Clostridium difficile: Ancient Weapons Against a Resilient Enemy

Sam Nourani MS MD
Digestive Health Associates
University of Nevada School of Medicine
Conflicts

• In no state of conflict or conflicted state.
Goals of Lecture

• The Clostridium difficile threat
• Describe the clinic aspects
• Review treatment options
• How to guide for fecal microbiota transplant
• Review of probiotics in this setting
CDC “Threat Report 2013”

• Three “Urgent Threats”
  – Clostridium difficile (and Carbapenem-resistant Enterobacteriaceae, drug-resistant Neisseria gonorrhoeae)
Current Guidelines

• Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) – 2010

• American College of Gastroenterology – 2013
  – Am J Gastroenterology 2013; 108:478-498
Current Guidelines: *Highlights*

- Prevention of C. Diff
  - Greater diligence with antibiotic administration
  - Isolation (when available),
  - Hand Hygiene/Contact Precautions
  - Neither recommends screening of asymptomatic patients or staff
  - Although “moderate evidence” that probiotics (particularly Lactobacillus GG and Saccharomyces boulardii) diminish antibiotic associated diarrhea, neither recommend their routine use to prevent CDI
Clostridium difficile

- Colonizes the GI tract after normal gut flora is altered by antibiotic therapy.
- As of 2013 it surpassed MRSA and is now the most common healthcare-associated infection.
- Significant cause of morbidity and mortality among elderly hospitalized patients.
- Carrier state:
  - 20% of hospitalized patient are C Diff carriers
  - 50% of patients in long term facilities
Classic presentation

• Watery diarrhea is the cardinal clinical symptom.
  – 10-15x/day
• Abdominal cramping
• Low grade fever
• Generally occurs in setting of antibiotic use or 5-10 days following.
  – Culprits: fluorquinolones, clindamycin, cephalosporins, pencillins.
Laboratory Findings

- Unexplained leukocytosis in hospitalized patients even in the absence of diarrhea

- Prospective study:
  - 60 patients
  - Unexplained leukocytosis (WBC>15K)
  - Positive stool C Diff toxin observed 58% cases vs 12% of controls.
  - When unexplained leukocytosis is due to CDAD, diarrhea develops in next 1-2 days.

Am J Med. 2003;115
Testing for C Diff

• PCR testing for toxin A and B genes
  – Highly sensitive and specific, 93% and 97%
  – Results in 1-2 hours.

• EIA for C Diff GDH
  – GDH antigen: essential enzyme produced by all C Diff; toxigenic and nontoxigenic strains
  – Therefore cannot distinguish

• EIA for C Diff toxins A and B
  – Sensitivity of 73% and specificity of 97%.
  – Therefore more than 1 sample needs to be assayed.
  – Three assays needed to approach >95% sensitivity.
Still, Let’s do an X-Ray just to be sure
Radiologic Findings
Pseudomembranous colitis with C diff
Toxic megacolon

• Colonic dilation (>7 cm in greatest diameter)
• Severe systemic toxicity
• Diarrhea may be less prominent due to pooling of secretions in dilated and atonic colon.
• Time to get surgery involved.
Current Guidelines: Highlights

• Treatment of C. Diff
  – Stop offending antibiotics if possible, avoid anti-peristaltics
  – Empiric Rx appropriate when high suspicion
  – Metronidazole 500mg TID x 10-14d (mild/moderate)
  – Vancomycin 125mg QID x 10-14d (severe disease, metronidazole intolerant, pregnant/breastfeeding, or failure to respond 5-7 days)
  – No routine post-Rx testing
  – PO or PR vanco plus IV metro for complicated disease
  – Early surgical evaluation for critically ill patients
Current Guidelines: Highlights

• Recurrent C. diff
  – Same Rx as prior, unless severe (vanco)
  – 2\textsuperscript{nd} recurrence: taper/pulse regimen
  – ACG explicitly recommends consideration of FMT after third recurrence and after taper (SHEA silent)
  – Taper: no data to guide
    • ACG: Vancomycin 125 mg pulsed Q3D for 10 doses
    • Vs. the widely used QID -> TID -> BID -> QD regimen
    • Vs. QID dosing at increasing daily intervals (Q2D, Q3D, Q4D)
New Rx: Surgical

• Consensus belief (and data) that early operative intervention is beneficial in severe disease (marked by shock, pressors, renal failure, MS changes, lactate >5 mmol/l, intubation)

• Traditionally sub-total colectomy with end-ileostomy

• Recent case-series (Univ of Pitt): loop ileostomy with intra-op colon lavage (PEG) and post-op antegrade colonic vancomycin flushes.

• Colon preservation in >90% of patients

• Significant increase in survival c/w historical controls (19% vs 50%)

• 83% laparoscopic procedure

• 93% had ultimate restoration of GI tract continuity.
Probiotic Prophylaxis: *Because everyone asks...*

- Cochrane meta-analysis:
  - 31 trials, 4,492 patients
  - 64% risk reduction (5.5% vs 2.0%) for CDAD
  - No reduction in C Diff incidence
  - “Moderate quality evidence suggests that probiotics are both safe and effective for preventing CDAD in patients who are not debilitated or immunocompromised”
Probiotic Prophylaxis: Because everyone asks...

• PLACIDE trial:
  – RPCT in 5 centers England and Wales; 2,941 patients
  – 21 Day Rx with combined lactobacilli anad bifidobacteria probiotics
  – No reduction in the risk of AAD (RR 1.04, 0.84-1.28)
  – No reduction in the risk of CDAD (RR 0.71, 0.34-1.47)
  – “We identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD”
New Rx (unapproved): Fecal Microbiota Transplant

• Not really a “new” Rx, as descriptions in ancient Chinese medicine texts dating back to the 4th century, and “transfaunation” described in veterinary literature for centuries

• Eiseman (1958) fecal enemas show “dramatic” resolution in 4 cases of pseudomembranous colitis (C Diff not yet described)
New Rx: FMT (open label)

• Open label retrospective case series
  – 77 (of 94 eligible) followed 3-68 months (mean 17)
  – Primary Cure rate: 91-98%
  – Secondary Cure rate: 98%
  – All late recurrences in setting of subsequent unrelated antibiotics
  – No overt adverse events, although 4 pts developed autoimmune diseases later (ITP, Sjogrens, RA)
New Rx: FMT (RCT)

- 43 patients (Netherlands) with >1 recurrence
  - A) Vanco 500 mg QID x 14d
  - B) Vanco 500 mg QID plus bowel lavage
  - C) Vanco 500 mg QID plus bowel lavage and then nasoduodenal infusion (donor pool)
    - *unblinded study with imperfections in methodology
- Terminated early after (unplanned) interim analysis after investigators “became aware” of treatment difference, felt “unethical to continue”
New Rx: FMT (meta-analysis 2013)

• 11 studies, 273 CDI pts
• Resolution 90% overall
  – Higher cure lower vs. upper route (91% vs 82%)
  – No adverse events reported
• Unanswered questions: route, individually identified donors vs. stool banks, “synthetic” stool, methodology variables, FDA regulations
• US blinded RCT underway
How to guide: Donor selection

• History and Physical
• Younger patient
• No to little chronic medical illnesses
• No diarrhea in past 3-6 months
How to guide: Donor selection

• Absolute exclusion criteria
  – Risk of infectious agent
  – HIV, HBV, HCV
  – High risk behavior; sex, drugs, rock n roll.
  – Tattoo or body piercing within 6 months
  – Incarceration
  – Travel within last 6 mos in area endemic for diarrheal illnesses
  – IBD
  – Antibiotic use in past 3 months
  – Immunosuppressive or antineoplastic agent use
  – Recent ingestion of potential allergen (e.g. nuts)
How to guide: Donor selection

• Laboratory evaluation
  – HIV, HAV, HBV, HCV
  – RPR.
  – Stool cultures for enteric pathogens: Salmonella, Shigella, Yersinia, Campylobacter, E. Coli O157:H7, Ova and parasites, Giardia, Cryptosporidium and Helicobacter pylori antigens
  – Clostridium difficile toxin B PCR.
  – CBC and CMP
Stool transplantation

- Recipient discontinues all antibiotics two days prior to transplant.
- Recipient undergoes standard bowel preparation.
- Full colonoscopy
- Administration of prepared liquefied stool throughout the colon.
Post treatment

• Abdominal pain resolves within hours.
• Nausea and appetite resolve by next morning.
• Bowel movement number decreases to 2-3 within 24-48 hours.
• Bowel movement consistent normalizes within days.
Take Home Points

• Current guidelines are rational and quite explicit, initial routine care should generally be concordant with these recommendations

• Metronidazole, Vancomycin, and Fidoxomicin are all effective, ? Cost : benefit

• FMT has a reached a “critical mass” and is likely the most appropriate “salvage” therapy currently available for multiple recurrent disease.
What can you do?

• “An ounce of prevention is worth a pound of cure.”*
• Prescribe antibiotics carefully
• Once culture results are available, check whether the prescribed antibiotics are correct and necessary.
• Order a C. difficile test (C Diff PCR) if the patient has had 3 or more loose stools within 24 hours.
• Discontinue Proton Pump Inhibitor
• Be aware of infection rates in your facility or practice, and follow infection control recommendations with every patient.
  – Use contact precautions (gloves and gowns)
  – Isolation for patients who are suspected to have C. difficile, and continuing those practices for those with positive test results.

*Benjamin Franklin
Thank you

- samnourani@gmail.com
- 858-336-2132