Clostridioides difficile

(formally known as *Clostridium difficile*)

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Agenda:

- Pathophysiology/Epidemiology
- Surveillance & Financial Impact
- Prevention Measures
- Risk Factors
- Testing methods
- Treatment

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)

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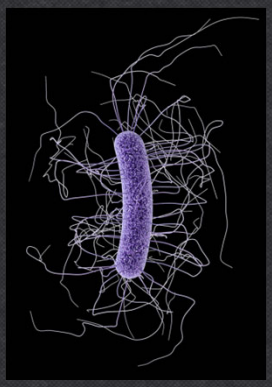
Background: *C. difficile*

- **Spore-forming, anaerobic, Gram-positive bacterium**
- **Found in environment and intestinal tracts of animals & humans**
- **Exotoxin production causing mild to severe diarrhea, pseudomenbranous colitis (PMC), toxic megacolon, or death**



IMPACT

C. diff causes close to half a million illnesses each year and can affect people of all ages.[1]

1 in 5 patients will get *C. diff* at least once more.[1]

One in 11 people over 65 diagnosed with a healthcare-associated *C. diff* infection die within a month.[1]

Source: https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf
[1] Table 3 from Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825-34. DOI: 10.1056/NEJMoa1408913

RISK

People on antibiotics are 7 to 10 times more likely to get *C. diff* while on the drugs and during the month after.[2]

Extended stays in healthcare settings, especially hospitals and nursing homes, also increase risk.

More than 80% of *C. diff* deaths occur in people 65 and older.

Source: https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf
[1] Table 3 from Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825-34. DOI: 10.1056/NEJMoa1408913

SPREAD

C. diff spreads when people touch surfaces that are contaminated with poop from an infected person.

Or when people don't wash their hands with soap and water.

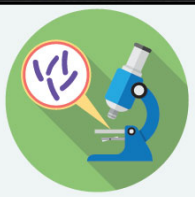
It can also happen when one healthcare facility fails to notify another when it transfers a patient with *C. diff.*

Source: https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf
[1] Table 3 from Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825-34. DOI: 10.1056/NEJMoa1408913

Healthcare professionals can help PREVENT *C. diff by:*

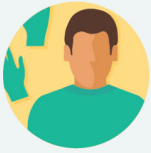
BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

Improving the way they prescribe antibiotics.

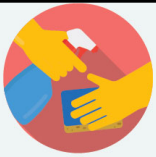


Using the tests that give the most accurate results.

Rapidly identifing and isolating patients with *C. diff*.



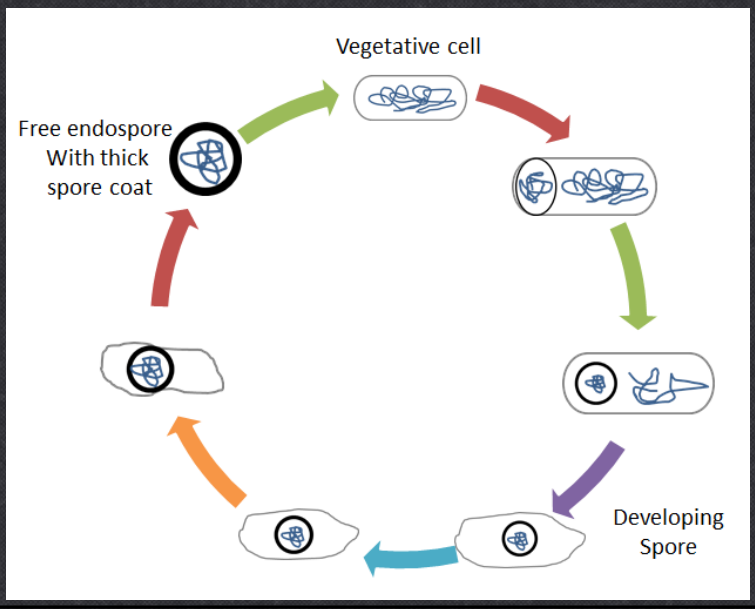
Wearing gloves and gowns when treating patients with *C. diff*—and remembering that hand sanitizer doesn't kill *C. diff*.



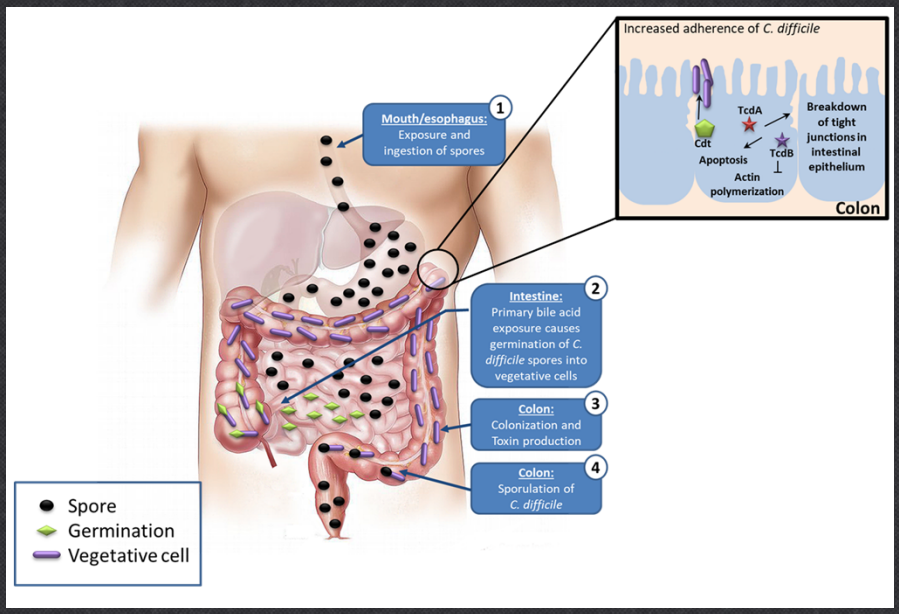
Cleaning surfaces in rooms where *C. diff* patients are treated with EPA-approved, spore-killing disinfectant (see List K).

Source: https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf
[1] Table 3 from Lessa FC, Mu Yi, Bamberg WM et al. N Engl J Med 2015;372:825-34. DOI: 10.1056/NEJMoa1408913

Life cycle of *Clostridioides difficile*



Development of Infection



Virulence factors

- Toxin A (TcdA)
- Toxin B (TcdB)
  - ~1000 fold more potent
- Binary toxin (Cdt) ~20%
  - Present in more severe disease
  - Not proven to cause disease by itself (except in immunocompromised)

Source: *Toxins*; Infection, Genetics and Evolution

Hypervirulent strains

- NAP1/BI/027
  - CDC reports as most common strain between 2009 - 2011
  - Increase severity in disease
  - Transmits more effectively
  - Posses gene coding for TcdA, TcdB, Cdt, TcdC deletion
  - Increase resistance to fluoroquinolones promoting dissemination
- Ongoing molecular typing for emerging novel strains

Surveillance

- Recommendation to use standardized case definitions
- CDC's National Healthcare Safety Network (NHSN) used for reporting purposes
  - LabID event:
    - Lab testing data without clinical evaluation
    - Attributed to the unit where specimen was collected
    - Considered hospital-onset (HO) on day 4 (admission to INPATIENT unit is counted as day one)
    - Duplicate cases—positive test in last 14 days

CDC's NHSN Definitions

<u>Community-Onset (CO)</u>

- ≤ 3 days after admission to inpatient unit
- Not previously discharged from inpatient location within same facility ≤ 28 days prior to specimen collection

<u>Community-Onset Healthcare Facility-Associated (CO-HCFA)</u>

- ≤ 3 days after admission to inpatient unit
- Discharged from inpatient location within same facility ≤ 28 days prior to specimen collection

CDC's NHSN Definitions (con't)

Healthcare Facility-Onset (HO)

- collected from an inpatient location >3 days after admission to the facility (specifically, on or after day 4)

Incident: specimen obtained >56 days after previous case or no previous case

Duplicate: specimen obtained within 14 days of previous case

Recurrent: specimen obtained >14 days and ≤ 56 days

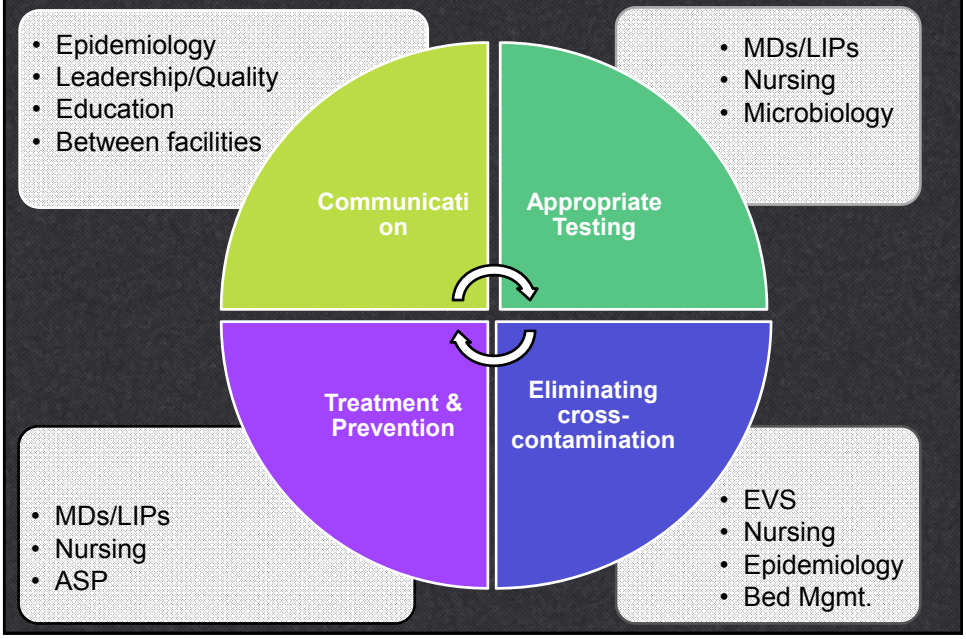
Comparing Infection Rates

- Standardized Infection Ratio (SIR)
  - Adjusts for various risk factors
  - Calculated through CDC's NHSN
  - Compares the actual number of infections to the predicted number

Hospital Financial Impact

- Affordable Care Act (ACA) focused on quality
- CMS initiated three incentive programs
  - Hospital-Acquired Conditions (HAC) Reductions Program
    - Penalty of 1% for quartile of hospitals with lowest performance
    - C. difficile infections (CDI) added in FY 2017

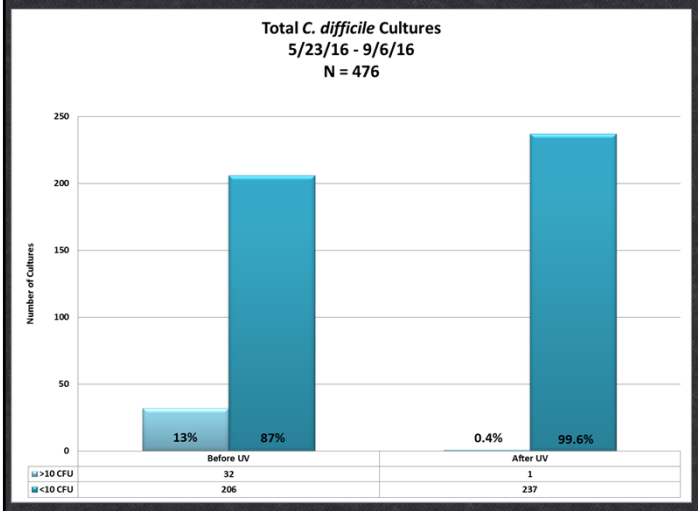
Prevention Teamwork



Eliminating Cross-Contamination: EVS

- Use of EPA-approved sporicidal (e.g. bleach) for daily and terminal clean of rooms with CDI cases (especially during sustained high rates)
- Clear delineation of who cleans what equipment (EVS vs. Nursing)
- Incorporate measures of cleaning effectiveness to ensure quality of environmental cleaning
  - Florescent markers
  - Adenosine triphosphate bioluminescence
  - Direct observation
  - **Best if feedback is given in real time**

Eliminating Cross-Contamination: EVS



Culturing before and after UV light disinfection:

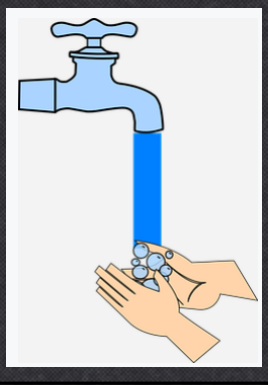
13% prior to treatment and 0.4% after treatment

Eliminating Cross-contamination: Patient Care

- Isolation (contact, enteric)
  - Private room (cohort only if necessary)
  - Gown & gloves (preemptively when test ordered)
  - Continue until at least 48 hours after diarrhea resolved (maintain until discharged if rates remain high)
  - Use of soap and water before and after patient contact to remove any spores (if high rates)
  - Use of disposable dedicated equipment (thermometers, stethoscopes, BP cuffs, etc.)

Eliminating Cross-contamination: Patient Care

- Encourage patient to wash hands often and shower
- Prevention measures (insufficient data for recommendation):
  - Discontinue proton pump inhibitors
  - Use of probiotics



Prevention Collaboration

- Antibiotic Stewardship Program (ASP)
  - Follows the ASP Core Elements defined by CDC
  - Define antibiotic usage and restrictions of high-risk therapy
  - Perform antibiotic time-out (ATO)
  - Recommendations on treatments for infection and to prevent recurrence
- Clinical Informatics
  - Best Practice Alerts (BPA)
    - Laxative usage prior to testing
    - Antibiotic Time-out

C. Diff Reduction Taskforce

- Multidisciplinary Team
- Leadership Support
- Scorecard Development
  - Hospital-onset CDI rate per 10,000 patient days
  - Days between admission and test collection
  - Percent rejected stool (formed)
  - Compliance with Hand Hygiene, Antibiotic time-out, UV light treatment, and cleaning technique
  - Antibiotic exposure prior to symptom onset
  - Antibiotic use data (high-risk antibiotics)

Communication

- CDI rates & Standardized Infection Ratios (SIR)
  - Compiled and report to leadership and units through Epidemiology/Infection Control for information and support
- Compliance rates
  - Current initiatives
- Resources
  - Inform leadership of resource needs
- Education
  - Staff
  - Patients/Visitors

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Treatment and Prevention

- Recognize high-risk populations
- Utilize appropriate and timely testing
- Institute prompt, effective treatment

Risk Factors

- Advanced age
- Hospitalization duration
- Antibiotic exposure
- Cancer chemotherapy
- Manipulation or surgery of the GI tract
  - Tube feeding
- Possibly - Acid suppression

CDI in the Community 2009-2011

- CA CDI cases
  - 82% had healthcare exposure within 12 weeks
- 36% did not report antibiotic use
  - 31% of the 36% received PPIs

Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. JAMA Intern Med 2013; 173:1359–67.

Populations at Increased Risk

- Inflammatory Bowel Disease
  - Risk >3% of CDI within 5 years
  - 33% more likely to have recurrent CDI[1]
- Solid Organ Transplant
  - Prevalence 7.4% [2]; risk of recurrence 20% [3]
- CKD and ESRD
- Hematopoietic stem cell transplants
  - Rate 9x greater than in hospitalized patient
  - Allo rate is twice as high as auto

1. Negron ME, Rezaie A, Barkema HW, et al. Ulcerative colitis patients with *Clostridium difficile* are at increased risk of death, colectomy, and postoperative complications: a population-based inception cohort study. Am J Gastroenterol 2016; 111:691–704.
2. Donnelly JP, Wang HE, Locke JE, Mannon RB, Safford MM, Baddley JW. Hospital-onset *Clostridium difficile* infection among solid organ transplant recipients. Am J Transplant 2015; 15:2970–7.
3. Paudel S, Zacharioudakis IM, Zervou FN, Ziakas PD, Mylonakis E. Prevalence of *Clostridium difficile* infection among solid organ transplant recipients: a meta-analysis of published studies. PLoS One 2015; 10:e0124483.

Appropriate Testing

- Well defined procedures rejecting formed stool
- Test only new-onset ≥ 3 unformed stools in 24 hours
  - NOT currently taking laxatives (except for special circumstances)
- New test method recommendations:
  - Use of nucleic acid amplification (NAAT) alone resulted in increased rates (Very sensitive—catching colonization)
  - Use a stool toxin test as part of a multistep algorithm
    - glutamate dehydrogenase [GHD] plus toxin;
    - GDH plus toxin, arbitrated by NAAT; or
    - NAAT plus toxin.

Appropriate Testing

- Do not test asymptomatic patients
- Do not perform repeat testing (within 7 days during same episode of diarrhea)
- Do not test for cure

Tests- Glutamate dehydrogenase immunoassays (GDH)

- Detects the highly conserved metabolic enzyme (common antigen) present in high levels in all isolates of *C. difficile*
- Antigen is present in both toxigenic and nontoxigenic strains
- Highly sensitive
- Lacks specificity and must be combined with another (usually toxin) test

Tests – Toxin A and B Immunoassays

- Monoclonal or polyclonal antibodies to detect *C. difficile* toxins
- Multiple commercial tests available
- Sensitivity = low; specificity = moderate

Tests – Nucleic Acid Amplification Tests (NAAT)

- Multiple available assays
- Detect gene targets including *tcdA*, *tcdB*, and 16S ribosomal RNA
- Sensitivity = high; specificity = low/moderate

Tests – Toxigenic culture

- Toxigenic culture – detect *C. difficile* vegetative cells or spores
- prereduced selective agar, cycloserine-cefoxitin-fructose agar or a variant of it, followed by anaerobic incubation
- The sample stool is treated with heat or alcohol shock prior to inoculating media
- Once there is growth, the organism is identified and a toxin test must be performed on the isolate
- Sensitivity = high

Tests - Cell cytotoxicity neutralization assay (CCNA)

- CCNA - preparation of a stool filtrate, which is applied to a cell line monolayer
- Following incubation, the cells are observed for cytopathic effect
- Duplicate testing is usually carried out simultaneously with neutralizing antibodies to *Clostridium sordellii* or *C. difficile* toxin, to ensure that the observed cytopathic effect is caused by *C. difficile* toxins and not by other substances in the stool
- Incubation can be up to 48 hours
- Most sensitive and specific test
- Gold standard

Testing Recommendations

What is the most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms?

- **Use a NAAT alone or a multistep algorithm for testing**

(ie, GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission

(weak recommendation, low quality of evidence)

Treatment - Initial CDI

- Vancomycin (VAN) 125mg PO Q6
- Fidaxomicin (FDX) 200mg PO BID
- Both for 10 days

Criteria for Severe CDI

- WBC count >15,000 cells/mL
- Serum Creatinine >1.5 mg/dL
- Exclude patients with hematologic malignancies or renal insufficiency

Treatment - Fulminant CDI

- Hypotension, shock, ileus or megacolon
- Metronidazole 500mg IV q8
- Higher doses of VAN
  - 500mg PO/NG Q6
  - 500mg in 100mL of normal saline by retention enema
  - May be appropriate to monitor serum vanco trough
- Surgical Intervention
  - Subtotal colectomy
  - Loop ileostomy with antegrade vanco lavage

Recurrent CDI

- Episode of symptom onset and positive assay result following an episode with positive assay result in the previous 2–8 weeks
- 25% of patients treated with VAN
- Recurrence rates are lower with FDX
- Risk factors
  - Abx administration during or after CD treatment
  - Defective humoral immune response
  - Advancing age/worsening disease
  - Continued PPI use

Louie TJ, Miller MA, Mullane KM, et al; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011; 364:422–31.
Cornely OA, Crook DW, Esposito R, et al; OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12:281–9.
Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. Arch Intern Med 2010; 170:772–8.
Kim YG, Graham DY, Jang BI. Proton pump inhibitor use and recurrent *Clostridium difficile*-associated disease: a case-control analysis matched by propensity score. J Clin Gastroenterol 2012; 46:397–400.

Recurrent CDI-First Recurrence

- Try VAN 125mg PO Q6 if metro used
- Try FDX 200mg PO BID if vanco used
- VAN taper
  - 125mg PO q6 for 10-14 days
  - 125mg PO BID for 7 days
  - 125mg PO Qday for 7 days
  - 125mg every 2-3 days for 2-8 weeks

Recurrent CDI- Second Recurrence

- VAN in a tapered and pulsed regimen
- VAN 125 mg PO Q6 for 10 days followed by rifaximin 400 mg PO TID for 20 days
- FDX 200 mg BID 10 days
- Fecal microbiota transplantation

Fecal microbiota transplantation (FMT)

- Diverse colon microbiota is protective
- Microbiota is destroyed by anti-bacterials
- FMT replenishes the colon microbiota
  - Route
  - Donor source
  - Hold treatment prior to Transplantation

N Engl J Med 2015; 372:1539-1548

FMT - Source

- Hx of recurrent or refractory CDI
- CD tx discontinued 24-48 hours prior to FMT
- Frozen versus fresh stool from same donor
  - mITT population - clinical resolution was 75.0% for the frozen FMT group and 70.3%for the fresh FMT group (difference, 4.7%[95%CI, –5.2%to]; *P* < .001 for noninferiority)

Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent *Clostridium difficile* infection: a randomized clinical trial . *JAMA*. doi:10.1001/jama.2015.18098.

Bezlotoxumab

- Monoclonal Antibody that binds to *C. difficile* toxin B
  - Blocks toxin B binding to host cells[1]
  - Half life is approximately 19 days
  - Should be administered while on CD treatment
- Adults with primary or recurrent CDI

1. Orth P, Xiao L, Hernandez LD, et al. Mechanism of action and epitopes of Clostridium difficile toxin B-neutralizing antibody bezlotoxumab revealed by X-ray crystallography. J Biol Chem 2014;289:18008-18021
2. N Engl J Med 2017; 376:305-317

Bezlotoxumab

- MODIFY I and MODIFY II
- 2655 participants at 322 sites in 30 countries
- MODIFY I Also tested Actoxumab – binds to Toxin A
  - Not efficacious
- Rates of recurrent infection in MODIFY I were 17% versus 28%, favoring bezlotoxumab (P<0.001); in MODIFY II, the rates were 16% versus 26%, also favoring bezlotoxumab (P<0.001)
- Adverse Reactions – infusion reactions, nausea, emesis

N Engl J Med 2017; 376:305-317

Prophylactic oral vancomycin

- Treating patients recently diagnosed with CDI
- Retrospective cohort study
- VAN 125mg or 250mg BID during abx therapy and for up to 7 days post completion
- Incidence of CDI 4.2% on oral VAN vs 26.2% in those without prophylaxis; odds ratio, 0.12; 95% confidence interval, .04–.4; P<.001.

Nicholas W. Van Hise, Alex M. Bryant, Erin K. Hennessey, Andrew J. Crannage, Jad A. Khoury, Farrin A. Manian, Efficacy of Oral Vancomycin in Preventing Recurrent *Clostridium difficile* Infection in Patients Treated With Systemic Antimicrobial Agents, *Clinical Infectious Diseases*, Volume 63, Issue 5, 1 September 2016, Pages 651–653, https://doi.org/10.1093/cid/ciw401

Summary

- Understand the sensitivity of your diagnostic test
- There are multiple ways to treat recurrences
- Limit PPI use
- Encourage Kefir or yogurt
- Consider PO VAN prophylaxis when needed
- Adhere to Isolation recommendations