Management of diarrhea in the era of epidemic C difficile infection

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In a patient with liquid stool, which of the following would be most suggestive of non-*C. difficile* diarrhea?

- A. Single negative stool *C difficile* toxin (EIA)
- B. Single negative *C difficile* common antigen
- C. Single positive *C difficile* common antigen with negative *C difficile* toxin (EIA)
- D. Negative fecal leukocytes
- E. Negative stool lactoferrin
Objectives

- Review common challenging aspects treating diarrhea in the era of epidemic *Clostridium difficile* infection:
  - Treatment/Management
  - Diagnosis
  - New and emerging therapies
Diarrhea

- Worldwide 1.6-2.5 million deaths per year, children < 5
- 7th most important cause of death in low-middle income countries after ischemic heart, cerebral vascular disease, HIV/AIDS, perinatal conditions, and COPD
- US: 200 million cases per year
  - 0.99/person/year
  - 41 million individuals sought medical attention
  - 6.6 million provided stool
  - 3.6 million hospitalized
  - Mortality 3100/yr
Acute diarrhea

- 3+ unformed stools/24h
  - Considering more stool passed than usual
  - Considering less form than usual
- <14 days (with exceptions)
- Associated with N/V/gas/abd pain, cramps, tenemus, fecal urgency, gross blood, mucus
- Viral, bacterial, parasitic
<table>
<thead>
<tr>
<th>Category</th>
<th>Descriptor</th>
<th>Prototypes</th>
<th>Nuisance/Life-threatening?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretory</td>
<td>Non-inflammatory, voluminous, watery without fever</td>
<td><em>Vibrio cholerae</em> O1, any enteropathogen</td>
<td>Either</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Nausea, vomiting +/- watery diarrhea</td>
<td>Usually viral or preformed toxin, <em>S. aureus</em>, <em>B. cereus</em></td>
<td>Usually Nuisance</td>
</tr>
<tr>
<td>Inflammatory (Colitis or Proctitis)</td>
<td>Distal gut mucosal inflammation with inflammatory markers in stool. Small volume, grossly bloody, Fever</td>
<td><em>C jejuni</em>, <em>Shigella</em> spp., <em>Salmonella</em>, invasive <em>E. coli</em>, <em>Aeromonas</em>, Non cholera <em>Vibrio</em>, <em>Entamoeba</em>. STD pathogens in MSM</td>
<td>Either</td>
</tr>
<tr>
<td>Persistent Diarrhea</td>
<td>&gt;14 days, intestinal protozoa, bacterial in persistently ill patients</td>
<td>Protozoa, “-sporas”, usual bacterial pathogens in persistently ill patients Non-infectious, IBD</td>
<td>Either, but more nuisance</td>
</tr>
</tbody>
</table>
## Others

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<tbody>
<tr>
<td>Day Care</td>
<td>Low-innoculum pathogens</td>
<td><em>Shigella, Giardia, Cryptosporidium, Rotavivirus</em></td>
<td>Usually nuisance, but can be life-threatening</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Profuse liquid stool, 20%+ recurrence rate</td>
<td><em>C. Difficile</em></td>
<td>Life-Threatening</td>
</tr>
<tr>
<td>Travelers’ Diarrhea</td>
<td>Travel outside usual region, bacterial, poor sanitation.</td>
<td>Many</td>
<td>Nuisance</td>
</tr>
<tr>
<td>Post-Infectious IBS</td>
<td>Diarrhea that persists after bacterial diarrhea, soft, mushy, not-normal</td>
<td>Post-Travel, Post CDI, etc.</td>
<td>Nuisance</td>
</tr>
<tr>
<td>Cruise Ships</td>
<td>Brief period of N/V/Diarrhea</td>
<td>Norovirus</td>
<td>Nuisance</td>
</tr>
<tr>
<td>Immune-compromised</td>
<td>-sporas, viruses, medications</td>
<td></td>
<td>Nuisance, but can be life-threatening</td>
</tr>
<tr>
<td>Intake</td>
<td>Probiotics, diet, meds</td>
<td></td>
<td>Nuisance</td>
</tr>
</tbody>
</table>
History

1893 Pseudomembranous colitis first described as “Diphtheritic colitis”. Finney *Bull Johns Hopkins Hosp*

1935 *Bacillus difficilis* isolated from feces of newborns. Hall & O’Toole *Am J Dis Child*

1950s+ Colitis was attributed to *staphylococcus aureus.*

1960 Doubt cast on above…*S. aureus* not always found. Dearing *Gastroenterology*


2000s *S aureus* may cause disease like *C. difficile*

2011 Fidaxomicin gains FDA approval
A 70 year old female is admitted to your service with liquid stool seven times a day. You are seeing her for the first time, and she has no orders entered yet.

Which of the following is the most appropriate next step?

A. Start on oral vancomycin 125mg PO q6h
B. Start on oral metronidazole 500mg PO q8h
C. C difficile Common Antigen
D. Take more history
E. Call ID
History

- She was recently treated with a course of amox/clav x 7 days for “bronchitis”
- She just finished her last dose the morning of admission
- She usually has one soft stool daily
- On amox/clav she went 3-4x/day mushy
- Now stool is 7x/day mostly liquid
- She has some abdominal discomfort
- She’s still tolerating PO
- WBC is 16k
- Crt 1.6
What to do now?

- A. Start metronidazole 500mg PO q8h
- B. Start metronidazole 500mg IV q6h and Vancomycin 125mg PO q6h
- C. Start vancomycin 125mg PO q6h and order C difficile assay
- D. Order C difficile assay, await result before starting
- E. Start a bulk-forming agent
C difficile testing methods

- **Toxin A/B EIA**
  - Inexpensive, fast, relatively poor sensitivity ~ 70-80%

- **Common antigen GDH**
  - Fast, high negative predictive value, detects toxigenic and non-toxigenic *C difficile*

- **PCR/Molecular**
  - Fast, sensitive and specific, expensive to do on every sample, gaining favor

- **Stool culture**
  - Slow, labor intensive, growth may be non-toxigenic

- **Colonoscopy/Path**
- **Abdominal CT scan**
- **History/Epidemiology**
- **Lactoferrin**
  - ? A role for severity measurement
Combination testing, tests of cure

- Currently IDSA makes no recommendation of best test
- EIA lacks sensitivity, GDH lacks specificity but has good NPV, Molecular is ideal as a single test, but is expensive
  - Test first with GDH
  - Resolve with Toxin (what to do with + GDH, - toxin?)
  - Resolve with Molecular (preferred)
- Cure is determined clinically
  - No test is good as test of cure
    - Risk of asymptomatic colonization
Testing principles-Update

- **Common Antigen**
  - Do only once, repeat only if stools change
  - Common, unlikely CDI
  - + Common, - toxin, same boat as before; clinical judgment should be exercised
  - + Common, - molecular, unlikely there is CDI

- **Only EIA available?**
  - If the first one is negative, it’s still not likely to be CDAD. Don’t go beyond two.

- **Molecular**
  - The result should be reliable

- **Don’t test formed stools. Test only if liquid.**
Metronidazole. First line?

- Metronidazole is still acceptable as first line therapy for MILD disease
  - Metronidazole 500mg PO q8h or 500mg IV q6h
- Vancomycin preferred for anything other than mild disease
  - No data to show that 250mg or 500mg of vancomycin better than 125mg PO q6h.
  - May have better toxin clearing, but no evidence of morbidity or mortality improvement.
Vancomycin vs. metronidazole as first line

- **If Severe, vancomycin**
  - Age > 65
  - Multiple comorbid conditions
  - Abdominal symptoms, peritonitis, radiographic findings
  - Leukocytosis >15k
  - Sepsis syndrome
  - (Pretty much anyone who can get admitted)

- **If Unable to PO, metronidazole 500mg IV q6h**

- **No proven benefit of vancomycin PO + metronidazole IV/PO**
Treatment

- **Stop antibiotics if possible**
- **For first time positive of mild disease**
  - Metronidazole 500mg PO q8h
  - Metronidazole 500mg IV q6hr if unable to PO
  - Alternative vancomycin 125mg PO q6h
  - Treatment generally 10-14d

- **Severe Disease**
  - Vancomycin 125mg PO q6h
  - Metronidazole 500mg IV q6hr if unable to PO
  - Treatment generally 10-14d

- **Generally**
  - No benefit of combining metronidazole and vancomycin
  - No benefit of 250mg or 500mg of vanc PO vs. 125mg
Case

- Vancomycin 125mg PO q6h started on hospital day #1
- Day 2-3, WBC improves, creatinine improves
- Day 3-4, little stool
- Day 5: Big loose, semi-formed BM, creat and WBC stable
- Which of the following is reasonable?
  - A. Increase vancomycin to 250mg PO q6h
  - B. Recheck stool C difficile assay
  - C. This happens…continue therapy as current.
  - D. Add lactobacillus and saccharomyces
  - E. ID Consult
Epidemic strain

- Not generally more resistant to vancomycin or metronidazole
  - Baines: JAC 2008 Aug 7, Emergence of reduced susceptibility to metronidazole in C difficile.
    - Interestingly for 001 ribotype England, NOT 027!!

- Makes more toxin, lacks negative regulator
- Can be more difficult to treat
- Can take longer to respond to therapy
Response to treatment

- Epidemic strain C Diff may take longer to respond to therapy
- Patients should be given 3-5 days on therapy with no improvement before being considered a treatment failure
- Any improvement in stool frequency, consistency, leukocytosis or abdominal pain is improvement
- Not uncommon for patients to improve to not having any stool, but then have a huge stool around this time
Epidemiology

- 10-20% of inpatients on antibiotics develop diarrhea
  - 20% of these from *C. diff.* Bartlett NEJM 2002, Cleary *Dis Colon Rectum* 1998

- Mortality 6-30% when pseudomembranous colitis is present

- 1% of hospitalized patients develop CDAD
  - 20% of cases are community acquired Buchner *Am J Gastro* 2001, Dallal *Annals Surgery* 2002.
Epidemiology

- CDAD continues to rise
- Discharge data:
  - 253 000 hospitalizations affected by CDAD 2005
  - Rate is doubled that of 2000
- Disproportionately affects patients over 65
- Attributable mortality direct and indirect up 7%/17%
  - Classic attributable mortality <1%
- Cost
  - Hospital costs (1990s) $2000-$5000
  - Mean lifetime cost $11000
Epidemiology

- Higher readmission rates
- Higher rates of patients to LTAC
- Number and rate increased 5-fold on death certificates between 1999 and 2004
- Previously low-risk patients are at risk
  - Pregnant and community onset patients are increasingly common, including lack of antibiotics
- More than half the states have Epidemic strain
States with BI/NAP1/027 strain of *C. difficile* (N=40), October, 2008

[Map showing states with BI/NAP1/027 strain of *C. difficile* (N=40), October, 2008]

CDC
Epidemiology

  - Wards with more CDAD patients had higher risk of patients developing CDAD
  - Association almost as strong as antibiotic use
Case

- You made no change to her therapy. Day 6-7, stools back to 1-3x/day, soft but “not perfect”. Feels better, hoping for discharge.

- What next?
  - A. Plan discharge and finish 14 day course of vancomycin 125mg PO
  - B. Recheck C difficle assays
  - C. Add lactobacillus and/or saccharomyces therapy
  - D. Stop PO vancomycin and Discharge
  - E. Consult ID. She still has diarrhea.
Patient was discharged, and she finished 14 days of PO vancomycin. After finishing the PO vancomycin, her stools returned to 1x/day, soft. Five days later you get a call...she has diarrhea. What next?

A. Restart vancomycin 125mg PO q6h
B. Start vancomycin 250mg PO q6h
C. Start metronidazole 500mg PO q8h
D. Get more history
E. Repeat C difficile assay
History

- Further history reveals that the patient is now having 3-4BM/day, soft and mushy, not liquid like it was when she was admitted. Eating ok, no abdominal pain. Next?
  - A. Restart the vancomycin 125mg PO q6h
  - B. Start vancomycin 250mg PO q6h
  - C. Probably not C difficile recurrence, watch the stool a little longer
  - D. Recheck the C difficile assay
  - E. Start a bulking agent.
CDI vs. Post-CDI irritable bowel

- **Life-threatening vs. nuisance**
  - CDI: Usually LIQUID-WATER consistency stool 6-7+/24h
  - Post-CDI IBS: Usually soft/mushy, persistent

- **Has the patient had CDI in past?**
  - Finishing up treatment course, may be post-CDI IBS
  - No treatment, or remote, probably not post-CDI IBS

- **Does it respond to therapy, or is it getting better on its own?**

- **Bulk formers, motility agents may be useful in post-CDI irritable bowel, but may predispose to toxic megacolon in CDI**
Is this Recurrence or post-CDI irritable bowel?

- Get down to the nature of the stool

- Is it...
  - Liquid? Any form in it?
  - >5x/day
  - Like it was before therapy? Better than it was before therapy but worse than baseline?

- Most stool that is better than it was before therapy, but worse than baseline is likely post-CDI IBS
  - Usually does not require treatment
  - Treatment indicated, if it does go back to what it was before treatment

- If persistent, look for other causes
Reservoirs and Colonization

  - Asymptomatic colonization
    - 15-70% of neonates. (<=1 yr)
    - < 5% of normal adults
      - 20% after 1 wk in hospital
      - 50% after >4 wks in hospital
  - 30% of newly colonized patients develop CDAD

- There is a greater chance of positive GDH or positive EIA/molecular that is not representative or disease
- Clinical presentation is key extremely important
- Testing in post-CDI IBS may be misleading
Pathogenesis

Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic toxin A antibody response result in CDAD.


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You elected to observe the patient. Her stools calmed to 1-2x/day, soft and mushy, but 10 days after her last dose of PO Vanc, she has 6 stools in one day that are liquidy. She thinks she overdid the tacos, and she doesn’t call until day 12. Now her stools are 1-2/day again. What do you do?

- A. Restart the vancomycin 125mg PO q6h
- B. Start vancomycin 250mg PO q6h
- C. Probably not C difficile recurrence, watch the stool a little longer
- D. Recheck the C difficile assay
- E. Start a bulking agent.
Case

Day 15 post-therapy: On day 14 and 15, she’s been having 7-8 liquid stools per day. What now?

- A. Restart vancomycin 125mg PO q6h x 14 days
- B. Restart vancomycin 250mg PO q6h x 14 days
- C. Not likely a recurrence, watch a little longer
- D. Start a bulking agent
- E. Add probiotic therapy
How do I treat a recurrence?

- Is it really a recurrence?
- Recurrence usually in first 14 days after therapy
- Recurrence rate is about 20% on metronidazole or vancomycin.
- Recurrence rate is similar with fidaxomicin when dealing with epidemic strain. Lower if non-epidemic
- Same course is usually indicated for first recurrence
  - May advocate going to vancomycin if previously on metronidazole
- Second Recurrence
  - 14-3-14 days?
  - 28 days?
  - Taper?
Treatment

- **Second Recurrence**
  - If continued response, same drug is appropriate—but would advocate using vancomycin instead
  - Many strategies
    - 14 days on 3 days off, 14 days on
    - Extended duration, 28 days
  - Change medication
  - Vancomycin Tapers
  - Metronidazole absorption/transit failure with improved symptoms?
How do I treat a recurrence?

- **Multiple recurrences**
  - No standard set
  - Multiple drugs
  - Ask a consultant
  - Verify it’s actually CDI
  - Colonscopy
    - Rule out Inflammatory bowel
    - *S. aureus*
    - Fungal overgrowth, bacterial overgrowth syndrome?
  - Rule out other medication induced.
- **Probiotics have a limited role**
- **Therapy must be individualized**
- **Binders, bulk-formers not of any benefit**
- **Fecal transplant?**
Follow-up studies in refractory patients

- IgG if possible IgG to toxin A
- Other history
  - Colectomy/Bowel Surgery
  - Medications/Probiotics
    - What goes in affects what comes out
What preventive measures can be taken?

- Prophylactic CDI therapies?
- Prophylactic probiotics?
Probiotics and Prophylaxis

- There are no good randomized clinical trials that suggest probiotics have any beneficial effect.
- There are documented cases of lactobacillus bacteremia and saccharomyces fungemia.
- “Prophylaxis” with these agents has not demonstrated fewer CDAD cases.
- “Prophylaxis” with metronidazole or vancomycin has not been shown to be effective.
- BMJ 335:80 (2007) Hickson et al, Efficacy with a Lactobacillus preparation for prevention of diarrhea. Small sample and does have methodological flaws
- Kale-Pradhan et al, Pharmacotherapy 2010;30(2); 119-126. Role of Lactobacillus in the Prevention of Antibiotic-Associated Diarrhea: A meta-analysis. Data heavy from one particular paper; suspect at best
- Other probiotic preps are under investigation.
What about these?

- **Probiotics** – NOT definitively helpful. Have been documented cases of lactobacillus bacteremia and Saccharomyces fungemia
  - Lactobacillus
  - Saccharomyces
  - Acidophilus
- **Bacitracin** – as effective as vancomycin, but higher residual toxin without more evidence of recurrent colitis
- **Cholestyramine** – NOT demonstrated to be helpful. Runs risk of binding other agents, especially vancomycin PO
Is there going to be anything that works better?

- Yes and No
Therapeutics

- **Accepted**
  - Metronidazole
  - Vancomycin PO
  - Fidaxomicin

- **Some studied success**
  - Nitazoxanide
  - Rifaximin
  - Tinidazole
  - Bacitracin
  - Ramoplanin

- **Controversial**
  - Probiotics
  - Cholestyramine
  - IVIG
  - Vancomycin retention enema
  - Stool transplant

- **Research compounds**
  - tolevamer (failed)
  - monoclonal Ab. A & B
  - Lipoglycopeptide?
  - Oxazolidinone + Fluoroketolide?
  - Vaccine?
Fecal biotherapy

- Randomized clinical trials lacking
- Some evidence of support, but mostly anecdotal
- Considered a last resort
- Need a standardized protocol for aesthetics and safety
MDX-066 (CDA-1) and MDX-1388 (CDB-1)

- Phase II Completed
- Human antibody-based monoclonal antibodies to neutralize CDTA/CDTB
  - Standard of care (metro vs. vanco) + MAb vs. placebo one time infusion.
  - Placebo recurrence rate 20%, consistent with literature
  - MAb recurrence rate reduced 70% compared with placebo (reduces recurrence to about 7%)
- Merck doing further development, phase III beginning soon.
OPT-80-fidaxomicin-Dificid

- APPROVED-5/2011
- NEJM 2/2011
  - 10 days OPT-80 vs. vancomycin PO
  - Similar Cure rates compared with vancomycin 92.1% vs 89.9%
  - Lower recurrence rates compared with vancomycin, 13.3% vs 24%
  - Global Cure rates higher compared with vancomycin, 77.7% vs. 67.1%
- Second Phase 3 data similar
- Newest data-Second Phase 3 trial
  - As above, but recurrence rate similar to vancomycin when dealing with epidemic strain
    - Recurrence trends toward favoring fidaxomicin in second trial, but not statistically significant.

Optimer Pharmaceuticals Press Release 11/10/2008
Where does fidaxomicin fit?

- Similar cure rates vs. vancomycin
- Lower recurrence risk vs. vancomycin (all comers)
  - Similar recurrence risk vs. vancomycin (epidemic strain)
- Response may be better in fidaxo patients with multiple concomitant antibiotics, immunecompromised.

- Cost
  - Vancomycin capsules ~$1200-1800
  - Vancomycin IV reconstituted oral solution ~$40-100
  - Fidaxomicin ~$2500

- Our approach
  - ID restricted
  - CDI failure x1 with vancomycin in previous 30 days or concomitant antibiotics or immunecompromised.
Outpatient Diarrhea

- Get a full history
- Get down to the poop
- Medication history
  - Abx associated diarrhea medications
  - Other laxatives/cathartics
  - OTC/Natural remedies
- Travel History
- Activities
- Dining History
- Sick Contacts
- Duration/Recurrence
Outpatient diarrhea

- Stool Ova and Parasite
  - Giardia
- Stool culture
  - Salmonella, Shigella, Yersinia, Campy
- Immune-compromised
  - Modified Acid-fast stains for “-sporidosis”
- C Difficile assays
Outpatient Diarrhea

- Base CDI therapy on index of suspicion
- Base any diarrhea therapy on index of suspicion
- Non-toxic and controllable stools?
  - It’s ok to observe without therapy!
Inpatient Diarrhea

- Get a full history
  - Start prior to or after admission?
- Get down to the poop
- Medication history
  - Abx associated diarrhea medications
  - Other laxatives/cathartics/tube feeds
  - OTC/Natural remedies
- Duration/Recurrence
- Some of the outpatient questions apply too
Inpatient diarrhea

- **Stool Ova and Parasite**
  - Generally don’t check unless admitted <48h and diarrhea started prior to admit

- **Stool culture**
  - Salmonella, Shigella, Yersinia, Campy

- **Immunocompromised**
  - Modified Acid-fast stains for “-sporidosis”

- **C Difficile assays**

- **Fecal WBC, lactoferrin?**
Inpatient Diarrhea

- Base CDI therapy on index of suspicion
- Base any diarrhea therapy on index of suspicion
- Doesn’t sound quite like CDI, and the stool is controllable, and the patient is “stable?”
  - It’s ok to observe without therapy!
  - Have a threshold to start.
Is it ok to use a bulk-former?

- Generally bulk-formers of little benefit
- If fairly certain CDI is not active, ie Post-CDI irritable bowel
  - Probably ok to use bulk-former
  - Probably ok to use gut slowing agent
- But monitor closely for recurrence or worsening
Summary

- Test stool where suspicion is high
- Do not treat asymptomatic disease
- Epidemic strains appear to produce more toxin
- Epidemic strains are more virulent, but not resistant
- Single recurrence does not indicate resistance
- Vancomycin PO is preferred for severe disease
  - Metronidazole is still first line for mild disease
- Surgical intervention indicated for severe cases/megacolon/obstruction
- Pursue other causes if CDI evaluation continues to be negative