**Clostridium difficile: How do we stop the flow?**

Chad Cannon, PharmD, BCPS
Critical Care Pharmacist
St. Vincent’s Medical Center-Riverside

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**Pharmacist Objectives**

- Review prevalence and risk factors associated with *C. diff*
- Outline updates needed to *C. diff* treatment guidelines
- Discuss preventative measures to help reduce *C. diff* rates
- Evaluate new therapies on the horizon for *C. diff*

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**Disclosure**

I do not have a vested interest or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

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**Clostridium difficile**

- Gram-positive, anaerobe, spore-forming bacillus organism
- Toxin A and B
- B1/NAP1/027
- Transmission person-to-person via fecal-oral route

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**Technician Objectives**

- Recall prevalence and risk factors associated with *C. diff*.
- Identify updates need in *C. diff* treatment guidelines
- Develop preventative measure to reduce *C. diff* rates
- Discuss new therapies for treatment of *C. diff*.

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**Environmental Contamination**

- Electronic rectal thermometers
- Inadequately cleaned commodes or bedpans
- Shared between patients
- Use household bleach in 1:10 dilution for best results
- Sporicidal
Pathogenesis


Prevalence

- 453,000 cases of C. diff infections
- 29,000 deaths associated with C. diff
- 15 cases per 1,000 hospital discharges
- 20 cases per 100,000 person-years in the community
- C. diff Infections (CDI) Annual expenditures $1.5 billion in U.S.

Risk Factors

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospitalization</td>
<td>Chemotherapy or immunocompromised</td>
</tr>
<tr>
<td>Gastrointestinal surgery or tube feeding</td>
<td>Proton pump inhibitors/histamine-2 blockers</td>
</tr>
</tbody>
</table>

Symptoms

- Presence of diarrhea
- Fever
- Abdominal cramping
- Peripheral leukocytosis
- Passage of mucus or occult blood in stool

Complications Associated with C. difficile

- Pseudomembranous colitis
- Toxic megacolon
- Perforations of the colon
- Sepsis
- Death
Toxin Side Effects: Asymptomatic colitis findings demonstrating pseudomembranous colitis.

Testing
- Glutamate dehydrogenase
  - Specificity < 90%
- ELISA
  - Increased sensitivity for low-level toxin production
- Polymerase Chain Reaction (PCR)
  - Detects B1/NAP1/027
  - Tissue Cytotoxic Assay
  - Sensitivity 94-100%

Guideline Recommendations

<table>
<thead>
<tr>
<th>Severity</th>
<th>Criterial</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate disease</td>
<td>Diarrhea per 24 hr or symptoms not resolving per or after 2 days</td>
<td>Metronidazole 500 mg po or iv x 10 days; if unavailable, vancomycin 10 mg/kg or qid x 5 days</td>
<td>If no improvement in 7 days, consider changes to vancomycin.</td>
</tr>
<tr>
<td>Source disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source and complicated disease</td>
<td>Any of the following with delay in onset of therapy: Admission to ICU for CDI; hypotension without use of vasoressors; fever &gt; 38.5 °C; mental status change; abdominal distension; WBC &gt; 15,000 or &lt; 2,000 cells/mm3; bicarbonate levels &lt; 2.2 mmol/L; renal failure</td>
<td>Vancomycin 125 mg po x 10 days and next oral vancomycin 500 mg or 500 ml iv in normal/gd</td>
<td>Surgical consult suggested</td>
</tr>
<tr>
<td>Fecal CDI</td>
<td></td>
<td></td>
<td>Consider fecal microbiota transplant or oral vancomycin 10 g id regimen</td>
</tr>
<tr>
<td>Fecal CDI after 3 weeks of completion of therapy</td>
<td></td>
<td></td>
<td>Consider fecal microbiota transplant or oral vancomycin 10 g id regimen</td>
</tr>
</tbody>
</table>

Phases of C. diff

- Antimicrobial exposure asymptomatically impairs the microbiome
- Antibiotic treatment of C. diff.
- Post treatment Normal microbiota vs. Regrowth of pathogen

Diagnosis
- Presence of diarrhea
- Passage of 3 or more unformed stools in 24 hour or less
- Stool test positive for toxigenic C. difficile
- Toxin or colonoscopy or histopathology findings demonstrating pseudomembranous colitis

Metronidazole
- Mechanism of action:
  - Induces microbial cell death by DNA disruption and inhibition of nucleic acid synthesis
- Dosing:
  - 500 mg tid oral or intravenous
- Metabolism:
  - 60-80% metabolized by liver; remaining excreted in feces
- Side Effects:
  - Metallic taste, headache, nausea, disulfiram reaction

Vancomycin
- Mechanism of action:
  - Inhibits bacterial wall synthesis
- Dosing:
  - 125 mg oral qid
  - 500 mg oral qid
  - 500 mg rectal qid
  - Taper
- Metabolism:
  - Excreted unchanged in feces
- Side effects:
  - Upset stomach and nausea
**Fidaxomicin**

- **Mechanism of action:**
  - Inhibits bacterial protein synthesis through inhibition of transcription that relies upon the sigma subunit of RNA polymerase
- **Dosing:**
  - 200 mg oral twice daily x 10 days
- **Excretion:**
  - Faces and Urine
- **Side Effect:**
  - Nausea, vomiting, abdominal pain

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**Treatment Options to Avoid**

- **Antidiarrheals/Antimotility**
  - Loperamide
  - Diphenoxylate
  - Bismuth

- **Complications**
  - Delay in resolution
  - Toxic Megacolon

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**Treatment Guideline Revisions?**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>No symptoms or signs</td>
<td>No treatment indicated</td>
</tr>
<tr>
<td>Mild</td>
<td>Mild diarrhea (3 to 5 unformed bowel movements per day)</td>
<td></td>
</tr>
</tbody>
</table>
  - Abdominal distension or tenderness                                                                 |
  - Nausea with occasional vomiting                                                                 |
  - Dehydration                                                                                       |
  - WBC > 15,000/mm3                                                                                  |
  - Blood urea nitrogen or Creatinine levels above baseline                                             |
  - Consideration of hospitalization and cessation of predosing antibiotics                          |
  - Hydration                                                                                         |
  - Monitoring of clinical status                                                                       |
  - Either administration or oral metronidazole 500 mg po tid or first line therapy with po vancomycin 125 mg qid for 14 days |
| Moderate        | Moderate abdominal diarrhea or tenderness                                                  | 
  - Nausea with occasional vomiting                                                                 |
  - Dehydration                                                                                       |
  - WBC > 15,000/mm3                                                                                  |
  - Blood urea nitrogen or Creatinine levels above baseline                                             |
  - Consideration of hospitalization and cessation of predosing antibiotics                          |
  - Hydration                                                                                         |
  - Monitoring of clinical status                                                                       |
  - Either administration or oral metronidazole 500 mg po tid or first line therapy with po vancomycin 125 mg qid for 14 days |

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**Fecal Microflora with C. diff therapies**

- **Single center, phase 2 and 3 study**
- **Specific objectives of study**
  - *C. difficile* present at diagnosis of CDI
  - Degree of impairment of normal microbiota
  - Comparison of clearance of *C. difficile* with different therapies
  - Pattern of recovery of the normal microbiota
Fecal Microflora cont’d

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Healthy Volunteers (n=5)</th>
<th>Patients w/ C. diff (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium spp</td>
<td>7.8 ± 4.1 CFU/g</td>
<td>6.7 ± 2.0 CFU/g</td>
</tr>
<tr>
<td>Bacteroides spp</td>
<td>11.8 ± 0.2 CFU/g</td>
<td>6.5 ± 3.2 CFU/g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>0 or 1</th>
<th>4</th>
<th>10</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>38-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolevar</td>
<td>7.3 ± 1.4 (24)</td>
<td>7.5 ± 1.1 (14)</td>
<td>7.5 ± 1.2 (13)</td>
<td>6.8 ± 1.6 (13)</td>
<td>5.8 ± 3.9 (11)</td>
<td>4.5 ± 2.0 (7)</td>
<td>2.5 ± 0.7 (5)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>7.5 ± 1.5 (20)</td>
<td>3.4 ± 1.8 (17)</td>
<td>2.3 ± 0.0 (18)</td>
<td>2.0 ± 0.0 (16)</td>
<td>4.2 ± 2.4 (15)</td>
<td>4.2 ± 2.2 (12)</td>
<td>4.4 ± 1.9 (8)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>5.7 ± 2.2 (14)</td>
<td>4.6 ± 1.2 (13)</td>
<td>4.6 ± 2.9 (13)</td>
<td>5.2 ± 2.8 (7)</td>
<td>4.9 ± 1.8 (7)</td>
<td>4.2 ± 2.5 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Guideline Revisions?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Severe or bloody diarrhea</td>
<td>Hospitalization</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous colitis</td>
<td>Oral or rectal vancomycin 500 mg qid with or without IV metronidazole 500 mg tid</td>
</tr>
<tr>
<td></td>
<td>Severe abdominal pain</td>
<td>Or oral fidaxomicin 200 mg po bid for 10 days instead of vancomycin if the risk of recurrence is high</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temperature &gt; 38.9°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WBC &gt; 20,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albumin level &lt; 2.5 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Vanco/Flagyl C. diff in Critically Ill

- Single centered, observational, comparative study
- Primary objective
  - In-hospital mortality
- Secondary objective
  - Clinical success at days 6, 10, and 21
  - Hospital length of stay after CDI diagnosis
  - Length of ICU stay after CDI diagnosis

Critically Ill Cont’d

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Monotherapy (n=44)</th>
<th>Combination (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>16 (36.4)</td>
<td>7 (15.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to death, days, median (range)</td>
<td>21 (5-174)</td>
<td>15 (6-32)</td>
<td>0.23</td>
</tr>
<tr>
<td>Clinical success day 6</td>
<td>9 (20.5)</td>
<td>6 (13.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Day 10</td>
<td>27 (61.4)</td>
<td>25 (56.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Day 21</td>
<td>33 (75.0)</td>
<td>37 (84.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Length of stay after CDI diagnosis, days, median (range)</td>
<td>20.5 (10-64)</td>
<td>18.0 (6-166)</td>
<td>0.99</td>
</tr>
<tr>
<td>Length of ICU stay after CDI diagnosis, days, median (range)</td>
<td>9 (4-60)</td>
<td>11.0 (0-68)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Treatment Guideline Revisions? Cont’d

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Recurrence</td>
<td></td>
<td>Oral vancomycin 125 mg po qid for 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or fidaxomicin po 200 mg po bid for 10 days</td>
</tr>
</tbody>
</table>

1st Recurrence Fidaxomicin vs. Vancomycin

- Multi-center, randomized, controlled trial
- Primary Objective
  - Recurrence within 28 days after completing therapy
- Secondary Objective
  - Time to recurrence
Vancomycin vs Fidaxomicin

- Recurrence within 28 days
  - No prior episode
    - Vanco 22.6 % vs. Fidaxomicin 11.7% (p < 0.001)
  - One prior episode
    - Vanco 35.5% vs. Fidaxomicin 19.7% (p= 0.045)
- Time to recurrence
  - Recurrence within 14 days
    - Vanco 27.4% vs. Fidaxomicin 7.6% (p=0.03)
  - Recurrence within 15 to 28 days
    - Vanco 11.1% vs. Fidaxomicin 13.1% (p=ns)

Fecal transplant for recurrence

- Single centered, open-label, randomized, controlled trial
- Primary Objective
  - Cure without relapse within 10 weeks after therapy
- Secondary Objective
  - Change in microbiota diversity

Antimicrobial Stewardship

Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms

Treatment Guideline Revisions?

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clinical Manifestations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second or further</td>
<td>Recurrence in a tapered and</td>
<td>Vancomycin in a tapered and</td>
</tr>
<tr>
<td>recurrence</td>
<td>pulsed regimen</td>
<td>pulsed regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fecal microbial transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or Fidaxomicin 200 mg po bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for 10 days</td>
</tr>
</tbody>
</table>

Fecal transplant cont’d

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>First Infusion of Donor Feces (N=16)</th>
<th>Infusion of Donor Feces Overall (N=16)</th>
<th>Vancomycin (N=13)</th>
<th>Vancomycin with Bowel Lavage (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of Cure</td>
<td>13/16 (81.3%)</td>
<td>15/16 (93.8%)</td>
<td>4/13 (31%)</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>without Relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stewardship Executive Order

Goals

- Slow the Emergence of Resistant Bacteria and Prevent the Spread of Antimicrobial Resistance
- Strengthen National One-Health Surveillance Efforts to Combat Resistance
- Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
- Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, and Antibiotic Research and Development

Targets for Combating Resistance by 2020

- Reduce by 50% the incidence of overall Clostridium difficile infection
- Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired
- Reduce by 35% multidrug-resistant Pseudomonas spp. infections acquired during hospitalization
- Reduce by at least 50% outpatient methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections
Restriction of Antibiotics

- **Title**: An Evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of Clostridium difficile infection in hospital setting
- **Study**: Single-center, retrospective study, April 2004 to June 2010
- **Intervention**: Restriction of high-risk antibiotics 2nd and 3rd generation cephalosporins, fluoroquinolones, and clindamycin
- **Primary Outcome**: Evaluate impact of restricting high-risk antibiotics and CDI incidence rates
- **Result**:
  - Use of high level antibiotics (coefficient -17.3, p < 0.0001)
  - Total antibiotic use (coefficient -14.2, p = 0.0074)
  - C. diff by 0.0047/100 bed-days per month (P = 0.0081)
- **Conclusion**: Antibiotic restriction policy contributed to a reduction in high-risk antibiotic usage and incidence of CDI

Penicillin Allergies

- PCN most common reported drug allergy
- Historical teaching 10% cross reactivity with cephalosporin
- Avoiding beta-lactams can potentially lead to adverse effects and/or inferior coverage
- True cross reactivity ≤ 2% with cephalosporin
  - Anaphylaxis ≤ 0.0015%

Penicillin Allergy and Resistance

- Retrospective, matched cohort study, 2010-12
- Kaiser Foundation Hospitals Southern California
- **Primary Objective**: Determine the total number of hospital days used in hospitalized patients with active penicillin allergy compared to patients with no penicillin allergy history
- **Secondary Objective**: Determine antibiotics used and prevalence rates of C. diff, MRSA, and VRE between cases and controls.
- **Results**:
  - Hospital days 0.59 (9.9%, 95% CI, 0.47-0.71)
  - C. diff prevalence 1.234 (95% CI, 1.156-1.317)
  - MRSA prevalence 1.141 (95% CI, 1.071-1.317)
  - VRE prevalence 1.301 (95% CI, 1.125-1.504)

Colorectal Surgery Prophylaxis

- Retrospective, case-control study, 2 surgical units
- July 2012- September 2013
- Identify risk factors among surgical patients for CDI
  - Ertapenem associated with increase risk of CDI
    - (Adjusted OR 3.13, [95% CI, 1.13-8.86], P = 0.028)
  - Cefazolin prophylaxis no association
    - (Adjusted OR 0.373, [95% CI, 0.129- 1.08], P = 0.68)

Acid Suppressors

- **Histamine-2 receptor antagonists**
  - Mechanism of Action: Competitive inhibition of histamine H2 receptors of the gastric parietal cells
  - Indications:
    - Acid reflux
    - Indigestion
    - GERD
  - Side Effects:
    - Headache, diarrhea, thrombocytopenia

- **Proton pump inhibitors**
  - Mechanism of Action: Inhibition of parietal cell H+K+ ATP pump
  - Indications:
    - GERD
    - Hypersecretory disorders
    - Duodenal ulcer
  - Side Effects:
    - Headache, dizziness, constipation

Indications for Stress Ulcer Prophylaxis

- **Intensive Care Unit**
  - Coagulopathy
  - Mechanical ventilation > 48 hours
  - Acute Kidney Injury
  - Acute/Chronic Hepatic Injury
  - Non-Intensive Care Inpatient
  - Not recommended
Acid Suppression and C. diff

- Proton pump inhibitors
  - Meta-analysis
  - Examined association between PPIs and CDI
  - CDI and PPIs adjusted: OR 1.65; (95% CI, 1.47-1.85)
- Histamine 2 receptor antagonist
  - Meta-analysis
  - Examined association between H2RAs and CDI
  - CDI and H2RAs OR 1.44, 95% CI (1.22-1.7)

Probiotics

- Live microorganisms that when ingested, produce some therapeutic or preventative health benefit
- Health-promoting concept ~ 100 years old
- Clinical studies validated use of probiotics
  - Viral diarrhea
  - Antibiotic-associated diarrhea
  - C. difficile-associated diarrhea
  - Traveler’s diarrhea
  - Pouchitis
  - Irritable bowel syndrome
  - Atopic dermatitis

Probiotic Literature

- Meta-analysis review
- Probiotics may be more effective in primary CDI prevention than in secondary prevention of recurrent CDI

Proton Pump Inhibitors and C. diff in Critically Ill

<table>
<thead>
<tr>
<th>Study</th>
<th>Single Center, Retrospective, Case-Control study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>408 patients from Beth Israel Deaconess Medical Center from 2001 to 2008</td>
</tr>
</tbody>
</table>
| Objective | Describe the relationship between PPI use and hospital-acquired CDI in critically ill patients
- Evaluate duration of inpatient PPI exposure as a risk factor for CDI |
| Results | Long PPI exposure (2 or more days): OR 2.03, 95% CI (1.23-3.36); p=0.006
- Antibiotic use: OR 3.52, 95% CI (1.33-9.18); p=0.012 |
| Conclusion | Duration of PPI use is significantly associated with C. diff associated diarrhea
- Risk is evident after only two days of therapy
- Consider alternative agents for stress ulcer prophylaxis |

Different Types of Probiotics

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florastor®</td>
<td>Saccharomyces boulardii, Lactobacillus acidophilus, Lactobacillus casei and Lactobacillus rhamnosus</td>
</tr>
<tr>
<td>Floranex®</td>
<td>Bio-K+®</td>
</tr>
<tr>
<td>Culturelle®</td>
<td>Capsules/Granules/Capsules/Liquid</td>
</tr>
</tbody>
</table>

Dosage:
- AD: 250mg 1-2 capsules every 8 hours or as needed
- Acute diarrhea: 200mg TID for 2 days followed by 100mg TID x 5days
- Culturelle: 2 capsules BID, 4 tablets or 1 packet TID-QID
- Bio-K+: Capsules: 1-2 capsules daily

New Therapies

- Phase 1: CRS3123
- Phase 2: Ramoplanin, SMT 1969
- Phase 3: Cadazolid, Surotomycin, Actoxumab/Bezlotox untab
**Ramoplanin**
- Glycolipodepsipeptide antibiotic
- Under Investigation for relapse prevention
- Mechanism of action:
  - Inhibits peptidoglycan biosynthesis by limiting lipid II availability
  - Exosporium may be target of killing
    - "ambush" type of vegetative killing

**Suromycin**
- Minimally absorbed, narrow-spectrum, cyclic lipopeptide
- Mechanism of Action:
  - Acts through depolarization of the membrane, leading to the loss of a proton gradient and cell death
  - Bactericidal killing
  - Administered orally
  - Exponential and stationary phase cell killer

**Cadazolid**
- Novel fluoroquinolone-oxazolidinone antibiotic
- Mechanism of action:
  - Inhibition of protein synthesis
  - Excreted unchanged in feces
  - Phase II: similar clinical cure as vancomycin
    - Decrease in recurrence rates in cadazolid group

**Actoxumab/Bezlotoxumab**
- Human monoclonal antibodies
- Mechanism of action:
  - Bind and neutralize TcdA and TcdB
  - Under investigation for prevention of recurrence
  - Phase II study
    - Administered with standard of care decrease recurrence

**Frozen Oral Stool Transplant**
- Open-label, single-group, feasibility study
- Primary Objective:
  - Evaluate the safety and rate of resolution of diarrhea following administration of Fecal microbiota transplantation
- Intervention:
  - Patients received 15 capsules on 2 consecutive days
- Results:
  - 14 of 20 patients had clinical resolution (OR 0.70, 95% CI, 0.47-0.85)
  - 19 of 20 patients had resolution after 2nd treatment (OR 0.90, 95% CI, 0.68-0.98)

**Conclusion**
- *C. difficile* infections continue to ↑
- Oral vancomycin 1st line therapy for hospitalized patients
- Bundle approach needed to ↓ *C. difficile* infection rates
- New therapies coming but can’t invent our way out of this problem!