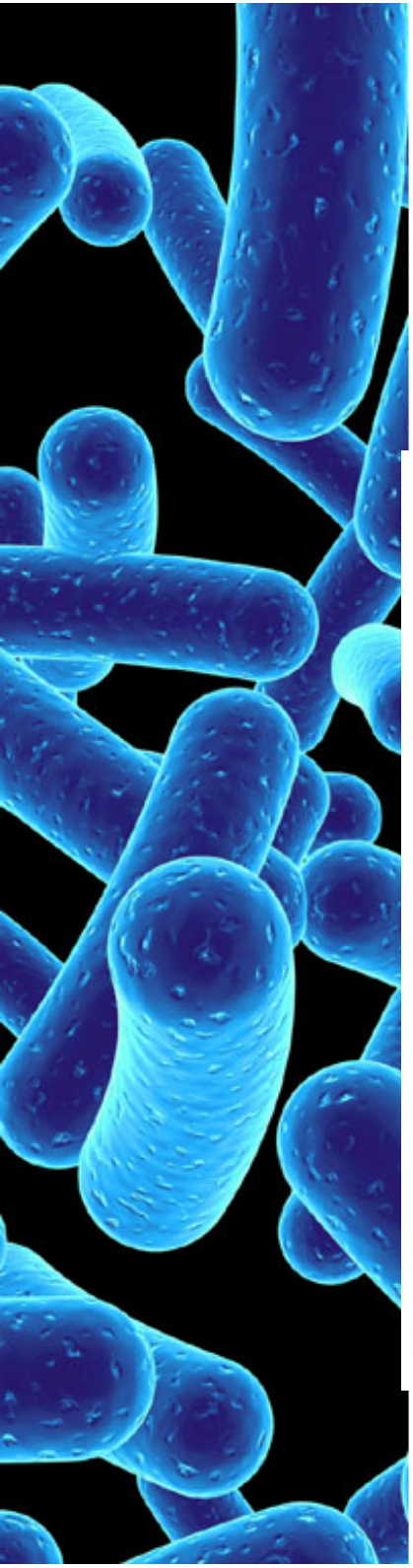
Reported Cases of C. diff infection (CDI) and Crude Incidence, According to Epidemiologic Cases, at 10 U.S. Emerging Infections Program Sites 2011-2017

Surveillance Year	Population ≥1 Yr of Age	Community-Associated CDI		Health Care–Associated CDI		All CDI	
		No. of Cases	Incidence per 100,000 Persons	No. of Cases	Incidence per 100,000 Persons	No. of Cases	Incidence per 100,000 Persons
	no.						
2011	10,971,319	5284	48.16	10,177	92.76	15,461	140.92
2012†	11,283,326	5967	52.88	10,482	92.90	16,449	145.78
2013	11,552,955	6441	55.75	9,938	86.02	16,379	141.77
2014	11,533,856	6669	57.82	9,662	83.77	16,331	141.59
2015	11,682,427	7697	65.89	9,655	82.65	17,352	148.53
2016	11,777,482	7915	67.20	8,881	75.41	16,796	142.61
2017	11,906,512	7539	63.32	7,973	66.96	15,512	130.28



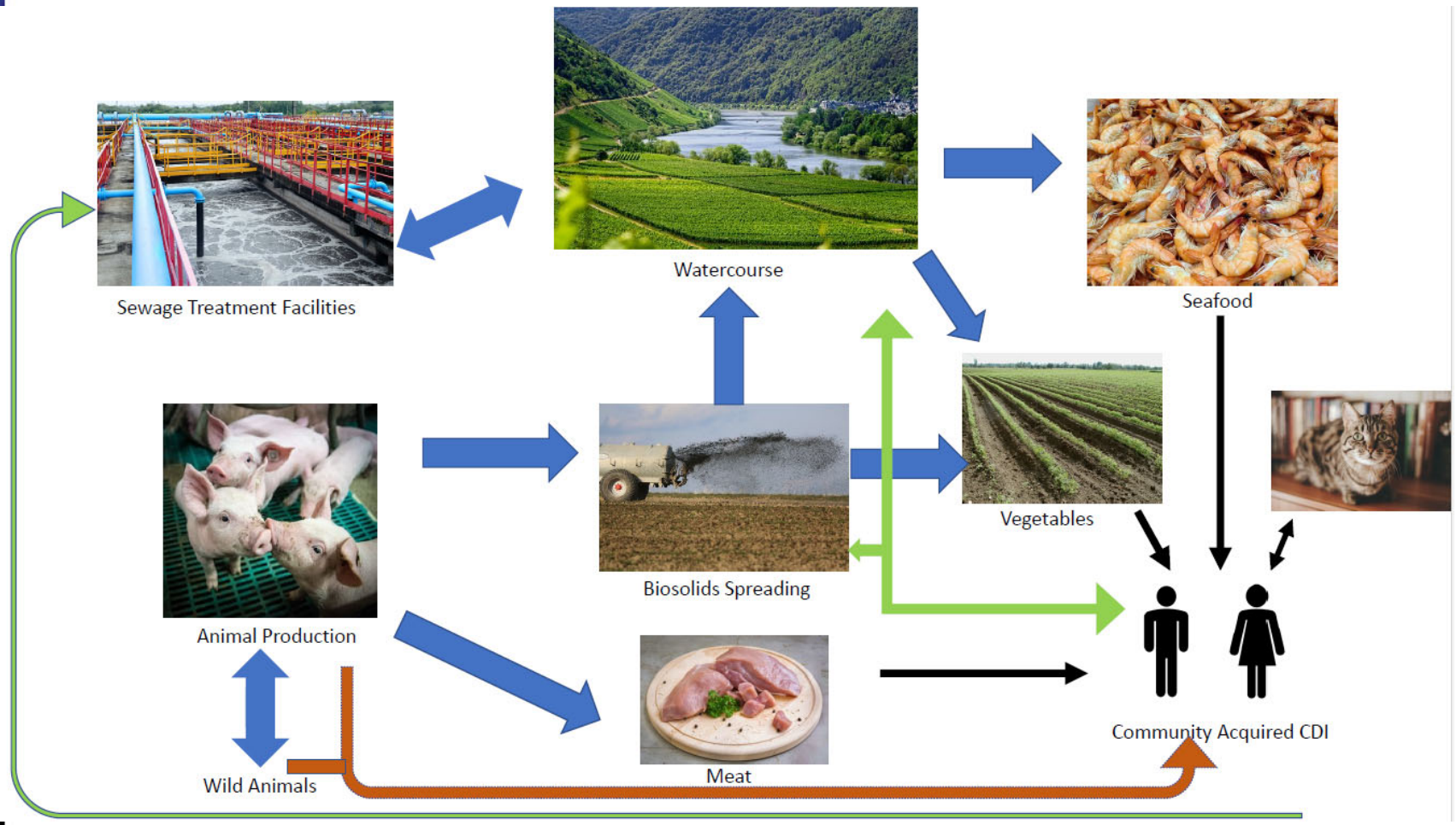
Community Acquired C. diff

- Recent Systematic Review & Meta-analysis 2000-2019 [8]
  - **Similar overall incidence**
  - **Trend toward increased CA CDI**
- Why CA CDI increasing?
  - **Possible foodborne route**
    - No foodborne illness outbreaks have been directly linked to C. difficile
      - Although spores can survive cooking
      - Can't grow due to lack of bile salts [9]
  - **Domestic pets as asymptomatic carriers?** [10]

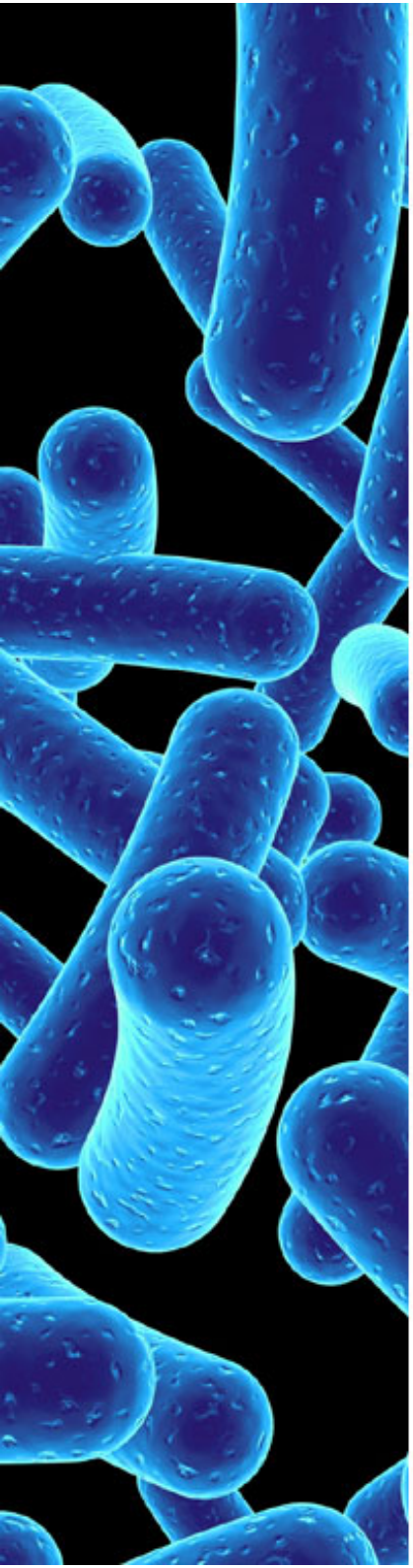


Community Acquired C. diff

- Fecal-oral route
  - **Several possible mechanisms** [9]

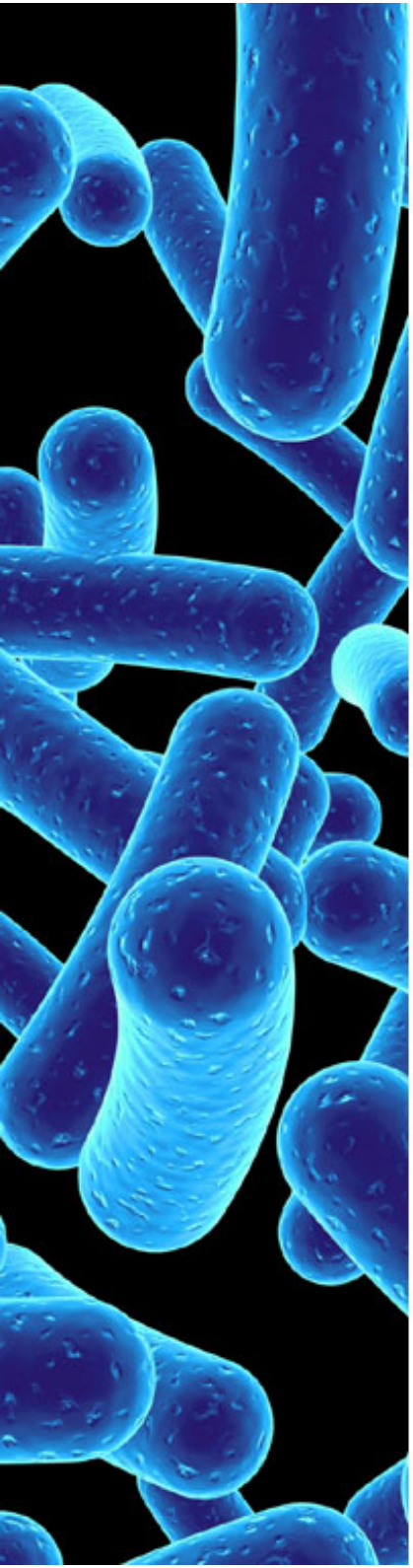


C. Diff cycling & recycling from environmental, zoonotic or foodborne sources implicated in community-associated infections.

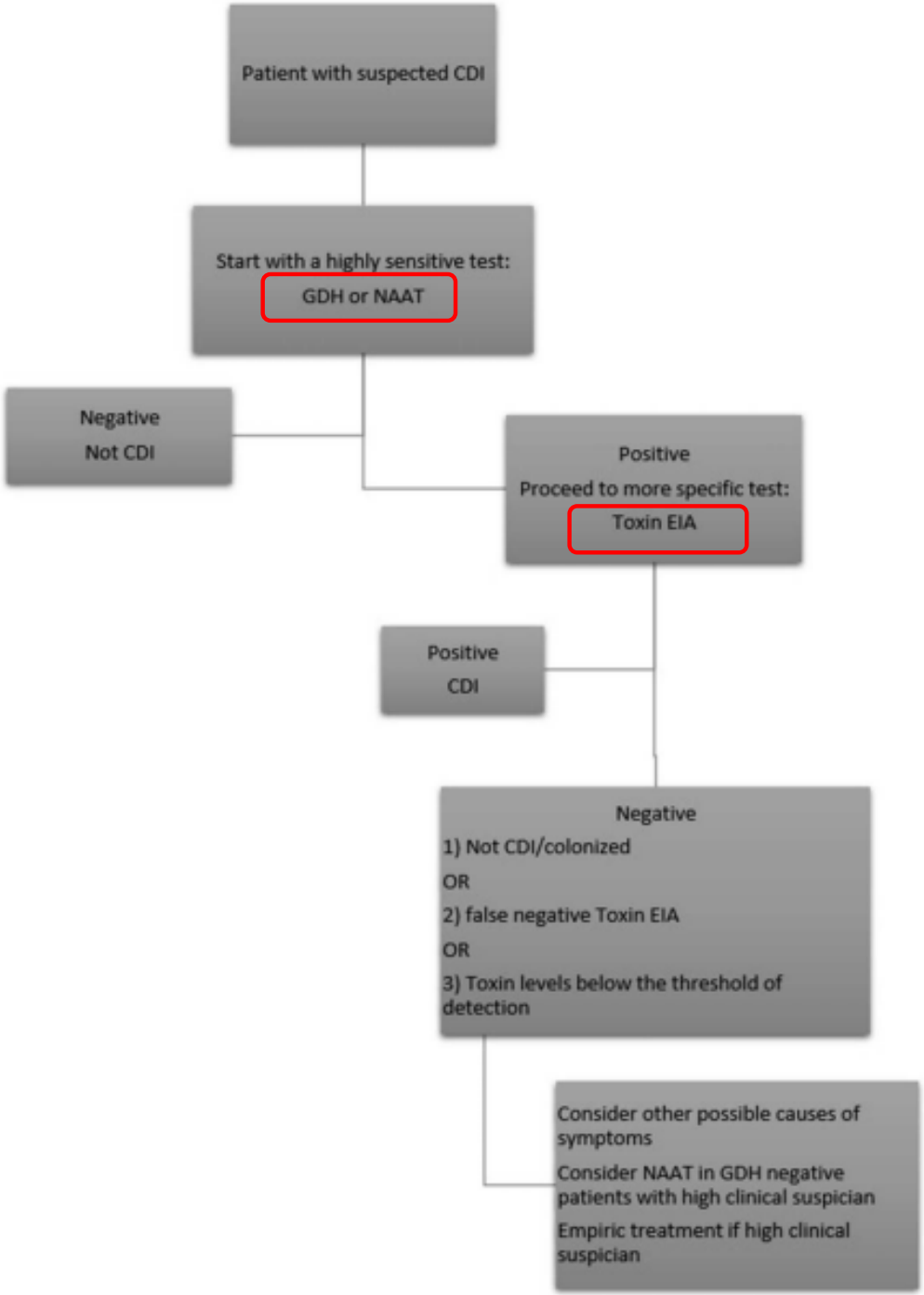


Diagnosis of C. diff

- Test patients with symptoms suggestive of active C. diff:
  - **≥ 3 stools in 24 hours with no laxative use**
- Highly sensitive tests: [15]
  - **Nucleic acid amplification testing (NAAT): PCR, loop-mediated isothermal amplification**
  - **Glutamate dehydrogenase (GDH)**
- Highly specific tests:
  - **Enzyme immunoassays (EIA): detects toxins A and B**



C. diff Testing Algorithm



Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147.

References

- 1. The Lancet Infectious Diseases. C difficile-a rose by any other name…. *Lancet Infect Dis*. 2019;19(5):449. doi:10.1016/S1473-3099(19)30177-X
- 2. Lawler AJ, Lambert PA, Worthington T. A Revised Understanding of Clostridioides difficile Spore Germination. *Trends Microbiol*. 2020;28(9):744-752. doi:10.1016/j.tim.2020.03.004
- 3. Ofori E, Ramai D, Dhawan M, Mustafa F, Gasperino J, Reddy M. Community-acquired Clostridium difficile: epidemiology, ribotype, risk factors, hospital and intensive care unit outcomes, and current and emerging therapies. *J Hosp Infect*. 2018;99(4):436-442. doi:10.1016/j.jhin.2018.01.015
- 4. Davies KA, Longshaw CM, Davis GL, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID). *Lancet Infect Dis*. 2014;14(12):1208-1219. doi:10.1016/S1473-3099(14)70991-0
- 5. Cataldo MA, Granata G, D'Arezzo S, et al. Hospitalized patients with diarrhea: rate of Clostridioides difficile infection underdiagnosis and drivers of clinical suspicion. *Anaerobe*. May 2021:102380. doi:10.1016/j.anaerobe.2021.102380
- 6. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015;372(9):825-834. doi:10.1056/NEJMoa1408913
- 7. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of Clostridioides difficile Infection and Outcomes. *N Engl J Med*. 2020;382(14):1320-1330. doi:10.1056/NEJMoa1910215
- 8. Marra AR, Perencevich EN, Nelson RE, et al. Incidence and Outcomes Associated With Clostridium difficile Infections: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(1):e1917597. doi:10.1001/jamanetworkopen.2019.17597
- 9. Warriner K, Xu C, Habash M, Sultan S, Weese SJ. Dissemination of Clostridium difficile in food and the environment: Significant sources of C. difficile community-acquired infection? *J Appl Microbiol*. 2017;122(3):542-553. doi:10.1111/jam.13338
- 10. Hernandez BG, Vinithakumari AA, Sponseller B, Tangudu C, Mooyottu S. Prevalence, Colonization, Epidemiology, and Public Health Significance of Clostridioides difficile in Companion Animals. *Front Vet Sci*. 2020;7:512551. doi:10.3389/fvets.2020.512551
- 11. McDonald LC, Gerding DN, Johnson S, et al. 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). *Clin Infect Dis*. 2018;66(7):e1-e48. doi:10.1093/cid/cix1085
- 12. von Braun A, Lübbert C. [Treatment of acute and recurrent Clostridium difficile infections : What is new?]. *Internist (Berl)*. 2018;59(5):505-513. doi:10.1007/s00108-018-0401-x
- 13. Tixier EN, Verheyen E, Luo Y, et al. Systematic Review with Meta-Analysis: Fecal Microbiota Transplantation for Severe or Fulminant Clostridioides difficile. *Dig Dis Sci*. March 2021. doi:10.1007/s10620-021-06908-4
- 14. Cheng Y-W, Fischer M. Fecal Microbiota Transplantation: Redefining Surgical Management of Refractory Clostridium difficile Infection. *Clin Colon Rectal Surg*. 2020;33(2):92-97. doi:10.1055/s-0040-1701233
- 15. Kelly C, Fischer M, Allegretti J et al. ACG Clinical guidelines: prevention, diagnosis, and treatment of Clostridioisis difficile infections. Am J Gastroenterol. 2021;116:1124-1147.

Management of C. diff Infection

- Guideline recommendations
- Fidaxomicin vs. PO vancomycin vs. metronidazole
- Recurrent C. diff therapies – old and new

IDSA C. diff Guideline 2021: Initial Episode Treatment

Preferred	Alternative	Alternative 2 (Non-severe*/ unavailable)
• Fidaxomicin PO 200 mg 2x day x 10 days	• Vancomycin PO 125 mg 4x day x 10 days	• Metronidazole PO 500 mg 3x day x 10-14 days

* Non-severe: WBC < 15,000 cells/µL and sCr level < 1.5 mg/dL

Johnson S, et al. Clin Infect Dis. 2021; 73(5):e1029-e1044.

IDSA C. diff Guideline 2021: Recurrence Treatment

First Recurrence:

- Preferred: fidaxomicin PO 200 mg 2x day x 10 d
- Alternative: vancomycin PO 125 mg 4x day x 10 d
- Alternative: vancomycin PO taper regimen
- Adjunct: bezlotoxumab IV 10 mg/kg once

Second or Subsequent Recurrence:

- Fidaxomicin PO 200 mg 2x day x 10 d
- Vancomycin PO 125 mg 4x day x 10 d → rifaximin 400 mg 3x day x 20 d
- Vancomycin PO taper regimen
- Fecal microbiota transplantation
- Adjunct: bezlotoxumab IV 10 mg/kg once

Johnson S, et al. Clin Infect Dis. 2021;73(5):e1029-e1044.

IDSA C. diff Guideline 2021: Fulminant C. diff

Definition:

- Hypotension or shock
- Ileus
- Megacolon

Pharmacologic Treatment:

- Vancomycin PO 500 mg 4x daily + metronidazole IV 500 mg q8h
- If ileus: add PR vancomycin 500 mg 4x daily

Surgical Treatment:

- Preferred: subtotal colectomy with rectum preservation
- Alternative: diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes

Johnson S, et al. Clin Infect Dis. 2021;73(5):e1029-e1044.

Fidaxomicin vs. PO Vancomycin

	Fidaxomicin (Dificid)	PO vancomycin
Mechanism of action	Selectively binds to RNA polymerase of C. diff and inhibits RNA synthesis	Inhibits cell-wall biosynthesis; alters bacterial-cell-membrane permeability and RNA synthesis
Dose	200 mg PO 2x day	125 mg PO 4x day
Half life	11.7 hours	4-6 hours
Adverse events	Abdominal pain, nausea, vomiting Anemia, neutropenia GI hemorrhage	Abdominal pain, hypokalemia, nausea, vomiting, diarrhea Nephrotoxicity, peripheral edema, hypotension
Cost	$4322.38 / 20 tabs of 200 mg	$100 / 40 caps of 125 mg

Lexicomp. 2023

Fidaxomicin vs. PO Vancomycin

Study	Population	Results
Louie T, et al. 2011 *Multi-center, double-blind, randomized*	548 patients in the US, Canada • Initial episode: 82.5-83.3%	• Clinical cure: 88.2% F vs. 85.8% V • Recurrence: 15.4% F vs. 25.3% V*
Cornely O, et al. 2012 *Multi-center, double-blind, randomized, non-inferiority*	509 patients in Europe, US, Canada • Initial episode: 84-86% • Severe: 23.7-25%	• Clinical cure: 91.7% F vs. 90.6% V • Recurrence: 19.5% F vs. 25.3% V
Guery B, et al. 2018 *Randomized, controlled, open-label, superiority*	362 patients in Europe • Initial episode: 78-80% • Severe: 36%-37% • From home: 58%	• 30-day clinical cure: 70% F vs. 59% V* • 90-day recurrence: 6% F vs. 19% V*
Mikamo H, et al. 2018 *Phase III, double-blind, parallel-group*	212 patients in Japan • Initial episode: 85-86% • Severe: 20.4-24% • No prior antibiotic use: 95-97%	• 28-day global cure: 67.3% F vs. 65.7% V • Recurrence: 19.5% F vs. 25.3% V

*P < 0.05

Louie T, et al. N Eng J Med. 2011;364:422-31.
Conely O, et al. Lancet Infect Dis. 2012;12:281-89.
Guery B, et al. Lancet Infect Dis. 2018;18:296-307.
Mikamo H, et al. J Infect Chemother. 2018;24:744-752.

Fidaxomicin vs. PO Vancomycin

- Fidaxomicin associated with less overgrowth of vancomycin-resistant Enterococcus (VRE) and Candida species
  - VRE: 7% fidaxomicin vs. 31% vancomycin*
  - Candida: 19% fidaxomicin vs. 29% vancomycin*

- Emergence of C. diff isolates with decreased susceptibility to vancomycin
  - 26% C. diff isolate resistant to vancomycin in one study

Nerandzic M, et al. Clin Infect Dis. 2012;55(suppl 2):S121-S126.
Darkoh C, et al. Clin Infect Dis. 2022;74(1):120-6.

*P < 0.05

Metronidazole vs. PO Vancomycin or Fidaxomicin

Metronidazole vs. PO vancomycin

- Equivalent for mild-moderate disease
- Vancomycin superior for severe disease
- 30-day mortality: 15% vancomycin vs. 20% metronidazole
- No difference in recurrence

Metronidazole vs. fidaxomicin

- Fidaxomicin superior for sustained clinical response and in the prevention of recurrent C. diff
- Superiority shown in the initial episode, first recurrence, non-severe, and severe C. diff

Stevens V, et al. JAMA Intern Med. 2017;177(4):546-553.
Polivkova S, et al. Int J Infect Dis. 2020;103:226-233.

C. diff Recurrence Treatment

- Bezlotoxumab
- Fecal transplantation
- Microbiome therapy

Bezlotoxumab (Zinplava)

- **Mechanism of action**: monoclonal antibody that binds to C. diff toxin B
- **Dose**: 10 mg/kg IV once
- **Half life**: 19 days
- **Adverse events**: nausea, headache, fever, heart failure
- **Caution**: in patients with **congestive heart failure**
  - HF exacerbation seen primarily in patients with underlying CHF
  - In patients with CHF, more deaths reported (19.5% vs 12.5%)
- **Cost:** $3,800 per 1000 mg vial

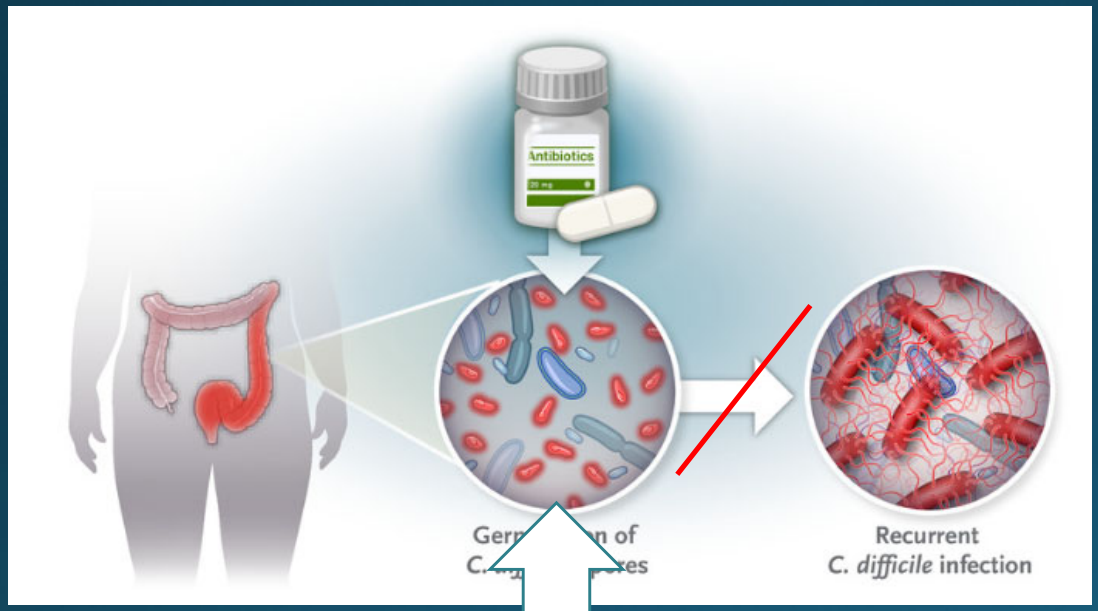
Lexicomp. 2023

Fecal Transplantation

- **Salvage therapy** for patients with multiple recurrences of C. diff and who have failed antibiotic options
- Trend towards **positive treatment effects**:
  - Lower rates of colectomy and mortality
- **Challenges in ICU patients:**
  - Broad spectrum antibiotics likely destroy transplanted bacteria
  - Patients with ileus: increased risk for aspiration or perforation
- **FDA safety alerts:**
  - Enteropathogenic E. coli (EPEC) transmission - 2 cases
  - Shigatoxin-producing E. coli (STEC) transmission - 4 cases

Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147.
FDA. Updated 2020.

Novel Therapy: Microbiome Restoration



Microbiome therapy

Microbiota

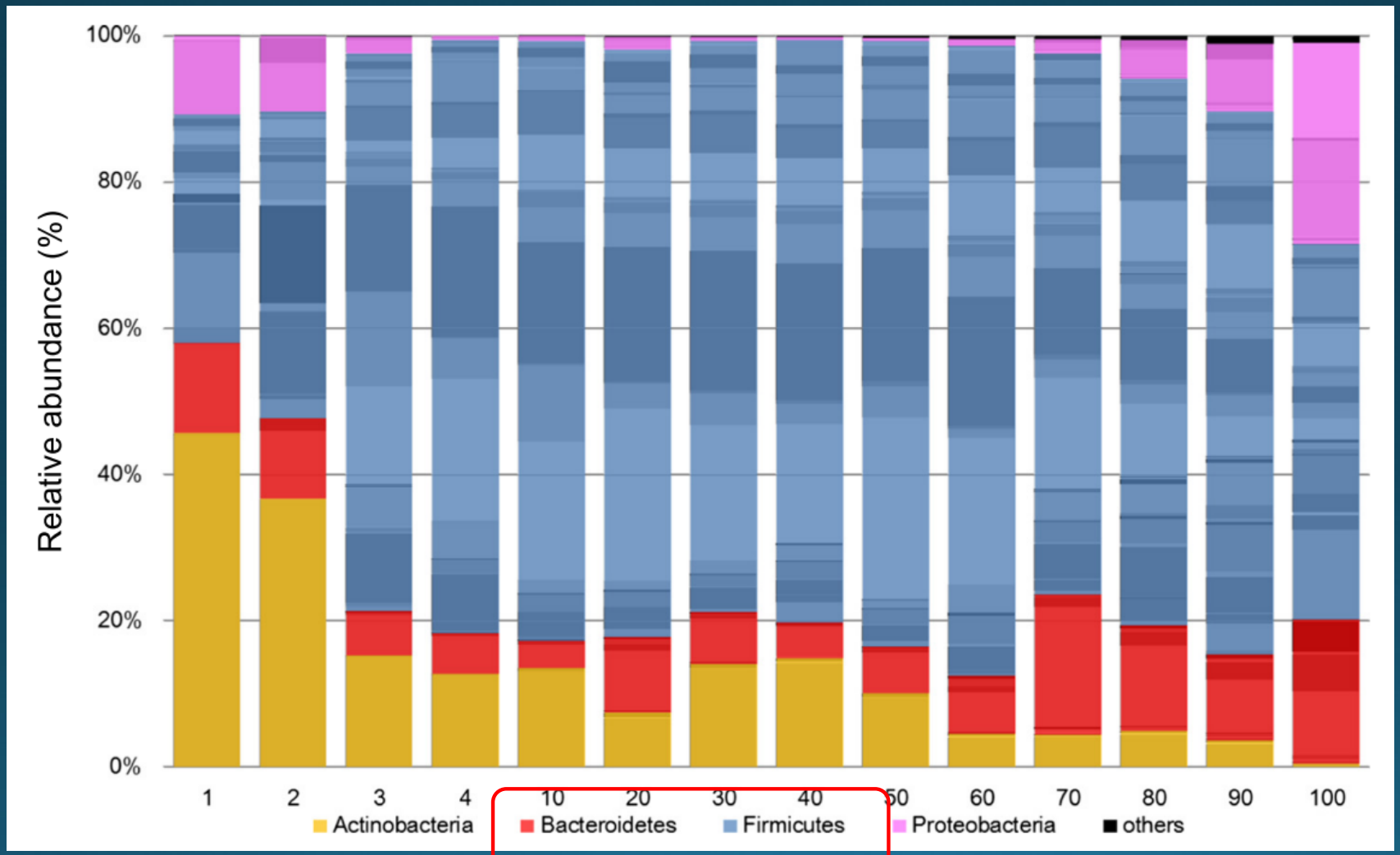
- A collection of microorganisms in a specific environment
- i.e. bacteria, virus, fungi

Microbiome

- Microbiota + their genes + the environment

Feuerstadt P, et al. N Eng J Med. 2022;386:220-9.

Age-Related Change in Gut Microbiota



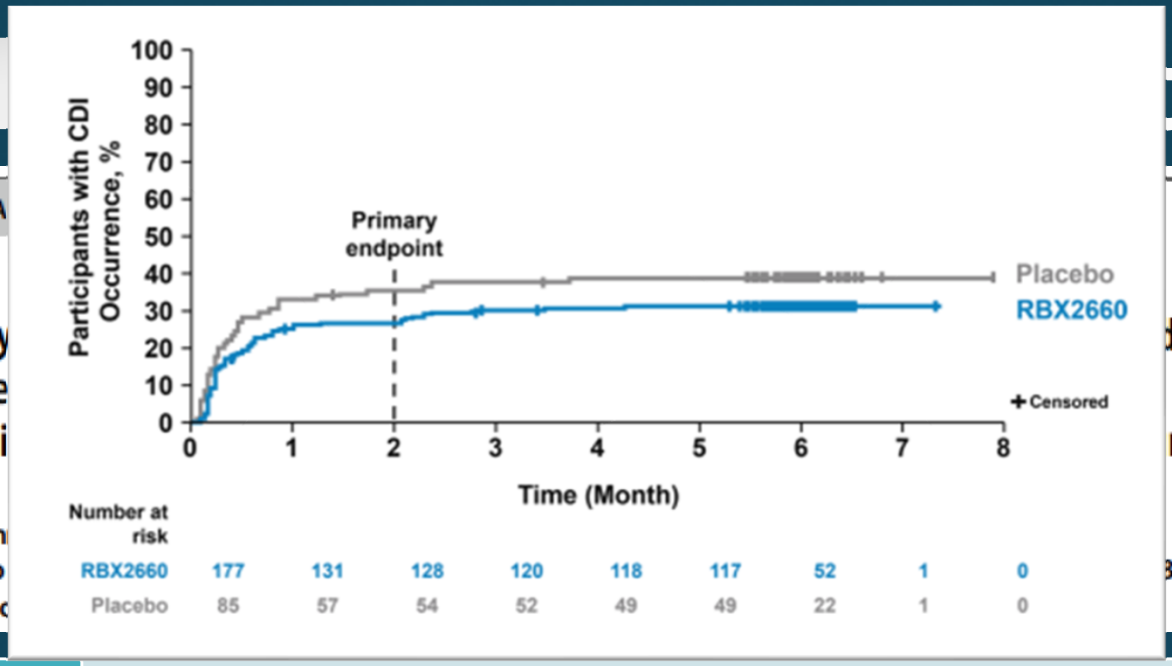
Odamaki et al. BMC Microbiol. 2016;16-90.

Microbiome Therapy Options

	Rebyota	SER-109
FDA Approval	2022	2023
Component	Microbes from human stool: mainly *Bacteroides* spp.	Bacterial stool substitutes: live *Firmicutes* spores
Dose	150 mL PR once	Four caps once daily x 3 days
Antibiotic washout	1-3 days	2-4 days
Bowel prep	None	10 oz of Mg citrate 1 day prior
Adverse Events	Mild-moderate gastrointestinal disorders i.e. abdominal distention, pain, diarrhea, nausea	
Cost	$10,000/dose	N/A

Khanna S, et al. Drugs. 2022;82:1527-1538.
Feuerstadt P, et al. N Eng J Med. 2022;386:220-9.

Rectal ta



Design	Phase 3, randomized, double-blind, placebo-controlled
Patients	With recurrent C. diff (≥ 1 recurrences) or ≥ 2 severe C. diff resulting in hospitalization within the past year
Intervention	RBX2660 vs. placebo (2:1) administered rectally once 24-72 hrs after the last dose of C. diff antibiotics
Results	Absence of recurrent C. diff infection within 8 weeks: 70.4% RBX2660 vs. 58.1% placebo
Conclusion	RBX2660 is a safe and effective treatment to reduce C. diff infection following standard of care antibiotics

Khanna S, et al. Drugs. 2022;82:1527-1538.

Oral Microbiome: SER-109


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection

Design	Phase 3, double-blind, placebo-controlled
Patients	Had symptom resolution after C. diff antibiotic treatment and at high risk for recurrence (≥ 3 C. diff infections in the previous year)
Intervention	SER-109 or placebo four caps once daily x 3 days
Results	Recurrence of C. diff infection within 8 weeks: 12% SER vs. 40% placebo*
Conclusion	In patients with recurrent C. diff infection, the standard care antibiotics followed by a microbiome-replacement therapy can reduce the risk of recurrence.

Feuerstadt P, et al. N Eng J Med. 2022;386:220-9.

*P < 0.05

C. diff Prevention

Discontinue unnecessary medications

- Antibiotics
  - Use the shortest duration of treatment possible
  - Avoid using clindamycin, cephalosporin, fluoroquinolone
- PPI

Questionable effectiveness

- Probiotics

Hygiene

- Good hand washing
- Contact precautions

Kelly C, et al. Am J Gastroenterol. 2021;116:1124-1147.

Patient Case Review

Category	Action	Assessment
Diagnosis	Fulminant C. diff (shock)	✓
Antibiotics treatment	PO vancomycin + IV metronidazole	✓
Monoclonal antibody	Bezlotoxumab	?
Surgical intervention	Colectomy/ileostomy	✓

Conclusion

- Community acquired C. diff is becoming more prevalent.
- Providers should consider C. diff as a possible diagnosis in patients presenting with risk factors and abdominal symptoms.
- Fidaxomicin is the first line drug of choice in C. diff unless fulminant.
- C. diff recurrence is common and treatment should be individualized by patient.

References

- Conely O, Crook D, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomized controlled trial. Lancet Infect Dis. 2012;12:281-89.
- Darkoh C, Keita K, Odo C, et al. Emergence of clinical Clostridioides difficile isolates with decreased susceptibility to vancomycin. Clin Infect Dis. 2022;74(1):120-6.
- Guery B, Menichetti F, Anttila V, et al. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomized, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis. 2018;18:296-307.
- Fecal microbiota for transplantation: safety alert – risk of serious adverse events likely due to transmission of pathogenic organisms. FDA Food & Drug. FDA.gov. Updated Apr. 7, 2020.
- Feuerstadt P, Louie T, Lashner B, et al. SER-109, an oral microbiome therapy for recurrent Clostridioides difficile infection. N Eng J Med. 2022;386:220-9.
- Fidaxomicin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. https://online.lexi.com. Accessed Mar. 20, 2023.
- Johnson S, Lavergne V, Skinner A, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Infect Dis. 2021;73(5):e1029-e1044.
- Kelly C, Fischer M, Allegretti J et al. ACG Clinical guidelines: prevention, diagnosis, and treatment of Clostriodioisis difficile infections. Am J Gastroenterol. 2021;116:1124-1147.
- Khanna, S, Assi M, Lee C, et al. Efficacy and safety of RBX2660 in PUNCH CD3, a phase III, randomized, double-blind, placebo-controlled trial with a Bayesian primary analysis for the prevention of recurrent Clostridioides difficile infection. Drugs. 2022;82:1527-1538.
- Louie T, Miller M, Mullane K, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Eng J Med. 2011;364:422-31.
- Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in a randomized, double-blind, comparative Phase III study in Japan. J Infect Chemother. 2018;24:744-752.
- Nerandzic M, Mullane K, Miller M et al. Reduced acquisition and overgrowth of vancomycin-resistant Enterococci and Candida speciese in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clin Infect Dis. 2012;55(suppl 2):S121-S126.
- Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol. 2016;16-90.
- Polivkova S, Krutova M, Capek V, et al. Fidaxomicin versus metronidazole, vancomycin and their combination for initial episode, first recurrence and severe Clostridioides difficile infection – an observational cohort study. Int J Infect Dis. 2020;103:226-233.
- Stevens V, Nelson R, Schwab-Daugherty E, et al. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile infection. JAMA Intern Med. 2017;177(4):546-553.
- Vancomycin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. https://online.lexi.com. Accessed Mar. 20, 2023.