Today

1. What are the best diagnostic tests for CDI?
2. How do I choose appropriate therapy for my patients with CDI?
3. When should I get a surgery consult for my patient with CDI?
4. How do I treat patients with recurrent CDI?
Common Risk Factors

- Age over 65
- Antibiotics – 2 months
- Multiple antibiotics
- Recent hospitalization
- Co morbid conditions
- Immunosuppression

New Risk Factors

- Community acquired
- Pregnant women
- IBD patients
- Cirrhosis
- PPIs
Epidemiology of Community-Acquired CDI

- Olmsted County 1991 – 2005
- Increased C. difficile rates – both inpatients and outpatients
- Outpatients – 41%
- Fewer with usual risk factors such as antibiotics

Khanna, et al Am J Gastroenterology 2011

Community Acquired vs. Hospital

- Younger
  - 50 yo vs 72 yo

- More women
  - 76% vs 60%

- Fewer with severe disease
  - 20% vs 31%
**CDI and IBD**

Patients hospitalized for CDI and IBD compared to only CDI or only IBD

- Younger (average age 42)
- More likely to die (4x)
- In hospital longer (3d)

(Ananthakrishnan et al, Gut 2007)

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**C. difficile in IBD**

- Rates have increased
  - Two fold - Crohn's
  - Three fold - Ulcerative colitis
- More severe disease
- May not have had antibiotics
- Risk factors:
  - Colonic disease
  - Immunomodulator therapy
- May not see pseudomembranes on colonoscopy
CDI and Proton Pump Inhibitors (PPI’s)

- 2 recent meta-analyses
- Both find increased risk of CDI
  - 65% increase in one study
  - Increased risk with PPI and antibiotic
  - Decreased risk with H₂RA
- Recommend prospective study – unlikely


1. What are the best diagnostic tests for CDI?
Diagnostic Testing

- Detection of toxin in stools
- Tests are imperfect and evolving
- Test only patients with diarrhea since 80% of infants and 5-15% of adults are carriers

Diagnostic Tests

- Toxigenic culture
- Cytotoxin B tissue culture
- Enzyme immunoassays (EIA) for toxin
- GDH antigen (Clostridial antigen)
- Polymerase Chain Reaction (PCR) – gene for Toxin B
EIA Tests

- Toxin A only – will miss 1-3% of Toxin B positive, A negative strains

- Toxins A + B
  - Specific but not sensitive

- Should not be stand alone tests

GDH Tests

- GDH is common antigen, glutamate dehydrogenase, Clostridial but not specific for toxin producing \textit{C. difficile}

- Very sensitive but not specific

- Used as screen
  - If negative – no further testing
  - If positive – second step is confirmatory testing like PCR
PCR

- Nucleic acid amplification test – PCR for Toxin B gene
  - Very sensitive and specific

- PCR real time
  - Expensive but quick and accurate
  - Rapid diagnosis can reduce hospital costs

Current Practice in Hospital Labs

- University Hospitals
  - 2/3 use PCR as stand-alone test
  - 1/3 use GDH with PCR confirmatory (cheaper)

- Community Hospitals
  - Some still use EIA test

Personal communication. Peter Gilligan, UNC, 2012
**C. difficile Tests**

- Can now use rectal swabs for PCR
  - Useful if patient has ileus
- Do not routinely test 3 stools
  - Low yield
- Don’t test for cure (usually)
  - Culture and toxin can stay positive for a month


**A Final Take Home Point**

PCR is probably the new gold standard

BUT diagnostic tests are imperfect

If you think your patient has *C. difficile* and is sick, start empiric therapy
2. How do I choose appropriate therapy for my patients with CDI?

3 Effective Oral Antibiotics for CDI

- Metronidazole
  - 500 mg tid x 10 days
- Vancomycin – (FDA approved)
  - 125 mg qid x 10 days
- Fidaxomicin – (FDA approved)
  - 200 mg bid x 10 days
What is Fidaxomicin?

- Macro cyclic antibiotic – Poorly absorbed
- Equivalent to vancomycin – mild to moderate CDI
- Fewer recurrences with fidaxomicin:
  - 15% (F) vs 24% (V)
  - Thus the cost is twice that of vanco
- Not tested in severe cases or recurrent cases

Cost of Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 day cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole pills (500mg)</td>
<td>$15-30</td>
</tr>
<tr>
<td>Vancomycin pills (125 mg)</td>
<td>$1,100</td>
</tr>
<tr>
<td>IV vancomycin given orally</td>
<td>$40-300</td>
</tr>
<tr>
<td>Fidaxomicin (200mg)</td>
<td>$2,700</td>
</tr>
</tbody>
</table>

Louie et al, NEJM 2011;364:422
CDI Treatment Depends on Severity

- Mild to Moderate

- Severe

- Severe and Complicated

Cohen et al. IDSA/SHEA guidelines, Infection Control Hosp Epi, 2010; 31:A21
Surawicz et al. ACG guidelines, Am J Gastroenterol (in press 2013)

Mild to Moderate CDI

- Diarrhea with no criteria for severe CDI

- Diarrhea $\geq$ 3 loose-stools/24-hours
Treatment of Mild to Moderate CDI

- Stop intercurrent antibiotics if possible
- Metronidazole
  - 500 mg tid x 10 days p.o.
- No antiperistaltics
  - Data poor but medico-legally risky
  - Lose a parameter to follow

CDI Treatment Depends on Severity

- Mild to Moderate

- Severe

- Severe and Complicated
Simple Clinical Diagnosis for Severe CDI

• Hypoalbuminemia (< 3) AND

• Abdominal distension/tenderness and/or

• Elevated WBC (> 15,000)

How did we come up with these criteria?

• Criteria have not been validated
  – Good negative predictive values but,
  – Poor at predicting poor outcomes

• Multiple scoring systems for CDI severity
  – Clinical, lab, x-ray criteria
Comparison of Clinical Severity Score Indices for CDI

- Tested all 8 scoring systems
- Prospective evaluation – 184 pts
  - non severe- 165
  - severe- 19
- Severe defined as
  - ICU
  - Surgery
  - Death

Fujitani et al, Infect Control Hosp Epi, 2011;32:220

Result

- None of the scoring systems was very good
- Four criteria correlated with severe CDI
  - Abdominal distension
  - Fever
  - WBC > 20,000
  - Albumin < 3
Simple Clinical Diagnosis for Severe CDI

- Hypoalbuminemia (< 3) AND

- Abdominal distension/tenderness and/or

- Elevated WBC (> 15,000)

Treatment of Severe CDI

- Vancomycin 125 mg qid x 10 days

- If not better, can increase Vancomycin to 1-2 gm/day
  empiric but may work
CDI Treatment Depends on Severity

• Mild to Moderate

• Severe

• Severe and Complicated

Severe and Complicated CDI

• Admission to ICU
• Hypotension
• Fever > 38.5 °C
• Ileus
• WBC > 35,000 or < 2000
• Serum lactate > 2.2 mmol/L
• Evidence of end organ failure (renal or pulmonary)
Treatment of Severe and Complicated CDI

Vancomycin 500 mg qid p.o. and Metronidazole 500 mg tid IV

• Continue enteral feeding if possible
  – Nutrition for microbiome

• Consider vancomycin enemas
  – 500 mg IV vancomycin in 100 ml NS via rectal tube, clamp 60 min. Repeat qid
Unproven Therapies

- Tigecycline IV
- Nitazoxanide p.o.
- IVIG (immune globulin)
- Fecal bacteriotherapy

Fulminant C. difficile Infection – Fecal Bacteriotherapy

- First reported surgical series: patients given stool enemas from healthy donors and showed clinical improvement
  (Eiseman 1958, Bowden, Amer Surgeon 1981)

- Case report - 68 y o man with fulminant CDI who improved after stool enema, daughter donor
  (You et al, Ann Int Med 2008)

- Anecdotal cases with success
Medical Treatment Summary

<table>
<thead>
<tr>
<th>Mild to moderate</th>
<th>Metronidazole orally (500 mg tid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Vancomycin orally (125 mg qid)</td>
</tr>
<tr>
<td>Severe + complicated</td>
<td>Vancomycin orally (500 mg qid) and metronidazole IV(500 mg tid)</td>
</tr>
<tr>
<td></td>
<td>Consider vancomycin enemas if ileus, toxic colon</td>
</tr>
</tbody>
</table>

Patient Evaluation on Daily Rounds

- Stools
  - Number and consistency
- Temperature
- Blood pressure
- Abdominal exam
  - Distension
- WBC count
- Albumin
- BUN/Creatinine
A Case – IBD + CDI

45 y o man referred from K C jail
Crohn’s diagnosed age 18
Resection – probably colon and some ileum
Off meds several years
Recent diarrhea, pain L > R

One Month Later

CT enterography
  2 segments thickened small bowel

Colonoscopy – ileitis, normal colon

Rx - Mesalamine
  Budesonide
Two Months Later

Better on Rx, less diarrhea and pain

Transitioned to azathioprine but still on budesonide

One Month Later

Admit to HMC – bloody diarrhea

Chills, HA, 40 lb wt loss

Fever 101.5°

Tender abdomen
Stool Testing

Initial stool  Toxin A (-)
Later  PCR toxin B +
Initial Treatment

Vancomycin (125 mg qid) + Lactobacillus (no good reason for this)

Then increased vancomycin (500 mg qid)

Added vancomycin enemas
Several days later...

Increased Abdominal Distension

Added IV metronidazole, D/C budesonide

NPO

Vancomycin per NG

Finally got better

IBD & severe CDI, but no colectomy needed
C. difficile and IBD

- Probably should start with vancomycin
- Probably continue immunosuppressive therapy (?maybe not steroids)
- Test all patients with flares
- Severe colitis; consider empiric CDI therapy and IBD therapy
- Seeing cases of acute CDI with IBD (trigger or co-infection?)
- J pouch infections occur

3. When should I get a surgery consult for my patient with CDI?
Case

• 56 y o man S/P liver transplant, with adenocarcinoma at the splenic flexure, detected on screening colonoscopy
• Preop: WBC 8100, Alb 3.5, Cr 1.5
• Left hemicolecctomy
• Next 3 days
  – Incisional pain
  – Ambulating
  – No flatus

Hospital Course

Day 5
  – ↑ abdominal distension and pain
  – WBC 18,000

Day 6
  – Dilated colon, transverse colon 13-14 cm diameter
  – Pain, fever, diarrhea
  – WBC 24,600
  – Albumin 2.2.
  – Cr 2.3
  – C. difficile Toxin A +
Treatment

Vancomycin p.o. + metronidazole IV

But:
- ↑ Diarrhea
- ↑ Colon distension

Course

- ↑ Creatinine
- ↑ WBC
- ↓ Albumin
- No response to maximal medical therapy
- Back to OR at day 10 for Colectomy / Ileostomy
Post-op Course

- Rocky post-op course but eventually did well
- WBC 10,300; Creatinine 1.2

Does the literature help us define criteria for surgical intervention?
Impact of Emergency Colectomy for Fulminant C. difficile Colitis

• January 2003 – June 2005, retrospective series of 161 patients
  – Surgery – 38
  – Medical Rx– 123

• In ICU due to CDI or ICU with CDI severe enough to warrant ICU

• Outcome 30 Day mortality

Indications for Colectomy

<table>
<thead>
<tr>
<th>Colectomy</th>
<th>38 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent shock</td>
<td>15</td>
</tr>
<tr>
<td>NR to med Rx</td>
<td>10</td>
</tr>
<tr>
<td>Megacolon</td>
<td>11</td>
</tr>
<tr>
<td>Perforation</td>
<td>2</td>
</tr>
</tbody>
</table>

Mortality – Overall

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Rx</td>
<td>58%</td>
</tr>
<tr>
<td>Surgery</td>
<td>34%</td>
</tr>
</tbody>
</table>
Predictors of 30 d Mortality

- ↑ Lactate > 5
- ↑ WBC > 20
- Shock/pressors
- Age > 75

Coloctomy survival benefit in this group

When to Get a Surgery Consult

- Hypotension / shock
- Sepsis
- Renal or pulmonary failure
- WBC > 50,000
- Lactate > 5
- Progressive abdominal tenderness or distension
- Severe and complicated and not better after 5 days of maximal medical therapy
**Earlier Surgical Consultation → Better Survival**

- Markers of severity have good negative predictive value but - - -
- Poor positive predictive value for need for colectomy
- When to operate?
  - More negative predictors
  - Before point of no return

Sailhamer et al, Arch Surg 2009;76:418
Butala, Divino Ann J Surg 2010;200:1315

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**Diverting Loop Ileostomy – Another Option**

- Loop ileostomy with PEG + vancomycin colon lavage
- Laparoscopic in most
- Colon preserved in most
- 80% hooked back up

### Loop Ileostomy – Results

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of pts</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2011</td>
<td>42</td>
<td>8/42 (19%)</td>
</tr>
<tr>
<td>Prior to 2011</td>
<td>42</td>
<td>21/42 (50%)</td>
</tr>
</tbody>
</table>

4. How do I treat patients with recurrent CDI?
RCDI Case

• 42 year old woman
  – Retained placenta after birth of first son
  – Prolonged hospitalization plus antibiotics
  – *C. difficile* – 3 episodes
    • Rx Metronidazole x 2
    • Final – Vancomycin taper and *Saccharomyces boulardii*

RCDI Case

• However, 10 months after 2nd son
  – Diarrhea
  – Recurs in 1 week, bloody
  – No intercurrent antibiotics
  – Continuous Vancomycin 9 mos
    • Rifampin
    • Taper
    • Still recurs
• Neither son with diarrhea
• Sees me in the GI clinic
• How to treat?
Treatment of Recurrent CDI (RCDI)

- RCDI is recurrence of CDI within 30 days of completion of therapy
- One recurrence – 10-20%
- After first recurrence – 40-60%

Pathophysiology – RCDI

- Impaired immune response
  - Patients with RCDI had ↓ IgG to Toxin A
  - In a vaccine study, lower levels of anti-toxin B Ab were associated with recurrence
- Altered colonic microbiota

McFarland et al, Am J Gastroenterol 2002;97:1769
Kyne, Lancet 2001
Leav et al, Vaccine 2009
RCDI – Evidence of the Altered Microbiome

• Evaluated microbiome in 7 pts with CDI and 3 controls
• Bacteroidetes and Firmicutes = majority
• 3 developed RCDI
  – Microbiota was less diverse
  – More other bacteria

**Treatment of RCDI**

- Repeat antibiotics are needed - with Metronidazole or Vancomycin
- Pulse and taper decreases recurrences
- I think pulse more important than taper
- Do not use Metronidazole long term

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**RCDI – Vancomycin Regimen**

- Vancomycin 125 mg qid x 10 days, then Vancomycin 125 mg a day every 3 days x 5
- Simple and not too expensive
“Rifaximin Chaser”

- 7 patients with very severe RCDI (5 – 7 episodes)
- Vanco, then 2 wk rifaximin
- 6/7 – no further relapses
  (Johnson et al, Clin Inf Dis 2007)
- Later series: 4/6 responded
  (Johnson, Anaerobe 2009)
- Not FDA approved for this

Fidaxomicin

<table>
<thead>
<tr>
<th></th>
<th>Fidax</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer recurrences</td>
<td>15.4%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Not with Nap1BI</td>
<td>24.4%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

- Approved but not for RCDI
  (Louie et al, NEJM 2011)
Immune Approaches

- IVIG – case reports
- Vaccines – 5 yrs away
- Oral monoclonal antibody to toxin A and B as adjunct to antibiotics promising but still in trials – phase 2 trial
  - Decreased recurrences
  - Even Nap 1 strains
  - Phase 3 trial starting

Lowy et al, NEJM 2010; 362:197

Probiotics

- *Saccharomyces boulardii*
  - Decreased recurrences by 50% with adjunct antibiotics
  - Recurrences with high dose Vancomycin
    - (15.7% vs 50%) but not with low dose Vancomycin or Metronidazole

- Risks:
  - Fungemia in immunosuppressed and in ICU patients with central lines

McFarland et al, JAMA 1994;271:1913
Surawicz et al, Clin Infect Dis 2000;31:1012
Probiotics- RCDI Treatment

Meta-analyses –
  – Benefit of *S. boulardii*
    41% risk reduction
    • McFarland, AM J Gastro 2006
    • Cochrane Review 2008

*S. Boulardii*
  – Protease inactivates toxin receptors *in vitro*
  – May explain efficacy

Probiotics- RCDI Treatment

• Other studies
  ◦ *Lactobacillus plantarum*
    • Small trial, benefit,
      Wullt Scand J I D 2003
  ◦ *Lactobacillus GG*—no benefit in 2 small trials
    Poehapin Am J Gastro 2000; Lawrence J Med Microbiol 2005
Probiotics and Prevention of AAD

- AAD (Antibiotic associated diarrhea)
- Prevention evidence good for *Saccharomyces boulardii* and *Lactobacillus GG*
- But this does not translate into prevention of CDI.

Our Patient 6 Months Later

- 3 recurrences
  - Vancomycin taper / pulse
  - *Saccharomyces boulardii*
    - Recurs within 1 week
- Stool transplant via colonoscopy
  - Husband donor
- No further recurrences since 2004
When was Stool Transplant First Documented?

A. 1700 years ago in China?

B. 1958 in post op patients in Denver?

C. On Grey’s Anatomy in 2008?

Answer = A

1700 years ago in China, 4th Century used human feces to treat severe diarrhea; 16th century used infant feces, called “yellow soup”

Grey’s Anatomy – 2008 “In the Midnight Hour”, done in emergency room

**Fecal Enemas**

- Fecal enema as adjunct in the treatment of pseudomembranous enterocolitis – 4 patients

- Fecal enemas to treat 16 patients with severe *Clostridium difficile* disease

  - Eiseman et al, Surgery 1958; 47:178-83
  - Bowden, Amer Surgeon, 1981; 47:179-83

**Successful Treatment of RCDI**

- Fecal enemas
  - 1 case RCDI

- Rectal instillates of microbes mixture of 10 aerobic and anaerobic species in 6 pts with RCDI

  - Schwan, Lancet,1983;2:845
FMT – Methods

- Colonoscopic route – healthy spouse donor stool to right colon via colonoscopy
- Stool Per NG tube – two series
- Per enema, done at home

Persky and Brandt, Am J Gastroenterol 2000; 95:3283
Aas et al, Clin Inf Dis 2003; 36:580
Silverman et al, Clin Gastro Hep 2010; 8:471

Terminology – Restoring the Normal Microbiota

- Fecal bacteriotherapy
- Fecal enemas
- Fecal flora reconstitution
- Stool transplant

Fecal microbiota transplant (FMT) = now the new accepted terminology
Results of FMT for RCDI - Systematic Review

- 317 patients, 27 papers, stool delivered by all routes
- 92% success
  - 89% after one treatment
  - 5% after retreatment
- Lowest response rate with NGT-76%

My Experience – 36 patients

Very successful
- 1 recurred with antibiotic treated with probiotics, resolved
- 2 re-transplanted with different donor with success
- 2 patient with Crohn’s – C. difficile gone
  but not the Crohn’s
- 2 with enemas alone
The Donor

- Screening
  - Blood
    - Hepatitis screen
    - HIV
    - RPR
  - Stool
    - Enteric pathogens
    - O + P
    - *C. difficile* (tell lab to test solid stool)
    - Giardia and Cryptosporidia antigens
- Donor Prep – laxative night before

Patient Prep

- Colonoscopy – standard
- Infuse 5 – 60 cc syringes of emulsified stool into cecum
- Loperamide immediately after
- Excellent results
Why Does It Work?

- Microbiota pre and post FMT - 1 case
  - Pre
    - Deficient in Bacteroidetes
    - Had more atypical populations
  - Post (2 wks)
    - Resembled donor stool
    - Bacteroidetes dominated
  - Post (33 days)
    - Bacteroidetes dominated

Khoruts et al, J Clin Gastro 2010; 44:354
Results

• 77 patients – 56 women
  – Duration – 11 months average
  – Age 22 – 88 (65 mean)
  – Ave 5 recurrences
  – Follow-up 3-68 months
• Resolution – within 6 days commonly
  – 91% immediate cure
  – Of 7 failures
    • 2 retransplanted
    • 4 retreated
### Duodenal Infusion of Donor Feces for RCDI

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 2 gm/day for 14 days</td>
<td>13</td>
</tr>
<tr>
<td>Vancomycin 2 gm/day for 4 days with gut lavage but no donor feces infusion</td>
<td>13</td>
</tr>
<tr>
<td>Vancomycin 2 gm/day for 4 days with gut lavage and donor feces via nasoduodenal tube</td>
<td>16</td>
</tr>
</tbody>
</table>
Results Vancomycin Resolution of RCDI

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin alone</td>
<td>4/13 (31%)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin and gut lavage</td>
<td>3/13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Vancomycin and gut lavage and donor stool</td>
<td>13/16 (81%)</td>
<td>2/3 responded to second infusion</td>
</tr>
</tbody>
</table>

Van Nood et al, NEJM, Jan 16, 2013

Does It Work And Is Colonoscopy Better?

- NIH funded RCT
- Drs. Colleen Kelly (Brown University) and Lawrence Brandt (A Einstein University)
- Control – colonoscopy with the patient’s own stool
- 4 patients enrolled so far
Unanswered Questions – if it Works

1. Is it safe?
2. Donor
   – Screening criteria and who pays
3. Best route, how much
   – Frozen OK?
   – Donor pool?
4. Are there other alternatives?

Standard Frozen Stool Prep

• 43 patients – RCDI
• Prescreened donor pool in many (two donors used for 33 patients)
• Efficacious – 70 - 92%
  Some retreated
  Some gas + irregular BMs - transient
• Frozen stool - odorless
  Hamilton et al, Am J Gastroenterol 2012; 107:761-767
  (Alex Khoruts)
My Opinion

- If we are still doing stool transplant in 5 years, scientists have failed us

- We should be able to identify and culture the essential “good” bacteria

Stool Substitute for RCDI – “RePOOPulating” the Gut

- Isolated 33 strains of bacteria from a healthy 41 y.o. female donor

- Synthetic stool given via colonoscopy

- Successful treatment of 2 RCDI patients – 6 month follow up

Petrof et al. Microbiome 2013; 1:3
RCDI Treatment

• 1st recurrence
  – Repeat initial regimen
• 2nd recurrence
  – Vancomycin pulse regimen
• 3rd recurrence
  – Consider FMT

Summary

• PCR for Toxin B likely new gold standard stool test
• Mild to moderate disease
  – Metronidazole
• Severe Disease
  – Vancomycin
• Severe and complicated disease
  – Vancomycin and IV Metronidazole
  – Surgery consult
• Recurrent CDI – a treatment challenge
Thank you