Update on *C. difficile*: Diagnosis and Therapy Including Fecal Transplant

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OBJECTIVES

• REVIEW THE CHANGING EPIDEMIOLOGY OF C. DIFFICILE

• UNDERSTAND HOW ALTERATIONS IN THE GUT MICROBIOTA RESULT IN SYMPTOMATIC INFECTION

• EXPLAIN HOW TO MAKE THE DIAGNOSIS AND AVOID COMMON PITFALLS

• DISCUSS CURRENT TREATMENT GUIDELINES AND ALTERNATIVE THERAPEUTIC OPTIONS
Epidemiology
EPIDEMIOLOGY

- **Most common cause of infectious diarrhea in healthcare setting.**
  - 3.4-8.4 cases/1000 admissions in acute care hospitals.

Miller MA et al. 2006.
Cohen SH Inf Cont and Hosp Epidem 2010.
**C. difficile**


Miller MA et al. 2006.  
Redelings MD EID, 2007  
Cohen SH Inf Cont and Hosp Epidem 2010.  
Lessa FC, et al. CID 2012:55
RIH DATA

• 2,109 cases of CDI in 1,951 unique patients

• Colectomy occurred in 42 patients (2%)

• 15% died during hospitalization

POPULATIONS PREVIOUSLY AT LOW RISK

• PERIPARTUM WOMEN

• COMMUNITY ACQUIRED

• HEALTHY PERSONS WITHOUT RECENT HEALTHCARE CONTACT

MMWR 2005
RISK FACTORS

- **Age > 65**
- **Exposure to Antibiotics**
- **Hospitalization**
- **Immunosuppression**
- **PPIs**
- **Inflammatory Bowel Disease**

Janarthanan, Am J Gastro; 2012
Kwok, Am J Gastro; 2012
C. difficile is caused by disruption of the normal gut microbiota.
Gut Microbiota

- Gut bacteria = 10 x number of human cells

- Dominated by anaerobes
  - Firmicutes (Gram +)
  - Bacteroidetes (Gram -)

- Important biologic functions
  - Metabolism, immune development and protection from pathogens

Musso G. Diabetes Care; 2010
Qin J. Nature; 2010
Prakash, S. et al. Biologics; 2011
**Clostridium difficile**

- Exposure to antibiotics alters indigenous flora
- Permits colonization & proliferation
- Toxin production by *C. difficile*
  - Inflammation
  - Mucosal injury
  - Fluid secretion

Pepin J. Clin Infect Dis; 2005
MAKING THE DIAGNOSIS
EXAMPLE CASE

• **59 y/o F** treated for ear infection with Cipro

• **Developed diarrhea shortly after finishing antibiotics**
  – *C. difficile* testing negative

• **Symptoms persisted; hospitalized**
  – *C. difficile* positive
### Testing Methods

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Availability</th>
<th>Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic culture</td>
<td>High</td>
<td>High</td>
<td>Limited</td>
<td>Gold standard Research &amp; epidemiologic studies</td>
</tr>
<tr>
<td>Toxin Enzyme Immunoassay (EIA)</td>
<td>Low (75%)</td>
<td>High (83-98%)</td>
<td>Widely</td>
<td>Tests for toxins A +/- B</td>
</tr>
<tr>
<td>C. Difficile Toxin PCR</td>
<td>High (92%)</td>
<td>High (94%)</td>
<td>Widely</td>
<td>Use only in symptomatic disease</td>
</tr>
</tbody>
</table>
Pitfalls

• Know your laboratory’s testing method(s)
  – Do not send repeat PCR testing

• Colonized patients (false +)
  – Do not test asymptomatic individuals/formed stool
  – No value in “test for cure”

• You think the patient clinically has C. difficile
  – Start empiric therapy

• Post-infectious IBS
TREATMENT
MILD-MODERATE INFECTION

- **Discontinue inciting antibiotic(s)**

- **Metronidazole 500 mg 3x/day x 10 days**
  - Effective; cheap ($2 per day)

- **Vancomycin 125 mg 4x/day x 10-14 days**
  - If allergic/intolerant to metronidazole or pregnant
  - Failing to respond to metronidazole within 5-7 days

- **Avoid anti-peristaltic agents**

Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
Severe Infection (uncomplicated)

- **WBC >15,000 cells/mm³**
- **Creatinine >1.5 Baseline**
- **Hypoalbuminemia (<3 grams/dL)**
- **Abdominal Tenderness**

Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
TREATMENT OF SEVERE INFECTION

• SUPPORTIVE CARE
  – CONTINUE ENTERAL FEEDING

• ORAL VANCOMYCIN 125 MG 4X/DAY X 10 DAYS
  – $70-140/DAY.
  – NO GOOD REASON TO EXTEND TO 14 DAYS IF BETTER BY DAY 10

• SUPERIOR TO METRONIDAZOLE FOR SEVERE DISEASE

• NO EVIDENCE FOR EXTENDING DURATION OF THERAPY IF PATIENT ALSO ON NON-CDI ANTIBIOTICS.

Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
COMPLICATED INFECTION

- Admission to Intensive Care Unit
- Hypotension or shock
- Fever > 38.5°C
- Ileus or significant abdominal distension
- Mental status changes
- WBC > 35,000 cells/mm³ or < 2,000 cells/mm³
- Lactate > 2.2 mmol/l
- Evidence of end organ failure (pulmonary/renal)

Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
**Complieated Infection**

- **CT Scanning of A/P**
  - Megacolon, perforation, severe colitis on CT

- **Oral Vancomycin 500 mg 4 x/day**

- **IV Metronidazole 500 mg Q8H**

- **Rectal Vanco 500 mg in 500 mL if patient has an ileus**

- **Surgical Consultation**

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Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
SURGERY

- Hypotension requiring vasopressor therapy
- Sepsis and organ dysfunction
- WBC > 50,000
- Lactate > 5
- Not improving after 5 days of medical therapy

Cohen SH Inf Cont and Hosp Epidem 2010.
Surawicz C. Am J Gastro 2013
RECURRENT DISEASE

• 20% AFTER INITIAL TREATMENT

• 40% AFTER FIRST RECURRENCE

• 60% AFTER 2 OR MORE RECURRENCES

• A SMALL NUMBER OF PATIENTS DO NOT SEEM TO CLEAR THE C. DIFFICILE AND BECOME “VANCOMYCIN DEPENDENT.”
  – 125 MG (1 BOX, 20 EA): $673.99
  – COST OF TAPER: $2864

Walgreens.com
MECHANISM

- **Metronidazole resistance**
- **Persistent spores**
- **Impaired host immune response**
  - **Lower anti-toxin antibody levels in patients with relapsing CDI**
- **Decreased diversity of colonic microflora that normally limits expansion of *C. difficile***.

TREATMENT OF RECURRENT CDI

• 1ST RECURRENCE: SAME REGIMEN AS INITIAL EPISODE

• 2ND RECURRENCE: PULSED VANCOMYCIN
  – 125 MG 4X/DAY X 10 DAYS; 125 MG/DAILY EVERY 3 DAYS FOR 10 DOSES (4 WEEKS)
  – MANY PHARMACIES CAN COMPOUND LIQUID VANCO FOR 1/10 THE COST

OTHER OPTIONS?

• IVIG IN PATIENTS WITH HYPOGAMMAGLOBULINEMIA

• FIDAXOMICIN
  – NON-SYSTEMIC, SELECTIVE ERADICATION OF C. DIFFICILE WITH “MINIMAL DISRUPTION” TO GUT FLORA
  – ROLE IN RECURRENT DISEASE NOT ESTABLISHED

• RIFAXIMIN (XIFAXAN®) “CHASER”
  – OFTEN USED; RARELY EFFECTIVE
  – LIMITED EVIDENCE IN RECURRENT DISEASE

• NITAZOXANIDE (ALINIA®)
  – OFF LABEL; ANTIPROTOZOAL

PROBIOTICS?

• **MAY REDUCE** *(relative risk .34)* **INCIDENCE OF CDI WHEN GIVEN PROPHYLACTICALLY WITH COURSES OF ANTIBIOTICS**

• *Saccharomyces boulardii*
  – “**Non pathogenic**” yeast
  – **Inactivates** *C. difficile* **toxin A receptors**
  – **Weak data for decreased recurrence**

• **Fungemia/bractereemia reported in immunocompromised & critically ill**
Fecal transplants beat antibiotics for curing diarrhea caused by C. difficile

Fecal Transplants: They Work, the Regulations Don’t

Fecal transplants successful in treating intestinal ailments
An infusion of feces from a healthy person is much more effective than an antibiotic in treating C. difficile, a recurrent intestinal infection, researchers find.

Fecal transplants show promise in infection fights
Fecal Microbiota Transplantation

- Administration of feces from a healthy individual to promote colonization with beneficial gut flora

- AKA: Fecal bacteriotherapy, Stool transplant, Fecal Flora Reconstitution

Borody TJ. J Clin Gastro; 2004
HISTORY OF FMT

• **4TH CENTURY CHINA: GE HONG**
  – Human fecal suspension by mouth: “dragon yellow soup”
  – Food poisoning & severe diarrhea

• **1958: EISEMAN**
  – Fecal enemas
  – Pseudomembranous enterocolitis

• **SINCE 1958: EUROPE & NORTH AMERICA**
  – Upper and lower GI administration
  – Refractory and recurrent CDI

Eiseman B. Surgery; 1958
Zhang, F. AJG; 2012
SUSPECTED MECHANISM
**Cumulative Evidence**

- **Recent rapid growth of FMT**

- **Systematic Review**
  - 11 Series; 273 CDI patients
  - 89.7% experienced clinical resolution
  - No reported AEs

Van Nood E, et al. NEJM; 2013
**DOES IT WORK?**

- RCT duodenal infusion of donor feces vs. vanco (+/- lavage)

- Fecal transplant was effective
  - 13/16 (81%) resolved after first infusion
  - 2/3 responded to second infusion (94%)
  - Response rates of 31% vanco and 23% vanco/lavage treated groups

- No differences in AEs between groups

- Effective = Study was stopped early

Van Nood E, et al. NEJM; 2013
WHY IT WORKS

• 61 y/o F with chronic diarrhea x 8 months repeated CDI relapse; rapid improvement after FT

• Fecal samples collected from patient 7 days before, day (0), 14 and 33 days post FT

• Donor sample analysis

• Characterised bacterial composition before and after transplant

Khoruts A. J Clin Gastroenterol; 2010
OUR EXPERIENCE

• 104 Patients; Ages 19-92

• Duration of CDI 1-84 months

• All had relapsed after metronidazole, repeated tapering courses of vancomycin and *S. boulardii*.

• 94% cure with 1 or 2 (n=4) FMT

• 1 transient UC flare post FMT; no other AEs

Kelly C. de Leon L. Jasutkar N. J Clin Gastroenterol; 2012
OUR PATIENTS

• **SAEs**
  – 3 patients with **Cardiovascular events within 4 weeks of FMT**
  – 1 post obstructive pneumonia
  – 1 recurrent cholangitis

• **9 Patients with IBD + CDI**
  – Effective treated CDI
  – Little effect on underlying IBD

• **Willing to Travel**
  – 50% RI, 30% New England
  – 20% other states (Carolinas, Georgia, Ohio, Florida)
  – Desperate inquiries from Hawaii, Italy, Brazil
FMT FOR RELAPSING C. DIFFICILE

• NIH (NIDDK) funded randomized controlled trial

• Co-investigator: Lawrence Brandt (Montefiore)

• Fecal Transplant via colonoscopy vs. sham
  – 48 subjects

• Stool samples: Donor and Subject (before after FMT)
  – Microbiome analysis
  – Alexander Khoruts (University of Minnesota)
**DONOR SELECTION**

- **DONOR:** OFTEN PARTNER, IMMEDIATE FAMILY OR HOUSEHOLD CONTACT
  - NOT NECESSARILY RELATED
  - VOLUNTEER DONORS

- **NO ANTIBIOTICS X 90 DAYS**

- **HEALTHY & “CLEAN LIVING”** (AABB DHQ)

- **EXCLUDE DONORS WITH IBD, AUTOIMMUNE, ATOPIC, NEUROLOGIC DISEASE, MALIGNANCY, FIBROMYALGIA/CHRONIC FATIGUE**

- **CLINICAL TRIAL EXCLUDES DONORS WITH OBESITY OR FEATURES OF THE METABOLIC SYNDROME**

PRE-PROCEDURE TESTING

• **DONOR**
  – HIV 1 and 2, Hepatitis (A, B, C), RPR
  – Stool for *C. difficile, Giardia, Cryptosporidium*, Ova and Parasites & routine bacterial culture for Salmonella, Shigella, Campylobacter, Yersinia and E. Coli O157
  – *Isospora/Cyclospora*, Rotavirus, *Listeria, Vibrio*

• **TIME LINE FOR TESTING**
  – HIV testing must be done within 2 weeks of donation
  – All other testing and AABB DHQ within 30 days

• **RECIPIENT**
  – HIV 1 and 2, Hepatitis (A, B, C), RPR

METHOD OF PROCESSING

• **DOSING**
  – 6-8 SPOONFULS/40-100 GRAMS
  – **DILUTE IN 500 CC SALINE**

• **HOMOGENIZE (SHAKE BOTTLE)**

• +/- **FILTRATION THROUGH GAUZE**

• **DRAWN INTO 60 CC SYRINGES (300-360 mL)**

• **INFUSE AT COLONOSCOPY (OR SIGMOIDOSCOPY) THROUGH THE BIOPSY PORT**
OTHER METHODS OF ADMINISTRATION

• Nasogastric or nasoduodenal tube
  (Aas et al. 2003; Rubin et al 2012)
  – LESS APPEALING TO PATIENTS
  – ASPIRATION RISK
  – ABILITY OF BACTERIA TO REACH/colonize lower GI tract

• Retention enemas
  (Silverman et al. 2010; Kassam et al 2012)
  – VARIABLE PATIENT ABILITY TO TOLERATE
  – DOES NOT REACH BEYOND SPLENIC FLEXURE
  – MAY REQUIRE MULTIPLE TREATMENTS
CONTRAINDICATIONS?

• **NO ABSOLUTE CONTRAINDICATIONS ESTABLISHED (NEUTROPENIA)**

• **CAUTION IN SEVERE IMMUNOCOMPROMISE**
  – AIDS, Bone Marrow Transplant, undergoing chemotherapy, solid organ transplant on full immunosupression.

• **AT RISK FOR INCREASED ADVERSE EVENTS**
  – Decompensated liver disease/ascites
  – anti-TNF, cyclosporine, steroids

CHALLENGES

- SAFETY ISSUES
- SOURCE OF DONOR MATERIAL
- REIMBURSEMENT
- REGULATORY
Key Points

- The epidemiology of *C. difficile* is changing: increased incidence & previously low risk populations.
- CDI results from disruption of the normal gut flora.
- Diagnosis should be based on patient’s history and results of fecal testing.
- Algorithms for management differ depending on severity of disease and alternative therapeutic options exist for recurrent disease.