• Epidemiology
• Emerging strain
• Pathogenesis
• Resistance
• Recurrence
• Lab testing
• Treatment
Epidemiology

- A leading cause of GI related hospitalization
- $3.2 billion annual cost to health care system
- Gram-positive spore forming bacteria
- Illness range:
  - Asymptomatic carriage
  - Mild diarrhea
  - Colitis
  - Toxic megacolon
Epidemiology

National rate of Clostridium difficile hospitalizations per 1000 nonmaternal, adult discharges [10].

Clin Infect Dis. 2015;60(suppl_2):S66-S71. doi:10.1093/cid/civ140
Epidemiology

Rising incidence

- Incidence rates rose by 23% per year from 2000-2005
- 1990’s: 30-40 cases per 100,000
- 2005: 84 per 100,000
- Incidence nearly doubled in all age groups, predominantly effecting the elderly

Increasing severity (mortality rate, longer hospital stays, complications, treatment failures)

- New at risk populations:
  - Younger healthier populations
    - Not previously exposed to Abx
    - Not exposed to hospital or health care environment
  - Young women in the peripartum period

Emerging strain – NAP-1/027

• Initially isolated in the 1984
• This strain is being isolated more frequently

Factors implicated in outbreaks:

– Increase production of Toxin A and B
  • Deletion mutation of TcdC protein
  • *A/B 16% and 23% higher

– Fluoroquinolone resistance
  • **82% resistance in Quebec outbreak

– Production of binary toxin
  • Thought to act synergistically with toxin A/B


Pathogenesis

1. Alteration of colonic microflora – antibiotics
2. Exposure to C-difficile spores
   - Infected patients
   - Environmental surfaces
   - Inanimate objects
   - Hands of health care workers
3. Toxin production (A/B) and toxin mediated intestinal damage
   - Increased IL-1, IL-8, TNF-alpha
   - Increased intestinal permeability, fluid secretion
   - Protective immune response – asymptomatic carriage
   - Inadequate immune response – diarrhea/colitis

Pathogenesis of *Clostridium difficile* infection.

Antibiotics

Other risk factors:
- Advanced age
- Gastrointestinal surgery
- Inflammatory bowel disease
- Immunosuppression

Abnormal colonic microbiota

Toxigenic *Clostridium difficile* exposure and colonization
or activation of prior colonization

Toxin production

Effective antitoxin response

Asymptomatic carriage

Inadequate immune response

Diarrhea and colitis

Effective antitoxin response and restoration
of colonic microbiota

Resolution

Inadequate immune response and reinfection

Recurrence

Resistance

• Prior to 2000, failure rates for Vancomycin and Metronidazole were nearly identical (3.5% vs. 2.5%)

• Increasing resistance reported with Metronidazole

• Failure rates up to 26%

Recurrence

- Recurrence rates range from 15-30%
- Rates similar between vancomycin and metronidazole

- Relapse – persistence of the same strain
  - Symptoms occur about 14 days after treatment of initial infection

- Reinfection – acquire a new strain
  - Reportedly 33-75% of cases
  - Symptoms usually occur around 40 days after treatment of previous infection

Recurrence

• Risk Factors:
  – Previous episode – 40% risk after 1\textsuperscript{st} recurrence to 60% after 2 or more recurrences
  – Inadequate antitoxin antibody response
  – Persistent disruption of colonic flora
  – Advanced age - >65
  – Continued use of non-C. difficile antibiotics
  – Long hospital stays
  – Continued use of antacid medications
• *Increase severity of repeat episodes

Lab Testing

- EIA GDH antigen
- EIA Toxin A/B
- PCR Testing
- Testing for cure is discouraged
Lab Testing

• GDH antigen
  – Produced by toxigenic and nontoxigenic strains
  – Sensitive not specific for c-difficile
  – Good negative predictive value
  – Often used in screening algorithm as initial test
Lab Testing

- EIA toxin A/B
  - Lower sensitivity than PCR testing
  - Concern for false negatives
  - Often used in algorithm for diagnosis
Lab Testing

• PCR Testing – NAAT
  – Tests for presence of c-diff toxin gene
  – Highly sensitive and specific
  – Does not test for active toxin production
  – False positives a concern (asymptomatic carriage)
Patient with diarrhea and risk factor(s) for *C. difficile* infection

Send stool for:
- GDH antigen test (EIA)
- Toxin A and B test (EIA)

GDH positive  
Toxin positive  

GDH positive  
Toxin negative  

GDH negative  
Toxin positive  

GDH negative  
Toxin negative  

Indeterminant result

Perform PCR for *tcdB* and *tcdC* genes

PCR positive

Testing consistent with *C. difficile* infection

PCR negative

Testing not consistent with *C. difficile* infection
Treatment

• Metronidazole
  – First line for mild disease
• Vancomycin
  – First line for more severe disease
  – First line for IBD
  – Second line agent for drug failure
• Fidaxomicin
  – First line treatment
  – Reduced recurrences (NAP1)
Treatment

• First recurrence – repeat treatment with same antibiotic

• Second Recurrence – A change is warranted
  – 6 week Vancomycin pulse-tapered dosing

• Third or subsequent recurrence
  – Vancomycin pulse-tapered dosing followed by additional strategies
  – Consider FMT

Table 3. Treatment of Recurrent *C. difficile* Infection

<table>
<thead>
<tr>
<th>Type of Recurrence</th>
<th>Treatment Options</th>
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</table>
| Initial recurrence | • 14-day course of oral metronidazole or vancomycin  
|                    | • Consider probiotics |
| Second recurrence  | • Tapered pulse dose oral vancomycin  
|                    |   • 125 mg 4 times daily for 1 week  
|                    |   • 125 mg twice daily for 1 week  
|                    |   • 125 mg daily for 1 week  
|                    |   • 125 mg every other day for 1 week  
|                    |   • 125 mg every third day for 2 weeks  
|                    | • Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy |
| Third or subsequent recurrence | • Tapered pulse dose oral vancomycin (see above)  
| Followed by        | • 14-day course of rifaximin, nitazoxanide, or toxin-binding resins  
|                    | • Consider 1-month course of probiotics starting in the final 2 weeks of antibiotic therapy  
|                    | • Consider intravenous immunoglobulin or fecal bacteriotherapy  
|                    | • Consider chronic low-dose suppressive therapy with oral vancomycin for elderly patients and those with multiple comorbidities |
Treatment

• Human Monoclonal Antibodies (toxin B)

• Bezlotoxumab
  • Prospective, randomized, double blind, placebo controlled-trial of 2655 patients (Phase 3 trial)
  • Monoclonal antibodies infused on day 1 of trx in individuals receiving standard of care Abx for symptomatic C-diff
  • Primary outcome with recurrence at 12 weeks
  • Recurrence 7% Ab, 25% placebo
  • Greatest impact was on highest risk patients

Lowy, I et al. Treatment with Monoclonal Antibodies against Clostridium difficile toxins. NEJM. 2010; 360:197-205.
Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.

Treatment

• Additional Strategies
  – EnteraGam – serum-derived bovine immune globulin
    • Considered a medical food product
    • Requires prescription
    • Used for diarrhea illnesses (HIV, IBS)
    • Thought to bind c-diff toxin A/B
    • Improves gut barrier function/permeability

Treatment

• Investigational agents
  – Various Vaccines currently under study
    • ACAM-CDIFF – phase I volunteer safety and immune response, phase II CDI, phase II CDI prevention
    • Intercell IC84 – phase I volunteer safety and immune response
    • Clostridium difficile vaccine – phase I volunteer safety and immune response
Treatment - FMT

<table>
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<th>size of poop</th>
<th># of people treated</th>
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<tr>
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</table>

THE MOST IMPORTANT THING YOU’LL DO ALL DAY!
FMT

- Rationale: imbalance of intestinal microbiota (dysbiosis) produces disease
  - Initial insult disrupts a balance
  - Re-establish equilibrium
  - Diversity matters
A Rates of Cure

- First Infusion of Donor Feces (N=16) 81.3%
- Infusion of Donor Feces Overall (N=16) 93.8%
- Vancomycin (N=13) 30.8%
- Vancomycin with Bowel Lavage (N=13) 23.1%

P-values:
- P<0.001
- P<0.001
- P=0.008
- P=0.003

B Microbial Diversity

- Healthy Donors
- Patients before Infusion
- Patients after Infusion

Simpson’s Reciprocal Index
- Range: 0-250

FMT

• Early evidence in 4th century China
  – Oral suspension
  – Food poisoning

• First reported in US 1958
  – Fecal enemas
  – Severe pseudomembranous colitis

• Cumulative cure around 91%
FMT

• Installation of normal stool
• How is it done?
  – NGT
  – EGD
  – Colonoscopy
  – Enema
  – Pills

Brandt. ACG.
FMT

- *Retrospective review of 18 pt. received stool transplant for recurrent C-diff
  - 15/18 were disease free at 90 days
- ** Retrospective review of 12 patients who received stool transplant for recurrent c-diff
  - 12/12 had “durable” clinical response
    - Symptom free at 3-5 days
    - Followed from 3 weeks to 8 years

FMT

• Good initial and sustained response to FMT
  – 91% at 3 months
  – 86% at 6 months
  – 80% at 18 months
  – Most recurrence related to repeat abx use

• Effective in critically ill
  • 17 patients with severe colitis – considered for colectomy
  • 88% response rate – avoided colectomy
  • 15/17 symptom free at 3 months
FMT

• RCT – evaluated FMT nasoduodenal route
  – 16 patients
  – Stopped early
  – 93% response with FMT
  – 30% vancomycin alone
• 97% would repeat FMT
• 58% would choose FMT as primary trx
• No major AE reported

Van Nood et al. NEJM 2013.
Brandt et al. AJG 2012.
FMT

• Systematic reviews
  – 13 studies (2 RCT)
  – Overall cure rate 85-89%
    • Upper – 77%
    • Colon – 90%
    • Enema – 78%
  – No major adverse events reported

FMT

• Pill form is likely next generation FMT
  – Recent study in JAMA
    • 20 patients with recurrent c-diff
    • Cure rate was 90%
    • No major adverse events

• Frozen specimens

• Universal donors

FMT

• Current practice
  – Family donor
  – Tested for various infections prior to donation
  – Stool collected and mixed with saline
  – Roughly 300mL slurry
  – Instilled in TI, cecum, ascending, transverse, descending
Guidelines – Diagnostic tests

• PCR for toxin gene is superior to EIA for toxin A/B as standard diagnostic testing for CDI
• Glutamate dehydrogenase (GDH) screening tests for CDI can be used in a 2 or 3 step screening algorithm
• Repeat testing is discouraged
• Testing for cure should not be done
Guidelines - Treatment

• Strong pre-test suspicion for CDI, treatment should be considered regardless of lab results
• Stop inciting Abx if possible
• Mild to moderate CDI – metronidazole 500mg tid for 10 days
• Severe CDI – vancomycin 125mg QID for 10 days
• No response in 5-7 days should prompt consideration for Abx change
Guidelines – Treatment Recurrence

• First recurrence – same Abx, if severe vancomycin
• Second recurrence – pulse dosed vancomycin
• Third recurrence – consideration for fecal microbiota transplantation
Questions?