Atrium Health

Clostridioides (*Clostridium*) *difficile*

Same crap, different name

Katie Hammer, Pharm.D., BCPS-AQ ID
Carolinas/Virginias Chapter Society of Critical Care Medicine
37th Annual Scientific Symposium
Pre-Conference: June 6, 2019

Disclosure Statement

- I do not have any financial or other interest that may be construed as constituting an actual, potential, or apparent conflict related to the content of this activity.

Atrium Health

Objectives

- Identify risk factors and preventative measures for the development of *Clostridioides* (*Clostridium*) *difficile*
- Review key updates from the 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Clinical Practice Guidelines for *C. difficile*
- Evaluate available data for emerging treatment including pipeline agents, fecal microbiota transplantation, and influence of the microbiome

Atrium Health

Outline

- Recap background information on *Clostridioides difficile* Infection (CDI)
- Update on classification
- Review risk factors
- Discuss preventative measures and secondary prophylaxis for CDI
- Analyze additions to the 2017 Clinical Practice Guidelines for *C. difficile*
- Review supporting literature of key updates/additions
- Examine emerging data for fecal microbiota transplantation
- Briefly discuss the influence of the microbiome
- List pipeline agents/mechanisms

Atrium Health

Audience Response Questions

When poll is active, respond at **PollEv.com/katiehammer833**
Text **KATIEHAMMER833** to **22333** once to join

Atrium Health

Test Question

What are you most excited about in attending CVCSCCM's 37th Annual Scientific Symposium?

Respond at **PollEv.com/katiehammer833** Text **KATIEHAMMER833** to **22333** once to join, then text your message

https://www.polleverywhere.com/free_text_polls/7MureyVbdBVOngb0lZTvK

Atrium Health

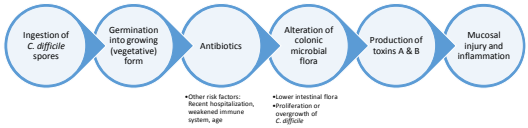
Microbiology and Epidemiology of CDI

- *C. difficile* is a spore-forming, Gram-positive, anaerobic bacillus that produces two exotoxins: toxin A and toxin B
  - Hypervirulent strain ribotype 027 (formerly referred to as NAP1/BI/027)
- May lead to complications such as pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis, and death (rarely)
  - ~20% patients treated CDI resolve within 2-3 days of discontinuing the antibiotic
  - Typically can be treated x10 days
- In 2011, an estimated 450,000 CDIs in the United States were reported
  - ~29,300 associated deaths (6.5%)
  - ~20% patients with CDI will have recurrence
  - ~12% of all healthcare-associated infections

https://www.cdc.gov/cdiff/clinicians/faq.html

Atrium Health

Pathogenesis



Carter GP, et al. Gut Microbes. 2010;1(1);58-64
https://www.cdc.gov/cdiff/pdf/Cdiff-progression-H.pdf

Atrium Health

Reclassification of *Clostridium difficile* as *Clostridioides difficile*

- *Clostridium spp*. now restricted to *Clostridium butyricum* and other members of *Clostridium sensu stricto* (aka rRNA cluster I)
- Based on 16S rRNA gene sequence analysis, the closest relative of *Clostridium difficile* is *Clostridium mangenotii* (aka rRNA cluster XI)
  - Produce abundant H_2 gas when grown in Peptone Yeast Glucose (PYG) broth
  - Located in the *Peptostreptococcaceae spp.* family
  - Latin suffix –oides, meaning "descendant of"

https://anaerobesystems.com/products/broth-media/peptone-yeast-extract-broth-with-glucose-fa-glc-pyg-fa-glc/

Anaerobe 40 (2016) 95-99.

Atrium Health

Patient Case 1

- EA 56 YOM with PMHx of HTN, HLD, DDKTx, IBS, and recurrent urinary tract infections who recently completed a course of ciprofloxacin three weeks ago and now presents with watery diarrhea, x 8-12 stools a day for the past three days. He was diagnosed with *C. difficile.* What are some of EA's risk factors for developing CDI?

I.) Age II.) DDKTx III.) IBS IV.) Antibiotics V.) Hospitalization VI.) HTN

A.) All of the above
B.) I, III, & IV
C.) I, II, III, & IV
D.) II, III, & IV
E.) II, III, IV & VI

https://www.polleverywhere.com/multiple_choice_polls/Kdk5RHUFqfocTMwEnykxY

Atrium Health

Risk Factors

- Age (≥65)
- Antibiotic therapy in the previous 12 weeks
  - Number of antibiotic agents prescribed
  - Duration of therapy
  - Every antibiotic associated with *Clostridioides difficile* Infection (CDI) through the years
    - Third/fourth generation cephalosporins
    - Fluoroquinolones
    - Carbapenems
    - Clindamycin
- Recent inpatient stay
  - Duration of hospitalization
- Chronic conditions
  - Liver, kidney disease, inflammatory bowel syndrome, cancer, solid organ transplant recipients, hematopoietic stem cell transplant patients, gastrointestinal surgery
- Proton pump inhibitors/histamine-2 blockers
  - Associated with CDI vs. non-tested controls
  - Not associated with CDI vs. tested-negative controls
  - PPIs induce diarrhea on their own, making it more likely patients are tested for CDI

Clinical Infectious Diseases 2018;66(7):e1–e48

Atrium Health

Cumulative Antibiotic Exposures Over Time and the Risk of *C. difficile* Infection

- Retrospective cohort 241 patients
- CDI risk was associated with:
  - Increasing cumulative dose (defined daily doses)
  - **Number of antibiotics**
  - **Days of antibiotic**

	1 vs. 2 antibiotics	1 vs. 3-4 antibiotics	1 vs. ≥5 antibiotics
Adjusted hazard ratios (HRs)	2.5 (95% CI, 1.6–4.0)	3.3 (95% CI, 2.2–5.2)	9.6 (95% CI, 6.1–15.1)
	<4 vs. 4-7 days	<4 vs. 8-18 days<4 vs.	>18 days
Adjusted hazard ratios (HRs)	*1.4 (95% CI, 0.8-2.4)*	3.0 (95% CI, 1.9-5.0)	7.8 (95% CI, 4.6-13.4)

Clin Infect Dis. 2011 Jul 1;53(1):42-8.

Atrium Health

Case 2

- Your infection preventionist reaches out to you, hoping to collaborate and develop a hospital-wide initiative to decrease rates of *C. difficile*. What are some suggestions that you could provide to help prevent *C. difficile*?
- A.) Implement contact isolation precautions/maintenance of contact enteric precautions, gloves and gowns, standardized signage, proper hand hygiene with soap and water
- B.) Design an algorithm to ensure *C. difficile* tests are being ordered appropriately
- C.) Develop an antimicrobial stewardship program to reduce unnecessary antimicrobials
- D.) In a select group of high risk patients, (i.e. requiring extended broad spectrum antimicrobials) consider prophylactic agents
- E.) All of the above

https://www.polleverywhere.com/multiple_choice_polls/YO1D4SaLTyemqB1ciNIEF

Atrium Health

Strategies to Prevent *C. difficile* Infection in Acute Care Facilities

- Isolate and initiate contact precautions for suspected or confirmed CDI
  - Nurse-drive protocol to facilitate immediate isolation
- Confirm CDI in patients
  - Consider non-infectious causes, discontinue laxatives
  - Once confirmed, do not repeat testing or test for cure, patients may remain positive for 6-8 weeks
- Perform environmental cleaning to prevent CDI
  - Create daily and terminal cleaning protocols and checklists for patient-care areas and equipment using sporicidal agents
- Develop infrastructure to support CDI Prevention
  - Monitor rates, include in infection prevention program, educate providers
- Develop a facility specific antibiotic stewardship program

https://www.cdc.gov/cdiff/clinicians/cdi-prevention-strategies.html

Atrium Health

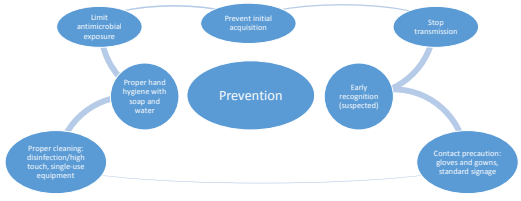
Infection Control and Prevention

- Place suspected and proven patients on contact precautions, in a single-patient room with a dedicated toilet
  - If single-patient rooms are not available, cohort like
  - Maintain contact precautions throughout the duration of hospitalization
  - Use dedicated patient care equipment
  - Gloves and gown prior to entering the room, before contact
  - Washing with soap and water is more effective at spore removal
- Minimize prescribing high-risk antibiotics
  - Clindamycin, carbapenem, fluoroquinolone, cephalosporin
  - Minimize multidrug therapy
  - Prescribe antibiotics for the shortest feasible duration

Clinical Infectious Diseases 2018;66(7):e1–e48
https://www.cdc.gov/cdiff/clinicians/cdi-prevention-strategies.html

Atrium Health

A Multifaceted Approach to the Prevention of *Clostridioides (Clostridium) difficile*



- A multidisciplinary team of administration, clinical nurses, infection prevention, nurses from the quality department, dietary services, environmental services, antimicrobial support network, and pharmacy was created
  - An evidence-based prevention bundle was implemented
  - Automated *C difficile* screening tool was included in the EMR
- A downward trend in CDI rates observed from 8.4% to 6.0%

Clin Nurse Spec. 2019 Mar/Apr;33(2):75-81.

Atrium Health

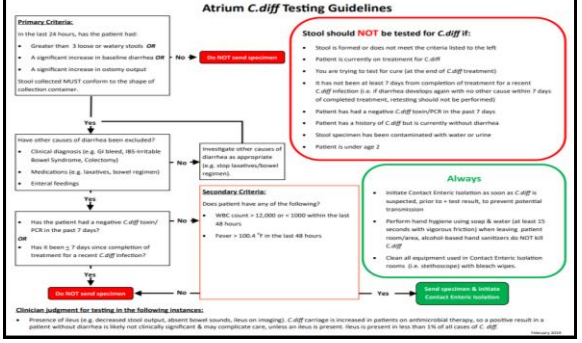
Design an algorithm to ensure *C. difficile* tests are being ordered appropriately

- Implement strict regulations on appropriate collection
  - Unexplained, new-onset diarrhea, ≥3 unformed stools in 24 hours
  - Limit samples to those not taking laxatives
  - Diagnostic testing can be with nucleic acid amplification test (NAAT) alone
- If not, a diagnostic algorithm is recommended
  - Ensure patient has worsening/prolonged diarrhea
  - Determine patients risk factors/relevant exposures
    - Immunosuppression and inflammatory bowel disease
    - Healthcare system and antibiotic use
  - Select a multistep test
    - Glutamate dehydrogenase (GDH) and *C. difficile* toxin B gene
    - NAAT and toxin
    - GDH and NAAT

Clinical Infectious Diseases 2018;66(7):e1–e48

Atrium Health

Example algorithm



Quasi-experimental Studies on the Association Between Antibiotic Stewardship Interventions and *C. difficile* Infection

Table 5. Quasi-experimental Studies on the Association Between Antibiotic Stewardship Interventions and *Clostridium difficile* Infection

Year [Reference]	Area	Time Frame	Setting (Bed Size)	Dominant Strain	Stewardship Method	Target	Targeted Antibiotics Decrease	Global Change in Hospital Antibiotic Use	CDI Rate Method	Pre-intervention	Post-intervention	Reduction in CDI Rates
1994 [272]	US	1990–1992	Hospital (168)	J7	Restrictive use	Clindamycin	>90%	NR	*	15.8	1.9	88%
1997 [273]	UK	1994–1995	Hospital (NR)	NR	Restrictive use	Cefuroxime	>90%	NR	*	5.3	2.3	57%
1998 [274]	US	1992–1996	Hospital (703)	Clonal strain A	Restrictive use	Clindamycin	>90%	No change	*	11.6	3.3	71%
2003 [275]	UK	1995–2000	Hospital (800)	NR	Restrictive use	Ceftriaxone	>90%	NR	*	14.6	3.4	77%
2003 [276]	US	1991–1998	Hospital (159)	NR	Prospective audit and feedback	Third-generation cephalosporins and aztreonam	75%	Decreased	*	2.2	0.3	86%
2004 [277]	UK	1997–2002	Hospital (24-ward beds)	NR	Restrictive use	Cefotaxime	83%	No change	*	46	22	52%
2004 [278]	US	2001–2003	LTCF (100)	A	Restrictive use	Gatifloxacin	>90%	No change	*	1.32	0.51	61%
2007 [279]	Canada	2003–2006	Hospital (683)	027	Restrictive use	High-risk antibiotics	80%	Decreased	*	2.03	0.82	60%
2007 [280]	UK	1999–2003	Hospital (78-ward beds)	NR	Prospective audit and feedback	Cephalosporins and amoxicillin-clavulanate	50%–75%	No change	†	NR	NR	65%
2011 [281]	UK	2005–2007	Hospital (495)	027	Restrictive use	High-risk antibiotics	50%–75%	No change	*	2.22	0.45	80%
2012 [282]	Canada	2008–2010	Hospital (48 ICU beds)	NR	Prospective audit and feedback	High-risk antibiotics	20%	Decreased	*	1.12	0.71	37%
2013 [283]	UK	2008–2011	Hospital (215)	NR	Restrictive use	Ceftriaxone and ciprofloxacin	70%–90%	NR	*	2.398	1.2	50%
2011 [284]	Ireland	2004–2009	Hospital (665)	027	Restrictive use	Quinolones	>90%	NR	*	0.8	0.366	*
2012 [285]	Ireland	2004–2010	Hospital (233)	NR	Restrictive use	High-risk antibiotics	70%–90%	Decreased	*	0.8	0.7	*
2012 [286]	US	2007–2010	LTCF (160)	NR	Prospective audit and feedback	High-risk antibiotics	25%–50%	Decreased	*	NR	NR	*

Clinical Infectious Diseases 2018;66(7):e1–e48

Atrium Health

Observational study of antibiotic exposure and *C. difficile* infection in two large academic medical centers

- 35,567 index visits with 412 CDI cases (11.6 per 1,000 discharges)
- CDI risk in those with high-risk antibiotics was 3 times higher vs. those with low-risk or no antibiotic exposure (RR=2.9, 95% CI: 2.3-3.5)

Risk of *Clostridium difficile* Infection (Hospital Onset and Post-Discharge) following High-Risk or Low-Risk Antibiotics compared to No Antibiotic Exposure

	# Days in Post-Discharge Window					
	0 (Hospital Onset)		42		180	
RR* Low-Risk Antibiotics† vs No Antibiotics	1.5	0.8-2.7	1.3	0.8-1.9	1.0	0.7-1.3
RR* High-Risk Antibiotics† vs No Antibiotics	3.6	2.3-5.6	3.1	2.3-4.2	2.8	2.2-3.6

*Data from two large academic centers participating in the Emerging Infections Program. Adjusted for gender, age, Gagne co-morbidity score, CDI pressure, hospital. RR: Relative risk; results expressed as a point estimate followed by the 95% confidence interval.

†High risk antibiotics were defined as: 3rd/4th generation cephalosporins; fluoroquinolones; beta-lactam/beta-lactamase inhibitor combinations. All other antibiotics were considered to be low-risk.

https://www.cdc.gov/antibiotic-use/healthcare/evidence/cdiff.html

Atrium Health

Oral Vancomycin for Secondary Prophylaxis of *C. difficile* Infection

- Oral vancomycin
  - Glycopeptide, poorly absorbed and achieves high concentrations in feces
- Summary of the evidence regarding oral vancomycin prophylaxis
  - Secondary prophylaxis ↓risk of recurrent *Clostridioides difficile* infections (RCDI)

Am J Gastroenterol. 2016;111:1834-1840.	Retrospective study within 90 days of primary or RCDI 557 patients on antibiotics 227 patients received oral vancomycin prophylaxis (OVP)	Single CDI: OVP did not affect recurrence (P = 0.69) RCDI: 49/90 (54%) OVP vs. 57/82 (70%) no prophylaxis had recurrence Number needed to treat (NNT) of 6.6 to prevent 1 RCDI (P < 0.0001)
Clin Infect Dis. 2016;63:651-653.	Retrospective study with history of CDI 203 patients on antibiotics 71 patients received OVP	RCDI: 3/71 (4%) OVP vs. 35/132 (27%) no prophylaxis had recurrence NNT of 5 to prevent 1 RCDI (P <0.001)
Antimicrob Agents Chemother. 2008;52:2403-2406.	Retrospective study on renal transplant 29 patients on antibiotics 12 patients received OVP	No instances of RCDI in the OVP group, vs. 2 in the control

Ann Pharmacother. 2019 Apr;53(4):396-401.

Atrium Health

Oral Vancomycin for Secondary Prophylaxis of *C. difficile* Infection

- Vancomycin 125 mg orally once or twice daily may be considered in high-risk patients receiving broad-spectrum antimicrobials
  - Caution is warranted before routine use as impact on long-term outcomes has not been assessed and the optimal regimen has not been defined
- Supporting a healthy microbiome with probiotics has been explored, although the data are inconclusive

Ann Pharmacother. 2019 Apr;53(4):396-401.

Atrium Health

Bezlotoxumab for Prevention of Recurrent *C. difficile* Infection

- Double-blind, randomized, placebo-controlled phase 3 trial
- Primary or recurrent *C. difficile* infection who were receiving oral standard-of-care antibiotics (N=2,655)

Endpoint	Bezlotoxumab alone vs. placebo	Subgroup of patients with ≥ 1 risk factor for recurrence (bezlotoxumab alone)	Subgroup of patients with ≥ 1 risk factor for recurrence (placebo)
Recurrent infection	MODIFY I: 17% vs. 28%* MODIFY II: 16% vs. 26%*	17%	30%
Rate of sustained cure	MODIFY I: 60% vs. 55% MODIFY II: 67% vs. 52%	Not evaluated	Not evaluated

*statistically significant

N Engl J Med. 2017 Jan 26;376(4):305-317

Atrium Health

Defining optimal formulation and schedule of a candidate toxoid vaccine against *C. difficile* infection: A randomized Phase II clinical trial

- Randomized, placebo-controlled, Phase 2 study in 661 adults 40–75 years old
  - Low (50 µg antigen), high (100 µg antigen), or placebo IM on Days 0, 7, & 30
  - Blood samples were obtained on Days 0, 7, 14, 30, 60, 180, & 210
  - IgG to toxins A and B was measured via ELISA
  - In vitro functional activity was measured by toxin neutralizing assay (TNA)
- Composite immune response against toxins A and B (% seroconverted for both toxins) highest in the high dose + adjuvant group at day 60
  - ELISA
    - A 97%
    - B 92%
    - Composite (A+B) 91%
  - TNA
    - A 97%
    - B 64%
    - Composite (A+B) 62%

Vaccine 34 (2016) 2170–2178

Atrium Health

Ongoing Phase III Trials

- https://clinicaltrials.gov/ct2/show/NCT03090191 (expected to be completed September 28, 2020) NCT03090191
  - Phase 3, placebo-controlled, randomized, blinded study to evaluate the **efficacy**, safety and tolerability of *C. difficile* vaccine in adults >50 years of age
  - Estimated enrollment 17,476 participants
- https://clinicaltrials.gov/ct2/show/NCT03579459 (expected to be completed August 12, 2019) NCT03579459
  - Phase 3, placebo-controlled, randomized, blinded study to evaluate safety, tolerability and immunogenicity of *C. difficile* vaccine in adults **>65-85 years**
  - Estimated enrollment 1,316 participants

Atrium Health

Patient Case 3

- TM is a 36 YOM with PMHx of HTN, HLD, DM recently treated for CAP by PCP with levofloxacin, completed his course 3 days ago, now with severe abdominal cramping and watery diarrhea x6-8 times per day. He is confirmed to have CDI. He is admitted to the floor given concern for dehydration. His WBC is 12, his creatinine is 1 mg/dL and he has never had CDI in the past. According to the 2017 Clinical Practice Guidelines for *C. difficile* which of the following would be a recommended antimicrobial agent and dose for TM?
- A.) Vancomycin 500 mg orally every 6 hours x 10 days
- B.) Metronidazole 500 mg orally every 8 hours x 10 days
- C.) Fidaxomicin 200 mg twice daily x 10 days
- D.) Fecal microbiota transplantation
- E.) Vancomycin Taper

https://www.polleverywhere.com/multiple_choice_polls/cgnTu9JevbEFH3N5ZIlgf

Atrium Health

Patient Case 3

- TM is a 36 YOM with PMHx of HTN, HLD, DM recently treated for CAP by PCP with levofloxacin, completed his course 3 days ago, now with severe abdominal cramping and watery diarrhea x6-8 times per day. He is confirmed to have CDI. He is admitted to the floor given concern for dehydration. His WBC is 12, his creatinine is 1 mg/dL and he has never had CDI in the past. According to the 2017 Clinical Practice Guidelines for *C. difficile* how would TM's CDI be classified?
- A.) Initial episode, fulminant
- B.) First recurrence
- C.) Initial episode, severe
- D.) Initial episode, non-severe
- E.) Subsequent recurrence

https://www.polleverywhere.com/multiple_choice_polls/BVkdujENdPALs6qtO1d2f

Atrium Health

Clinical Practice Guidelines for *C. difficile* Infection in Adults and Children: 2017 Update by the IDSA and SHEA

Definition	Supportive Data	Recommended Treatment
Initial episode, non-severe	WBC ≤15 000 cells/mL AND SCr <1.5 mg/dL	• VAN 125 mg 4 times daily x 10 days • FDX 200 mg twice daily x 10 days • Alternate if above agents are unavailable: Metronidazole 500 mg 3 times daily x 10 days
Initial episode, severe	WBC ≥15 000 cells/mL AND SCr >1.5 mg/dL	• VAN 125 mg 4 times daily x 10 days • FDX 200 mg twice daily x 10 days
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN 500 mg 4 times daily (PO or NG) AND IV metronidazole 500 mg every 8 hours • May add rectal VAN if ileus is present (500 mg in 100 mL NS PR normal 4 times daily)
First recurrence	If metronidazole initial	• VAN 125 mg 4 times daily x 10 days

	If vancomycin initial	• VAN Taper
		  • 125 mg 4 times daily x 10-14 days
		  • 125 mg 2 times daily x 7 days
		  • 125 mg daily x 7 days
		  • 125 mg every other day x 2-8 weeks
		• FDX 200 mg twice daily x 10 days

	If fidaxomicin initial	• VAN Taper • See above
Second or subsequent recurrence		• VAN Taper • See above • FDX 200 mg twice daily x 10 days • VAN 125 mg 4 times daily x 10 days, then rifaximin 400 mg 3 times daily x 20 days • Fecal microbiota transplantation

Clinical Infectious Diseases 2018;66(7):e1–e48.

Atrium Health

Case 4

- Why was metronidazole removed from the 2017 Clinical Practice Guidelines for *C. difficile*?
- A.) High cost compared to oral vancomycin
- B.) Metronidazole found to be superior to vancomycin in resolution of diarrhea and absence of severe abdominal discomfort
- C.) Patients treated with vancomycin had significantly reduced risk of all-cause 30-day mortality compared to metronidazole
- D.) Metronidazole can cause peripheral neuropathy with prolonged use
- E.) All of the above

https://www.polleverywhere.com/multiple_choice_polls/6sWuYG8rkGtoJnaE2YfnS

Atrium Health

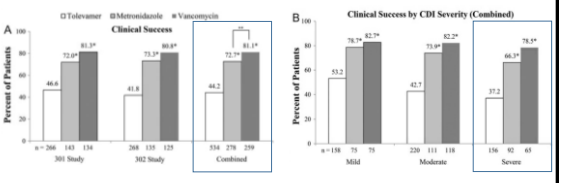
Vancomycin, metronidazole, or tolevamer for *C. difficile* infection: results from two multinational, randomized, controlled trials

- 1071 patients with CDI were randomized in a 2:1:1 ratio
  - Tolevamer 9 g (loading dose) followed by 3 g every 8 hours for 14 days (n=534)
  - Vancomycin 125 mg every 6 hours for 10 days (n=259)
  - Metronidazole 375 mg every 6 hours for 10 days (n=278)
- Primary endpoint clinical success
- A post-hoc multivariate analysis that excluded tolevamer looking at factors that were strongly associated with clinical success

Clinical Infectious Diseases. 59(3):345-54, 2014 Aug 01.

Atrium Health

Vancomycin, metronidazole, or tolevamer for *C. difficile* infection: results from two multinational, randomized, controlled trials



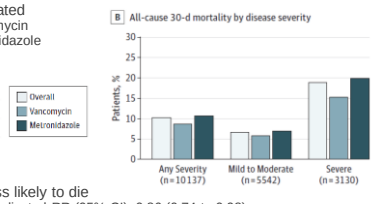
- Post-hoc multivariate analysis associated with success OR (95%CI);P
  - Vancomycin treatment vs. metronidazole 1.7 (1.1-2.5); P = 0.01
  - Treatment-naive status vs. experienced 1.8 (1.2-2.7); P = 0.004)
  - Mild or moderate vs. severe 1.5 (1.1-2.4); P = 0.045

Clinical Infectious Diseases. 59(3):345-54, 2014 Aug 01.

Atrium Health

Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With *C. difficile* Infection

- Retrospective, propensity-matched cohort
  - Recurrence: second positive laboratory test result within 8 weeks of the initial CDI
  - All-cause 30-day mortality: death from any cause within 30 days of the initial CDI
- 10,137 CDI treated
  - 2,068 vancomycin
  - 8,069 metronidazole



- Vancomycin less likely to die
  - Any severity adjusted RR (95% CI); 0.86 (0.74 to 0.98)
  - Severe adjusted RR (95% CI); 0.79 (0.65 to 0.97)

JAMA Intern Med. 2017;177(4):546-553.

Atrium Health

Case 5

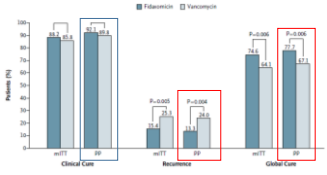
- When might fidaxomicin be an option to use first-line?
- A.) When the patient is taking concomitant antimicrobials
- B.) NAP1/BI/027 strains
- C.) When the patient is uninsured and makes >60,000/year
- D.) When the patient is at high risk for recurrence
- E.) All of the above

https://www.polleverywhere.com/multiple_choice_polls/ONJOtY8IEOiyVZfUunGq0

Atrium Health

Fidaxomicin versus Vancomycin for *C. difficile* Infection

- Double-blind, randomized, parallel group clinical trial comparing the efficacy and safety of fidaxomicin vs. vancomycin in treating *C. difficile* infection
- 548 patients were evaluated for per-protocol analysis
  - Fidaxomicin (200 mg twice daily) PO x 10 days
  - Vancomycin (125 mg four times daily) PO x 10 days
- Primary endpoint was clinical cure
- Secondary end points
  - Recurrence
  - Global cure

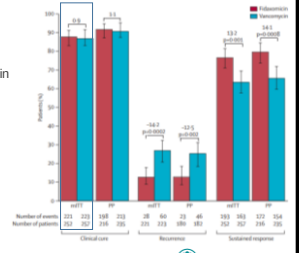


N Engl J Med 2011;364:422-31.

Atrium Health

Fidaxomicin vs. vancomycin for infection with *C. difficile* in Europe, Canada, and the USA

- Double-blind, non-inferiority, parallel-group, randomized controlled trial
- 509 were included in the modified intention-to-treat (mITT) population
  - Fidaxomicin (200 mg twice daily) PO x 10 days
  - Vancomycin (125 mg four times daily) PO x 10 days
- Primary endpoint was clinical cure
- Subgroup analysis receiving concomitant antibiotics had higher cure rate with fidaxomicin
  - 46/51 (90.2%) vs. 33/45 (73.3%); p=0.031



Lancet Infect Dis. 2012 Apr;12(4):281-9.

Atrium Health

Treatment of First Recurrence of *C. difficile* Infection: Fidaxomicin Versus Vancomycin

- Two phase 3 randomized, double-blind trials were conducted at 154 sites in the United States, Canada, and Europe to compare fidaxomicin vs vancomycin in treating CDI (focus on recurrence)
- 128 patients were evaluated for per-protocol analysis with recurrence
  - Fidaxomicin (200 mg twice daily) PO x 10 days
  - Vancomycin (125 mg four times daily) PO x 10 days
- Primary end point was clinical cure
  - Clinical cure was similar for both drugs (>90% cure)
- Secondary end point was 28-day recurrence
  - 28 day recurrence 36% vancomycin vs 20% fidaxomicin (P = 0.045)
  - 14 day recurrence 27% vancomycin vs 8% fidaxomicin (P = 0.003)

Clin Infect Dis. 2012;55 Suppl 2:S154-61.

Atrium Health

Patient Case 6

- SL a 78 YOF with PMHx of obesity, HTN, HLD, DM, CKD, diverticulitis, CDI, recent 21 day hospitalization for diverticulitis, treated with 14 days of ciprofloxacin, metronidazole now presents with severe diarrhea and dehydration, noted to be in AKI with creatinine of 2.5 mg/dL (baseline creatinine of 1.1 mg/dL). She is otherwise hemodynamically stable and found to have CDI. You discover that 4 weeks prior she had a positive CDI result and was treated with PO vancomycin at this time. She has otherwise never had CDI. What would you recommend for SL during this hospitalization?
- A.) Vancomycin 125 mg PO 4 times daily x 10 days
- B.) Metronidazole 500 mg 3 times daily x 10 days
- C.) Fecal microbiota transplantation
- D.) Fidaxomicin 200 mg twice daily x 28 days
- E.) Vancomycin Taper (125 mg 4 times daily x 10-14 days, 125 mg 2 times daily x 7 days, 125 mg daily x 7 days 125 mg every other day x 2-8 weeks)

https://www.polleverywhere.com/multiple_choice_polls/3O80nRPxKXBmaljkMoKkl

Atrium Health

Vancomycin Taper

- 29 patients with recurrent episodes of *C. difficile* disease (RCDD)
  - "tapered" started at one dose and decreased stepwise
  - "pulsed" (125-500 mg) every 2-3 days; may have followed a 10-14 day course
- Tapered and pulsed dose vancomycin both resulted in significantly fewer recurrences (31%, p = 0.01) and (14%, p = 0.02), respectively

Table 3. Description of Vancomycin Taper and Pulsed Antibiotic Regimens

Taper (beginning dose to ending dose)	Recurrence (n = 9)	Cure (n = 20)	
500–125	1 (20%)	4	
750–375	1 (50%)	1	
1000–125	2 (22%)	7	
2000–250	5 (42%)	7	
3000–750	0 (0%)	1	
Total tapered	9 (31%)	20	$p = 0.01$*
Mean days of taper	25.4 ± 13.3	19.5 ± 8.0	$U = 107$, ns*
No. of tapers followed by pulses	2 (20%)	8	
Mean days of pulses	3.0 ± 0	6 ± 4.2	$t = 0.97$, ns*
Pulse only	n = 1	n = 6	
500-mg pulse	0	4	
250-mg pulse	1	1	
125-mg pulse	0	1	
Total pulsed only	1 (14.3%)	6	$p = 0.02$*
Mean days pulsed	9 ± 0	20.3 ± 11	$t = 0.95$, ns*

* Recurrence vs cure.

Am J Gastroenterol. 2002 Jul;97(7):1769-75.

Atrium Health

Patient Case 6

- SL is treated with a 6 week taper of vancomycin, and she now represents with 12-15 stools/day only 4 days after completing her taper. She remains hemodynamically stable, without evidence of ileus. Which option is most appropriate for SL?
- A.) Vancomycin 125 mg PO 4 times daily x 10 days
- B.) Metronidazole 500 mg 3 times daily x 10 days
- C.) Fecal microbiota transplantation
- D.) Fidaxomicin 200 mg twice daily x 28 days
- E.) Vancomycin 500 mg PO 4 times daily and IV metronidazole 500 mg every 8 hours x 14 days

https://www.polleverywhere.com/multiple_choice_polls/d1BIr9Vo2KClauiEPyaa8

Atrium Health

Fecal microbiota transplantation (FMT)

- Instillation of processed stool collected from a healthy donor into the intestinal tract of patients with recurrent CDI
- "Down-side"
  - Typically need to instill via nasogastric tube or colonoscopy
  - Donor stool introduces potential transmission of resistant organisms
  - Blood-born pathogens risk
  - Potential for unexpected adverse events
    - Metabolic or immune-based disorders
    - Risk of aspiration (or upper gastrointestinal delivery; naso-enteric or oral)
    - Perforation, bleeding, sedation related aspiration (colonoscopy)

Clin Infect Dis. 2018 Mar 19;66(7):987-994.

Atrium Health

Fecal microbiota transplantation (FMT)

- Informed consent required
- Safety test capsule
- D/c antibiotics 48 hours PTI
- Initiate a PPI 48 hours PTI
- NPO for 2 hrs prior, and 1 hr post
- Clear liquid diet the day of FMT
- Consider contraindications (oral)
  - Dysphagia/aspiration risk
  - Food allergies
  - Intestinal obstruction/gastroparesis
  - Severely immunocompromised
- Direct observation by MD
- 30 tablets within 90 minutes
- Mandatory clinical follow up

Atrium Health

Duodenal infusion of donor feces for recurrent *C. difficile*

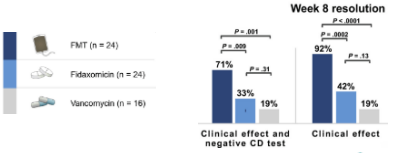
- Open-labeled randomized trial of PO vancomycin vs. bowel lavage vs. FMT in those with ≥2 recurrent episodes of CDI
- 43 patients
  - Vancomycin 500 mg PO four times per day for 14 days (n=13)
  - Vancomycin 500 mg PO four times per day for 14 days with bowel lavage Klean-Prep 4 liters of macrogol solution on day 4-5 (n=13)
  - Vancomycin 500 mg PO four times per day for 4-5 days with bowel lavage and FMT via a nasoduodenal tube (n=16)
- Primary endpoint was response without relapse x10 weeks
- Investigation terminated early after interim analysis (P < 0.001)
  - 13/16 (81%) in the FMT arm had a sustained resolution of diarrhea
  - 7/26 (27%) treated with vancomycin had sustained resolution

N Engl J Med. 2013 Jan 31;368(5):407-15.

Atrium Health

Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *C. difficile* Infection

- Open-labeled, single-center, randomized trial
- 64 patients
  - Vancomycin 125 mg PO 4 times daily x4-10 days followed by FMT (n = 24)
  - 10 days of fidaxomicin 200 mg twice daily (n = 24)
  - 10 days of vancomycin 125 mg 4 times daily (n = 16)
- Primary endpoint was combined clinical resolution and negative result from a toxin polymerase chain reaction test 8 weeks after treatment
- Secondary end points included clinical resolution at week 8



Gastroenterology. 2019 Apr;156(5):1324-1332

Atrium Health

Effect of Oral Capsule vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *C. difficile* Infection (RCDI)

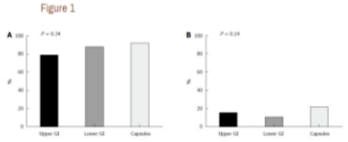
- Noninferiority, unblinded, randomized trial in 3 academic centers
- 105 patients
  - 57 capsules
  - 59 colonoscopy
- Primary endpoint was RCDI 12 weeks after FMT
  - Oral capsules were not inferior to colonoscopy
  - 96.2% in both capsule group (51/53) and colonoscopy group (50/52)
- Rates of minor adverse events
  - 5.4% for capsule group vs. 12.5% for colonoscopy group
- Participants rated their experience "not at all unpleasant" with capsules
  - 66% vs 44% (P = 0.01)

JAMA. 2017 Nov 28; 318(20): 1985–1993.

Atrium Health

Five years of fecal microbiota transplantation - an update of the Israeli experience

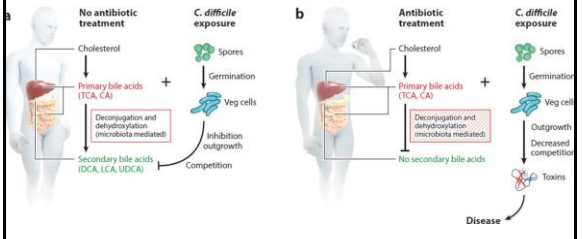
- Retrospective, observational trial of FMT for recurrent or refractory CDI
- 111 FMTs for CDI
  - 50 (45%) were treated *via* the lower gastrointestinal (colonoscopy) route
  - 37 (33%) *via* capsules
  - 24 (22%) *via* the upper gastrointestinal (UGI) route
- Primary outcome was FMT success
- Secondary outcome 6 month recurrence



World J Gastroenterol. 2018 Dec 21;24(47):5403-5414.

Atrium Health

Microbiome



Annu Rev Microbiol. 2015;69:445-61.

Atrium Health

Pipeline agents

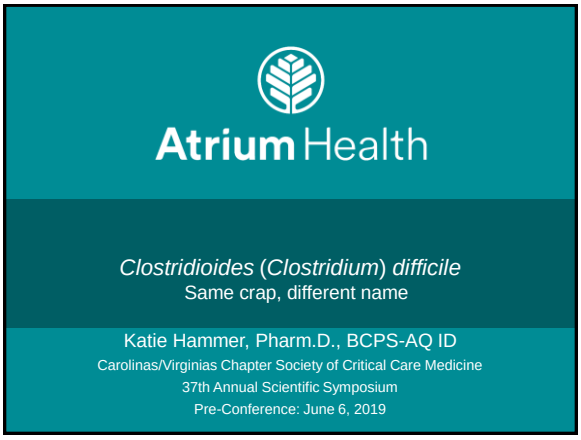
Drug type	Description of action
Antibiotics/ non antibiotic anticlostridial therapies	Direct effect on the causative microorganism/target certain molecular components of *C. difficile* with the aim of eliminating the bacteria in an already established infection
Toxin- neutralizing Agents	Toxin-neutralizing drugs aim not to eliminate *C. difficile*, but to prevent its cytotoxic effect on colonocytes (inactivate C. difficile toxins impeding them from reaching their target cells)
Immunotherapy	The preparation of the host immune system for a potential encounter with *C. difficile*
Modulators of intestinal environment	Preservation and/or restoration of colonization resistance of the intestinal microbiota/ protection against toxigenic C. difficile colonization or its elimination from the colon Agents with goal is to neutralize the effect of the antibiotic on the microbiota of the gastrointestinal (GI) tract, thus preserving "colonization resistance" of the microbiota against *C. difficile*. However, it cannot interfere with absorption of oral antibiotics in the upper gastrointestinal tract, but must do so in the lower GI tract or colon to protect the microbiota.
Enteroprotective agents	Alleviate the inflammation of the colon in CDI patients

Infect Dis Ther (2017) 6:1–35

Atrium Health

Pipeline Agents

Drug type	Compound		
Antibiotics/ non antibiotic anticlostridial therapies	Kibdelomycin OPS-2071 **Rifaximin** Rifalazil MGB-BP-3 Tigecycline Omadacyclin RBx 11760 RBx 14255 **Fusidic acid** LFF571 CRS 3123 Bolasome-antisense gapmer	Nanocomplexes **Nitazoxamide** Amixicile **Teicoplanin** **Ramoplanin** Oritavancin N-substituted Demethylvancomycin Actagardine V15F NVB302 SQ641 **Surotomycin** Thuricin CD	Native phage tail-like particles Av-CD291.2 PlyCD1-174 **Cadazolid** MCB3681 MBX-500 Ramizol Human a-defensin-5 Virgin coconut oil Ridinilazole Berberine Bovine lactoferrin PACT
Toxin- neutralizing Agents	**Tolevamer** Cholestyramine	Calcium aluminiosilicate anti-diarrheal (CASAD) IP2S4	
Immunotherapy	Hyperimmune bovine colostrum **IVIG** **Actoxumab/bezlotoxumab** PolyCAb UCB Mab CANmAbA4/CANmAbB4 Mab A2/Mab B2/Mab B1 ABA	VNA2-Tcd **ACAM-CDIFF** PF-06425090 VLA84 Toxin A RBD Toxin B RBD Toxin A RBD/toxin B RBD Crude SLP	SlpA Cwp84 FliD FliC PS-I PS-II PS-III (lipotecichoic acid)
Modulators of intestinal environment	RBX2660/stool SER-109/stool SER-262/live bacterial products MET-1	NTCD-M3/non-toxigenic strain of *C. difficile* *C. difficile* CD37 Ursodeoxycholic acid CamSA	DAV132 SYN004 Cephalosporinase-producing Bacteria Ribaxamase
Enteroprotective agents	Alanyl-glutamine	Adenosine A2A receptor agonists	


Atrium Health
Clostridioides (*Clostridium*) *difficile*
Same crap, different name
Katie Hammer, Pharm.D., BCPS-AQ ID
Carolinas/Virginias Chapter Society of Critical Care Medicine
37th Annual Scientific Symposium
Pre-Conference: June 6, 2019