CLOSTRIDIUM DIFFICILE: IMPROVING DIAGNOSIS AND TREATMENT

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Learning Objectives

• Recognize patients who are highest risk for C. diff infections
• Appropriately use and interpret available C. diff tests.
• Choose the best treatment option for patients with C. diff infections
• Determine when alternate therapies are needed.
**Clostridium difficile**

- Gram-positive, anaerobic, spore-forming, toxin-producing bacillus first identified in 1935
- First identified as cause of antibiotic-associated colitis in the 1970s
- Most commonly identified infectious cause of antibiotic- and healthcare-associated diarrhea
Impact of *C. difficile* in the US

- In 2011:
  - 453,000 cases of *C. difficile* in US
  - 29,300 patients died
  - 293,000 cases healthcare associated
  - 159,700 cases community associated
  - 107,600 cases hospital acquired

- Estimated costs:
  - $20,693 per hospitalized patient with primary CDI
  - $45,148 per patients with recurrent CDI

Impact at ROPER ST. FRANCIS

• At RSFH’s three hospitals between 2013-2014:
  • *C. difficile* possibly contributed to up to 8 deaths
  • Inpatient hospitalizations for *C. difficile* cost up to $993,080
Risk Factors for *C. difficile* Colonization

- Hospitalization within the last 12 months
- Exposure to corticosteroids
- History of *C. difficile* infection
- Presence of antibody against toxin B
- Chemotherapy
- Use of PPI or H2 antagonists
- Chronic dialysis

Risk Factors for Active *C. difficile* Infection

- **Host-mediated Factors**
  - Recent antibiotic use
  - Use of PPIs
  - Chemotherapy
  - Physical effects of abdominal surgery and NG tubes
  - Advanced age (age ≥ 65 years)
  - Multiple comorbidities
  - Suppressed immune system
  - Inflammatory bowel disease
  - Dense intestinal co-colonization with enterococci
  - Absence of IgG and IgA antibodies to *C. difficile* toxins A & B

- **Pathogen Factors**
  - Colonization with non-toxigenic strains of *C. difficile* (protective)

Colonization vs. Symptomatic CDI

Risk factors for C. difficile colonization
- Previous hospitalization
- Exposure to antibiotics
- Chemotherapy treatment
- Corticosteroid use
- Haemodialysis / renal disease

Exposure to C. difficile spores leading to asymptomatic C. difficile colonization

Factors that protect against progression to symptomatic CDI
- Increased levels of IgG and IgA
- Intact indigenous microbiome
- Colonization by less virulent C. difficile strain

Risk factors for symptomatic CDI
- Increased age
- Exposure and duration of antibiotics
- Presence of nasogastric tube
- Severe underlying disease
- Prolonged hospital admission
- Exposure to drugs that reduce stomach pH

Healthy intestinal epithelial cells with intact microbiome in an individual with asymptomatic C. difficile colonization

Legend
- Clostridium difficile cell
- Normal colonic flora
- Clostridium difficile spore
- Toxin A
- Toxin B

Damaged intestinal epithelial cells in an individual with symptomatic CDI

Risk Factors for Recurrent CDI

- Older age
- \( \geq 10 \) unformed stools per 24 hour period
- Serum creatinine \( \geq 1.2 \) mg/dL
- PPI use
- Continued exposure to antibiotics
- Comorbidities (DM, CKD, higher Charlson score)
- Failure to mount serum antibody do C. difficile toxins

Risk Factors for Complications of CDI

- Age $\geq 80$ years
- Abnormal blood tests
  - WBC count $< 4 \times 10^9/L$ or $\geq 20 \times 10^9/L$
  - Albumin $< 2.5$ g/dL
  - BUN $> 20$ mg/dL
  - CRP $\geq 15$ mg/dL
- Abnormal vital signs
  - Heart rate $> 90$/minute
  - Respiratory rate $> 20$/minute

Antibiotic Use and CDI

- Pathophysiology:
  - Disruption of the barrier function of the normal colonic flora
  - Development of *C. difficile* antibiotic resistance leading to strains with increased virulence
- Degree and duration of CDI after cessation of antibiotics is poorly understood.
- Perioperative antibiotic prophylaxis to prevent infrequent and relatively benign infections may not be beneficial in some older adult patients.
- A “herd effect” of antibiotic use has been theorized.

# Antibiotics Associated with CDI

**Frequently Associated**
- Clindamycin
- Fluoroquinolones
- Cephalosporins (broad-spectrum)
- Penicillins

**Occasionally Associated**
- Macrolides
- Trimethoprim-sulfamethoxazole

**Frequently Associated**
- Aminoglycosides
- Tetracyclines
- Metronidazole
- Vancomycin

Adapted from Lamont, JT. “Clostridium difficile in adults: Clinical manifestations and diagnosis.” www.uptodate.com.
Gastric Acid Suppression and CDI

- Risk of CDI increases with both H2 antagonists and PPIs.
- Risk of CDI is 1.4 - 2.75 times higher among patients exposed to PPI vs. those without PPI exposure.
- Relationship between risk of CDI and PPI dose and duration is uncertain.

http://www.fda.gov/drugs/drugsafety/ucm290510.htm (Accessed on November 5, 2016)
Factors Complicating Diagnosis

1. Colonization by *C. difficile* is common among hospitalized patients
2. CDI explains less than 1/4\(^{\text{th}}\) of antibiotic-associated diarrhea cases in the hospital setting

When to test for *C. difficile*

- Relevant risk factors PLUS either:
  - Clinically significant diarrhea (≥3 loose stools in 24 hours)
  - Ileus

*Lab testing does not distinguish between CDI and asymptomatic carriage*

*No role for repeating lab testing for cure or for testing while receiving treatment for CDI*

*Diagnostic approach for suspected recurrent *C. difficile* is the same as the approach for initial infection.*
Laboratory Testing

- PCR testing
- EIA for *C. difficile* GDH antigen
- EIA for *C. difficile* toxins A & B
- Selective anaerobic culture
- Cell culture cytotoxicity assay
PCR Testing

• Tests for one or more genes specific to toxigenic strains
• Typically tests for gene tcdB (encodes for toxin B)
• High sensitivity (0.86-0.92) and specificity (0.94-0.97)
• Does not test for active toxin production
• Only a single stool sample should be tested
• Results can be available within an hour

## Enzyme Immunoassays for *C. difficile*

### EIA for GDH Antigen
- Essential enzyme produced by both toxigenic and non-toxigenic *C. difficile* isolates
- High sensitivity, low specificity
- Typically only used in a multistep approach
- Results within an hour

### EIA for Toxins A & B
- Toxin B is critical for pathogenicity
- Testing for both A & B gives higher sensitivity
- High specificity, lower sensitivity
- Relatively high false negative rate
- More than one stool can be tested
- Results within an hour

Cultures for *C. difficile*

**Selective Anaerobic Culture**
- Does not distinguish between toxigenic and non-toxigenic strains
- In combination with toxin testing, it is most sensitive diagnostic method
- Slow and labor intensive
- Useful in epidemiologic studies

**Cell Culture Cytotoxicity Assay**
- More sensitive than EIA
- Lacks standardization
- Slow turnaround (approximately 2 days)

Algorithm for Diagnosis of C. difficile

1. Patient with diarrhea & risk factor(s) for CDI
2. Send stool for:
   - GDH antigen test (EIA)
   - Toxin A & B test (EIA)
3. GDH positive
   - Toxin positive
   - GDH negative
   - Toxin negative
4. Indeterminate result
   - Perform PCR for tcdB & tcdC genes
5. PCR positive
   - Testing consistent with CDI
6. PCR negative
   - Testing not consistent with CDI
Factors Influencing Treatment Recommendations

- Severity of disease
- Number of previous discrete bouts of CDI
- Underlying infection requiring prolonged use of antibiotics

## Classification of CDI by Severity

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsevere illness (mild to moderate)</td>
<td>Must have all: Nonbloody diarrhea (&lt;6 watery stools/day), afebrile, mild abdominal pain, creatinine &lt;1.5x baseline, WBC &lt;15,000/mm³</td>
</tr>
<tr>
<td>Severe illness</td>
<td>Must have at least one: Advanced age, mental changes, serum albumin &lt;2.5 g/dL, WBC &gt;15,000/mm³, creatinine &gt;1.5x baseline, or abdominal tenderness and ileus</td>
</tr>
<tr>
<td>Severe complicated illness</td>
<td>Must have at least one: Hypotension/shock with serum lactate &gt;2.2 mmol/L, need for ICU confinement for CDI, organ failure, or WBC &gt;35,000/mm³ or &lt;2,000/mm³</td>
</tr>
</tbody>
</table>

Treatment Options for 1st Episode of CDI

- Metronidazole
- Vancomycin (PO only)
- Fidaxomicin
- Tigecycline
- Nitazoxanide
- Rifaximin
- Colonic surgery (colectomy or loop ileostomy)

*Initial antibiotics causing CDI should be stopped if possible*
Metronidazole

- Cost is low
- Shown to be inferior to oral vancomycin for CDI in setting of recurrent and/or severe infections
- Should be used only in mild cases of CDI
- Can be given IV if patient unable to take PO
  - Ileus
  - Shock
  - Toxic megacolon
- Dosing: 500 mg 3 times daily for 10-14 days (PO or IV)

Vancomycin

- Expensive (capsules >$1000 for 10 days)
- Compounded liquid vancomycin cheaper if available
- Superior to metronidazole for moderate to severe CDI
- Can use during pregnancy or breastfeeding
- May increase risk of VRE

Dosing:
- Mild to severe cases: 125 mg PO 4 times daily for 10-14 days
- Severe complicated cases:
  - 250-500 mg PO 4 times daily
  - For ileus or inability to be given enterally, consider 500 mg of vancomycin in 100-250 mL NS per rectum every 6 hours as a retention enema

Fidaxomicin

- Expensive (>\$3000 for 10 days)
- Lower rate of recurrence for non-NAP1/BI/027 strains
  - 8% vs 26% compared to vancomycin for initial CDI
  - 20% vs 36% compared to vancomycin for initial recurrence of CDI
- Narrower antimicrobial spectrum
- Less likely to increase risk of VRE
- Dosing: 200 mg PO twice daily for 10 days

Tigecycline

- Not FDA approved for treatment of CDI
- Limited studies in critically ill patients with refractory CDI
- Can be used as rescue treatment in severe CDI refractory to treatment with vancomycin and/or metronidazole
- Randomized, controlled studies are needed
- Dosing: 100 mg IV, then 50 mg IV twice daily

Nitazoxanide

- Not FDA approved for treatment of CDI
- Expensive (> $1500 for 10 days)
- Comparable efficacy to metronidazole and vancomycin in preliminary studies
- More studies needed
- Dosing: 500 mg PO twice daily for 10 days

Rifaximin

- Not FDA approved for treatment of CDI
- Expensive ($900-1000 for 14 days)
- Effective in CDI unresponsive to metronidazole
- Has been used with tigecycline with or without vancomycin for refractory CDI
- May cause less disruption to normal colonic flora
- More studies needed
- Dosing: 400-550 mg PO twice daily for 14 days

Surgery

- Optimal timing of surgery is uncertain
- Indicated in severe, refractory CDI with:
  - Toxic megacolon
  - Perforation or impending perforation
  - Necrotizing colitis
  - Rapidly progressive/refractory disease with SIRS and multiorgan system failure
  - Peritoneal signs
  - Severe ileus

- Colectomy most beneficial for:
  - Immunocompetent patients aged >65
  - WBC count >20,000 cells/uL
  - Lactate between 2.2-4.9 mEq/L

Surgical Approaches

- Total colectomy with permanent ileostomy
- Subtotal colectomy with ileostomy
- Diverting loop ileostomy with colonic lavage (needs further study)

Initial Recurrence of CDI

- Occurs in ~25% of patients treated with metronidazole and vancomycin
- Symptoms typically similar to those of initial CDI
- Other causes of diarrhea should be considered (i.e. other infections, IBD, IBS, etc)
- Recurrence due to antibiotic resistance is not common
- Nonsevere – metronidazole can be used
- Severe - vancomycin or fidaxomicin recommended

Subsequent Recurrence of CDI

- Risk further recurrences after initial recurrence is between 40-65%
- Treatment strategies:
  - Vancomycin taper or pulsed dosing
  - Vancomycin with rifaximin “chaser”
  - Fidaxomycin for longer duration (21 days)
  - Fecal microbiota transplantation (FMT)
  - Intravenous immunoglobulin (IVIG)
  - Monoclonal antibodies to *C. difficile* toxin(s)

Vancomycin Tapered and Pulsed Dosing

**Tapered dosing:**
- 125 mg 4 times daily for 7-14 days
- 125 mg 2 times daily for 7 days
- 125 mg 1 time daily for 7 days
- 125 mg every other day (4 doses)
- 125 mg every 3 days (5 doses)

**Pulsed dosing:**
- 125 mg 4 times daily for 10-14 days (optional), then
- 125 mg every 2 days or 500 mg every 3 days for 3 weeks

Rifaximin “chaser”

- Limited data but has been effective in small case series
- Given sequentially following therapy with vancomycin
- Use may be limited if rifampin-resistant *C. difficile* is a concern
- Dosing: 400-550 mg twice daily for 14 days

Fecal Microbiota Transplantation (FMT)

- Goal is to restore normal colonic microbiota with the use of intestinal microorganisms from a healthy donor
- Can be given via NG tube, colonoscopy, enema, or capsules with frozen product
- Efficacy of over 90%
- Response seen within 24 hours to 12 days
- Response typically durable and well-tolerated
- Considered most effective therapeutic approach for patients with $\geq 3$ recurrences of CDI

### Donor exclusion criteria for fecal microbiota transplant

**Absolute**

#### Risk of infectious agent
- Known HIV, hepatitis B or C infections
- Known exposure to HIV or viral hepatitis (within the previous 12 months)
- High-risk sexual behaviors
- Use of illicit drugs
- Tattoo or body piercing within six months
- Incarceration or history of incarceration
- Known current communicable disease (eg, upper respiratory tract infection)
- Risk factors for variant Creutzfeldt-Jakob disease
- Travel (within the last six months) to areas of the world where diarrheal illnesses are endemic or risk of traveler's diarrhea is high

#### Gastrointestinal comorbidities
- History of Inflammatory bowel disease
- History of IBS, idiopathic chronic constipation, or chronic diarrhea
- History of gastrointestinal malignancy or known polyposis

#### Factors that can or do affect the composition of the intestinal microbiota
- Antibiotics within the preceding three months
- Major immunosuppressive medications (eg, calcineurin inhibitors, exogenous glucocorticoids, biological agents, etc)
- Systemic antineoplastic agents

#### Additional recipient-specific considerations
- Recent ingestion of a potential allergen (eg, nuts) where recipient has a known allergy to this (these) agent(s)

### Relative exclusion criteria that might be appropriate to consider

#### History of major gastrointestinal surgery (eg, gastric bypass)

#### Metabolic syndrome

#### Systemic autoimmunity (eg, multiple sclerosis, connective tissue disease)

#### Atopic diseases including asthma and eczema, eosinophilic disorders of the gastrointestinal tract

#### Chronic pain syndromes (eg, chronic fatigue syndrome, fibromyalgia)
• Cost per FMT preparation: $485 + S&H
Performing FMT

- Some advocate pretreatment with oral vancomycin (500 mg twice daily for 7 days) when possible.
- Bowel preparation with PEG-based bowel purgative is thought to increase efficacy even if giving FMT by route other than colonoscopy.
- For colonoscopic delivery:
  - 200-300 g of donor stool is suspended in 200-300 mL of sterile saline, homogenized in blender, then strained through gauze pads.
  - Administered via syringe or spray catheter during colonoscopy into the ileum and proximal colon.
- Some advocate also giving an FMT enema the day after colonoscopic FMT

FMT at ROPER ST. FRANCIS

- FMT Protocol started between 2014-2015
- Data from 2015:
  - 25 patients with recurrent CDI received FMT
  - 21 via colonoscopy, 3 via sigmoidoscopy, 1 via NG tube
  - 23/25 (92%) asymptomatic at 8 week follow up
  - No reported adverse events
  - Estimated hospitalization savings of $282,125
  - Microbiota investment: $6,250
Summary

- Risk factors for CDI include recent antibiotic use, recent hospitalization, PPI use, advanced age, suppressed immune system, and others.
- PCR alone or in combo with EIAs is the most common diagnostic tests used now.
- Testing should only be performed on symptomatic patients with risk factors for CDI to avoid overtreatment of patients with asymptomatic colonization.
- Resistance to anti-CDI antibiotics is rarely a problem, so initial recurrence can be retreated with same antibiotic.
- Vancomycin or fidaxomicin are superior for initial recurrence of severe CDI.
- FMT should be considered for all patients with more than one recurrence of CDI.
QUESTIONS?
C. Difficile and Probiotics

- Mechanisms of probiotics:
  - Alteration of intestinal flora (only temporarily)
  - Antimicrobial activity
  - Intestinal barrier protection
  - Immunomodulation
- Benefit of probiotics for prevention of CDI is uncertain
- Benefit of probiotics as adjunct in treatment of nonsevere CDI is suggested in a couple of meta-analyses
- No data supporting use in severe CDI
- Small number of case reports of bacteremia or fungemia attributed to probiotics, but none noted in clinical trials
<table>
<thead>
<tr>
<th>Publication date</th>
<th>Probiotic regimen studied</th>
<th>Study population</th>
<th>Study findings</th>
<th>Similar (commercially available) product*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies in adults</strong></td>
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<tr>
<td>Beausoleil et al (2007)</td>
<td><em>L. acidophilus</em> and <em>L. casei</em> (25 x $10^9$ CFU/day for 2 days, then 50 x $10^9$ CFU/day for duration of the antibiotic course)</td>
<td>89 adults (inpatients)</td>
<td>Antibiotic-associated diarrhea occurred in 16% of treated patients and 36% of patients in placebo group (OR 0.34; 95% CI 0.12 to 0.94; p = 0.05)</td>
<td>Bio-K</td>
</tr>
<tr>
<td>Hickson et al (2007)</td>
<td><em>L. casei</em> (19 x $10^9$ CFU/day), <em>L. bulgaris</em> (1.9 x $10^9$ CFU/day), and <em>S. thermophiles</em> (19 x $10^9$ CFU/day) within 48 hours of starting antibiotic therapy until 7 days after discontinuation</td>
<td>135 adults (inpatients)</td>
<td>Antibiotic-associated diarrhea occurred in 12% of treated patients and 34% of patients in placebo group (p = 0.007; aRR 0.17 [0.07–0.27]).</td>
<td>Actimel (also known as Danactive in United States and Canada)</td>
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<tr>
<td><strong>Studies in children</strong></td>
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<tr>
<td>Kotowska et al (2005)</td>
<td><em>S. boulardii</em> (10 x $10^9$ CFU/day) for duration of the antibiotic course</td>
<td>269 children (72 inpatients and 197 outpatients)</td>
<td>Antibiotic-associated diarrhea occurred in 3% of treated patients and 17% of patients in placebo group. (RR 0.2, 95% CI 0.07–0.5).</td>
<td>Florastor</td>
</tr>
<tr>
<td>Ruszczyński et al (2008)</td>
<td><em>L. rhamnosus</em> GG (2 x $10^{10}$ CFU/day) for duration of the antibiotic course</td>
<td>240 children (134 inpatients and 106 outpatients)</td>
<td>Antibiotic-associated diarrhea occurred in 2.5% treated patients and 7.5% of patients in placebo group (RR 0.33, 95% CI 0.10–1.1).</td>
<td>Culturelle</td>
</tr>
</tbody>
</table>
C. Difficile Vaccine

- Vaccine consisting of detoxified, purified toxins A and B currently being investigated.
- Phase 1 trial showed vaccine was immunogenic and well-tolerated.
- Efficacy to prevent CDI, optimal dose, and immunization schedule not yet established.