Objectives

1. Review the epidemiology of *C. difficile* infection
2. Understand the advantages and limitations of the diagnostic tests for *C. difficile* infection
3. Recommended therapies for the initial episode of *C. difficile* infection
4. Management strategies for recurrent *C. difficile* infection

**C. Difficile epidemiology**

- Increased rates of *C. difficile* infection (CDI) in the past 20 years
- National hospital discharge survey
  - Doubling of CDI Diagnosis from 31/100,000 cases in 1996 to 61/100,000 cases in 2003
- Increased rates of colectomy and mortality
  - 2011
  - Estimated 453,000 cases
  - Incidence rate 141 cases/100,000 persons
  - Greatest amongst those ≥65 years old
  - 65% of cases considered hospital onset
- More virulent and resistant strain: NAP1/BI/027
  - Has resulted in more severe cases


**C. difficile–Associated Disease (CDAD) United States 2000–2005**


**C. difficile–Related Mortality United States, 1999–2004**

Epidemic Strain of *C. difficile* Associated with Outbreaks of CDI, United States

- 187 *C. difficile* isolates from 8 health care facilities in 6 states (Georgia, Illinois, Maine, New Jersey, Oregon, and Pennsylvania)
- Isolates characterized by
  - Restriction-endonuclease analysis (REA)
  - Pulsed-field gel electrophoresis (PFGE)
  - Toxinotyping
- Compared with a database of >6000 isolates obtained before 2001


C. Difficile colonization

- Colonization is seen in up to 26% of adults in acute care hospitals
  - ~10% in residents of LTACs
  - 3-5% of the general population with no health care exposure
  - Estimated that a person can be colonized for a week or more before symptoms develop (if at all)


C. Difficile Diagnosis

- Diagnosis relies on patient presentation, risks for *C. difficile* infection (CDI)
- Presence of diarrhea
  - ≥3 unformed stools per day
- No explanation for the diarrhea
  - Not taking a laxative or stool softener
  - No other diagnosis for the diarrhea
- Detection of presence of *C. difficile* by Polymerase Chain Reaction (PCR) or toxin assay

Predicting *C. difficile* Toxin Positivity in Hospitalized Patients With Antibiotic-Associated Diarrhea

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery diarrhea</td>
<td>17.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Functional capacity score of 2 or 3</td>
<td>9.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use of proton pump inhibitor</td>
<td>6.1</td>
<td>.024</td>
</tr>
<tr>
<td>Albumin level &lt;2.7 mg/dL</td>
<td>3.8</td>
<td>.001</td>
</tr>
<tr>
<td>Use of histamine blocker</td>
<td>3.1</td>
<td>.024</td>
</tr>
<tr>
<td>WBC count &gt;13,000 cells/mL</td>
<td>2.7</td>
<td>.004</td>
</tr>
</tbody>
</table>


*C. Difficile* Diagnostic Methods

- **Cell Cytotoxicity Assay**
  - Growth of *C. difficile* in culture
  - Identification of plaques related to toxin production
  - Can detect small amounts of toxin
  - Labor intensive
  - Long turn around time

- **EIA for Toxin A/B**
  - Detection of *C. difficile* specific toxins
  - Low sensitivity (75-80%)
  - Toxin A assays will miss Toxin B only strains

- **Glutamate Dehydrogenase**
  - Enzyme produced by all *C. difficile* strains
  - Good sensitivity (~90%)
  - Cannot distinguish between toxin and non-toxin strains
  - Primary use is to screen stool for the presence of *C. difficile*

- **C. difficile Nucleic Acid Amplification Testing (NAAT)**
  - Tests for the Toxin B gene (*tcdB*) or the Toxin Regulatory Gene (*tcdC*)
  - Very sensitive (90%) and specific (96%)
  - Can provide early and accurate conformation of CDI
  - Positive predictive value does decrease with decreasing prevalence of *C. difficile* (esp. <20%)

**Difficulty with Interpretation of C. difficile NAAT**

- Study of outcomes for NAAT and Toxin assays
- Testing over 2 time periods (one in 2008 and one on 2009)
- 23 toxin-negative, NAAT-positive patients who were not treated
- Recurrence of CDI was more common in patients with both assays positive vs. NAAT alone positive
- Treatment based on test results
  - Prospective, observational cohort study at a single center
  - Natural history and need for treatment of patients who were toxin EIA positive compared with toxin negative/PCR positive
  - Multivariable model, frequency of CDI-related complications was highest in the toxin-positive/PCR-positive group
  - >50% of the toxin negative/PCR positive patients received NO treatment
  - No difference in outcomes compared to toxin and PCR negative patients


**C. difficile Testing Algorithm**

- Stool
  - Glutamate dehydrogenase EIA or C difficile PCR
    - GDH - a common C. difficile antigen
  - Report: Negative for toxigenic Strain of C. difficile
- C. difficile culture or C. difficile NAAT
  - Test the isolate for toxin A/B with EIA
  - Report: Positive for toxigenic strain of C. difficile

**Treatment of Initial Episode of C. difficile Infection**

- Assess severity of disease
  - Mild vs. severe vs. severe complicated disease
- Severe disease: (≥2 of the following)
  - Age >60 years
  - Temp >38.3°C
  - WBC >15,000 cells/µl
  - Cr >1.5 times pre-morbid level
  - Albumin <2.5 mg/dl
- Severe, complicated: as above with signs of shock, ileus or megacolon

Treatment of Initial Episode of CDI

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Criteria</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Mild or Moderate Diarrhea | - Vancomycin (VAN) 125mg 4x/day for 10 days  
- Fidaxomicin (FDX) 200mg Q-12h for 10 days | |
| Severe WBC >15k OR serum Cr >1.5 mg/dl | - VAN 125mg 4x/day for 10 days  
- FDX 200mg Q-12h for 10 days | |
| Severe Complicated Hypotension Shock Ileus Megacolon | - VAN 500mg 4x/day PLUS  
- Fidaxomicin 1000mg Q-8h intravenous  
- If ileus may consider adding rectal instillation of vancomycin | |
| First Recurrence Recurrence within 8 wks of completion of therapy | - VAN 125 mg 4x/day for 10 days if metronidazole used initial episode  
- VAN taper/pulse  
- FDX if vancomycin used initial episode | |
| Second recurrence | - VAN taper/pulse  
- VAN for 10 days followed by rifaximin 400 mg daily for 20 days  
- FDX x 10 days  
- Fecal microbiota Transplantation | |


Metronidazole
- Long considered an effective therapy for mild disease
- Higher failure rates recently reported
- Musher et al.   
  - 207 patients treated with metronidazole  
  - 50% cured, 22% with continued diarrhea, 28% with relapse <90 days  
  - 33% mortality in non-responders vs. 21% in responders
- Pepin et al.   
  - 1991-2002: 21% recurrence rate, 29% ≥65yo  
  - 2003-2004: 47% recurrence rate, 58% ≥65yo


Vancomycin versus Metronidazole
- Stratified by severity of disease
- Prospective, randomized, double blind, placebo trial
- Metronidazole 250mg QID for 10 day
- Vancomycin 125mg QID for 10 days

<table>
<thead>
<tr>
<th>Clinical Cure</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Disease</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>Severe Disease</td>
<td>76%</td>
<td>97% (p&lt;.02)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>


Response to Treatment of C. difficile–Associated Disease with Metronidazole and Vancomycin

Clin Infect Dis 2008; 47:56–62
Fidaxomicin

- Macroyclic antibiotic
- 8-fold more active vs. C. difficile than vancomycin
- Bactericidal against C. difficile
- Prolonged post-antibiotic effect
- Minimal systemic absorption
- High fecal concentrations
- Limited activity vs. normal gut flora


Fidaxomicin versus Vancomycin for the treatment of CDI*

<table>
<thead>
<tr>
<th></th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure</td>
<td>88.2%</td>
<td>85.8%</td>
</tr>
<tr>
<td>Relapse Rate</td>
<td>15.4%</td>
<td>25.3%</td>
</tr>
<tr>
<td>(P=0.005)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity of Illness: Clinical Cure Rates

<table>
<thead>
<tr>
<th>Severity</th>
<th>Fidaxomicin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>59/64 (92.2%)</td>
<td>68/80 (85%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>102/111 (91.9%)</td>
<td>88/106 (83%)</td>
</tr>
<tr>
<td>Severe</td>
<td>92/112 (82.1%)</td>
<td>109/123 (86.6%)</td>
</tr>
</tbody>
</table>

*Fidaxomicin 200 mg PO BID vs. vancomycin 125 mg PO QID x 10 days
*Down side to fidaxomicin ➔ $2000 for a 10 day course


Monoclonal Antibodies for the Treatment of CDI

- Actoxumab monoclonal anti-toxin A
- Bezlotoxumab monoclonal anti-toxin B
- Early data demonstrated lower rates of recurrence with addition of bezlotoxumab
- MODIFY I & MODIFY II
  - Aztoxumab+bezlotoxumab, bezlotoxumab or placebo
  - Aztoxumab alone arm in MODIFY I discontinued at interim analysis
  - Single dose monoclonal antibody while on anti-C difficile therapy
  - Oral therapy for CDI was 10-14 cays of metronidazole (47%), vancomycin (47%) or fidaxomicin (4%)


Bezlotoxumab to prevent recurrence of CDI

Recurrent *C. difficile* Infection

- 15-30% risk of single recurrence
- Up to 65% of those with 1 recurrence will have continued relapsing disease
- Increase cost, morbidity and mortality
- Difficult to treat and control
- May be secondary to:
  - Impaired immune response
  - Shift to a more toxigenic strain (NAP1/BI/027)
  - Alterations in the gut microbiota


Risk Factors for Recurrent CDI

- Inadequate antitoxin antibody response
- Persistent disruption of fecal microbiota
- Advanced age
- Type of anti-bacterial therapy
  - Especially fluoroquinolones
- Prolonged hospital stay
- Prolonged antacid medications
  - Especially Proton Pump Inhibitors


Impaired Immune Function

- Those with recurrent CDI have lower levels of IgG to toxin A
  - 40 patients with recurrent disease had less IgG and IgA response to toxin A
  - Increased levels of toxin-A specific IgM and IgG associated with decreased risk of recurrence
- Study of *C. difficile* vaccine
  - Protective response in 3 individuals given the vaccine with an IgG response to toxin

Kyne. et Lancet 2001;357:189-193

Toxin A Antibody Levels and Risk of CDAD Recurrence

Lancet 2001; 357: 189–93
**Treatment of Recurrent Disease**

- **Vancomycin taper/pulse**
  - 10-14 days 125mg QID, then 125mg TID x7 days, then 125mg BID x7 days, then 125mg daily x7 days
  - 125mg every other day for 2-8 weeks
  - Fidaxomicin 200 mg BID for 10 days
  - Vancomycin 125mg QID x14 days then rifaximin 400mg daily x 20 days
- **Fecal Microbiota Transplantation**


**Vancomycin Taper/Pulse**

- Patients from the placebo arm of 2 studies evaluating a probiotic
- Overall recurrence rate was 44.8%
- Recurrence for tapering course of vancomycin was 31%
- Recurrence for pulsed dosing of vancomycin was 14%
- Trend for less recurrences with ≥2 grams/day of vancomycin vs. ≤1 gram/day


**Fidaxomicin for recurrent disease?**

- Subgroup analysis of the the original fidaxomicin study
- 128 cases of had recent *C. difficile* disease
- Initial response to fidaxomicin or vancomycin similar
- Recurrence within 28 days
  - 36% in vancomycin group
  - 20% of the fidaxomicin group


**Fecal Microbiota Transplant (FMT)**

- Elie Metchnikoff
  - Early 1900s noted the longevity of Eastern European populations that drank fermented milk
- Healthy gut microbiome
  - 10^{13} microorganisms
  - Aids in digestion, metabolism, mucosal integrity and possibly immune function
- Gut microbiome of those with CDI (initial & recurrent)
  - Stark changes in microbiome
  - Change in predominate bacterial phyla
  - Decreased diversity

  1. Metchnikoff E, Mitchell PCS. The Prolongation of Life: optimistic studies, 1907
**Rationale for FMT**

- Disruption of colonic flora
- Reduction of “colonization resistance”
- Continued growth of pathogenic *C. difficile*
- Reintroduction of normal flora via donor feces:
  - Corrects the imbalance
  - Interrupts the pathogenic cycle of *C. difficile*
  - Reestablishes normal bowel function


**Case Data for FMT**

- 1958: Eiseman and colleagues\(^1\)
  - Used fecal enemas to cure 4 patients with *pseudomembranous colitis*
- Cure rates have been high
  - Review of 27 cases series, 317 patients
  - 89% resolution of symptoms\(^2\)

2. Gough E, et al. CID 2011;53:994-1002

**Rarefaction analysis comparing overall diversity of indigenous microbiota in healthy control subjects and patients.**


**Outcome Achieved in Patients Treated with Fecal Microbiota Transplantation for *C. difficile* Infection**

<table>
<thead>
<tr>
<th>Studies, no.</th>
<th>Resolution</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>All procedures</td>
<td>28</td>
<td>284/317 (89%)</td>
</tr>
<tr>
<td><strong>Instillation Method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscope</td>
<td>9</td>
<td>55/62 (88.7%)</td>
</tr>
<tr>
<td>Enema</td>
<td>11</td>
<td>105/110 (95.4%)</td>
</tr>
<tr>
<td>Gastroscope or NG tube</td>
<td>4</td>
<td>55/72 (76.4%)</td>
</tr>
<tr>
<td>Rectal catheter</td>
<td>2</td>
<td>44/46 (95.6%)</td>
</tr>
<tr>
<td>&gt;1 method</td>
<td>2</td>
<td>19/21 (90.5%)</td>
</tr>
<tr>
<td>NR</td>
<td>2</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td><strong>Donor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related</td>
<td>19</td>
<td>195/209 (93.3%)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>4</td>
<td>21/25 (84%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>57/72 (79.2%)</td>
</tr>
<tr>
<td>NR</td>
<td>3</td>
<td>11/11 (100%)</td>
</tr>
</tbody>
</table>

2. Gough E, et al. CID 2011;53:994-1002
Nasogastric Tube versus Colonoscopy

Youngster et al CID 2014;58(11):1515-1522

FMT vs. Oral Vancomycin

- Evaluation of efficacy of FMT vs. medical therapy
- 16 patients in the duodenal infusion group
- 13 patients in the vancomycin group
- 13 patients in the vancomycin and bowel lavage group


Rates of Cure without Relapse for Recurrent C. difficile Infection

Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors


Donor Fecal Transplant vs. Auto-stool Transplant

- Patients
  - Adult patients with >3 recurrent episodes of CDI who did not maintain a cure with pulse or tapered course of vancomycin
  - Donor: Patients could pick a donor or choose stool from healthy volunteers
- Intervention
  - Randomized 1:1 Donor vs. auto FMT
  - Randomization at time of FMT
- Comparison
  - Donor vs Auto-FMT
- Outcomes
  - Clinical cure at 8 weeks, no recurrence of CDI and ≤ 3 formed stools per day without need for anti-C. difficile medication
  - C. difficile PCR was not used to define cure

Donor Fecal Transplant vs. Auto-stool Transplant

- Why did 62.5% of the auto-FMT have a cure?
  - Most of the auto-cures where seen in the NY group
  - These patients had more recurrences overall
  - More courses of fidaxomicin
  - Longer courses of oral vancomycin
  - More Clostridia spp. in the stool of the NY pt
  - May have “outcompeted” the *C. difficile*
  - Many patients may have had a post-CDI IBS and not true recurrent CDI

Poop in a Pill?

- The procedure of FMT can be “distasteful” to certain individuals
- A group on Canada has developed “poop in a pill”
- 100 grams of donor stool are suspended in 600-800ml PBS
- The resultant fluid is pipetted into 25-35 gelatin capsules
- Recipient takes the capsules on the day of the “Transplant”
- 27 pts have had the procedure
- All had arrested CDI
- Increases in *Bacteroides, C. coccoides, Prevotella, Bifidobacteria*
- Decreases in *Enterobacteriaceae and Veillonella*
Conclusions

• *C. difficile* infection (CDI) is a major hospital acquired infection and has been increasing in incidence over the past 20 years
• The **most important risk factor for developing CDI is antibacterial use**
• Testing for CDI should be focused on
  — Those individuals with unexplained diarrhea with NAAT alone OR
  — Using of a step-wise algorithm to detect *C. difficile* toxin
• **Initial treatment should be with oral vancomycin or fidaxomicin**
  — Metronidazole is no longer considered appropriate initial therapy
• Treatment of recurrent CDI can be difficult
• Fecal microbiota transplantation offers an efficacious treatment option
  — More comparative trials are needed
  — Exact mechanism needs to be elucidated