Question 1

A 42-year-old man presents with severe diarrhea 2 weeks after receiving a course of antibiotics. On exam, there is mild abdominal tenderness, and an abdominal CT scan done in the emergency room shows colon wall thickening in the left colon. Stool for *C. difficile* toxin by PCR is positive. He is started on vancomycin 125 mg four times a day. Two days later he has abdominal distension, and the serum albumin has dropped. Which is the most appropriate next step?
Question 1

A. Oral metronidazole should be added.
B. IV vancomycin should be given with IV metronidazole.
C. IV metronidazole should be given and vancomycin can be increased
D. Rifaximin should be added to the metronidazole.
E. Metronidazole enemas should be given.

Question 2

A 50-year-old woman has had two episodes of *C. difficile* infection. Each time she was retreated with antibiotics, first with 2 weeks of metronidazole and then with 2 weeks of vancomycin. The diarrhea resolved with treatment, but symptoms recurred within 5-7 days after antibiotics are discontinued and stool test is positive for *C. difficile*. Which is the most appropriate management strategy?
**Question 2**

A. Six weeks of high-dose metronidazole, followed by a tapering dose  
B. Ten days of vancomycin followed by a pulse regimen  
C. Cholestyramine powder given with antibiotics  
D. A probiotic such as VSL #3 as an adjunct to metronidazole  
E. Rifampin monotherapy

**Question 3**

A 65-year old man presents with severe diarrhea 2 weeks after receiving a course of antibiotics for hip osteomyelitis. On exam, there is moderate abdominal tenderness and WBC 16,000. Stool for *C. difficile* toxin by PCR is positive. He is started on high dose vancomycin and IV metronidazole. Two days later he has more abdominal distension, a CT scan shows colon wall thickening. The serum lactate is 3.4. Which is the most appropriate next step?
Question 3

A. Oral metronidazole should be added
B. The antibiotic for osteomyelitis should be stopped.
C. Oral vancomycin should be stopped and IV metronidazole should be increased
D. A surgery consult is indicated.

C. difficile Update – Difficult Patients

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

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?

CDI Treatment Depends on Severity

• Mild to Moderate

• Severe

• Severe and Complicated

Cohen et al, IDSA/SHEA guidelines, Infection Control Hosp Epi, 2010; 31:431
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 one or both
• Abdominal distension/tenderness
• 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
Treatment of Severe and Complicated CDI

- 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

3. What about Immune Suppressed Patients?
Immune Compromised Patients

- Higher rates of CDI
  - Post transplant 3 – 11%
- Risks
  - Cancer and Chemotherapy
  - Solid organ transplant (especially lung)
  - Cirrhosis
  - Steroids
- Any diarrheal illness: test for *C. difficile*

CDI and IBD

- ↑ Morbidity and mortality (4 – 6 x)
- ↑ Colectomy rates in UC
- Risks
  - UC > Crohn’s
  - Colonic disease
  - Severity of disease
  - Immune suppression – 3 x ↑ risk especially steroids

(Ananthakrishnan et al, IBD 2011; 17:976-83)
CDI and IBD

• Test all flares
  Inpatient and outpatient

• Test pouchitis

• Test unexplained increased ileostomy output

Therapy

• Mild to Moderate CDI and IBD
  – Treat CDI first
  – Keep immune suppression therapy going
  – Don’t escalate IBD therapy
    3 days?
    ? Retest for C. difficile - controversial

• Severe IBD with possible CDI
  – Start treatment for both
4. When should I get a surgery consult for my patient with CDI?

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

LaMontagne et al, Ann Surg 2007

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

*Colectomy 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 Am J Surg 2010
Diverting Loop Ileostomy – Another Option

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

Neal et al, Ann Surg 2011

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>
5. How do I treat patients with recurrent CDI?

**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

Surawicz et al, Clin Infect 31:1012;2000
RCDI – Vancomycin Regimen

- Vancomycin 125 mg qid x 10 days, then Vancomycin 125 mg a day every 3 days x 10
- Simple and not too expensive

Courtesy of Dr. Scott Curry, U. of Pittsburgh

Other Antibiotics?

- Rifaximin “chaser” (2 wks vanco + 2 wk rifaximin)
  - Two small series
- Fidaxomicin
  - No trials in RCDI
- Neither drug FDA approved for RCDI
Immune Approaches

• IVIG – case reports

• Vaccines – 5 yrs away

• IV monoclonal antibody to toxin A and B as adjunct to antibiotics promising but still in trials – phase 3
  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
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” (Zhang et al, Am J Gastroenterol 2012; 107:1755 letter)

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; 47:178-83

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%

Gough et al, Clin Inf Dis, 2011; 53:994-1002

Duodenal Infusion of Donor Feces for RCDI

# 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 - 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 patients own stool
- Several patients enrolled so far

FDA no longer requires IND for FMT
Safety of FMT?

- Overall appears effective and safe
- Two cases of norovirus (asymptomatic donor)
- Several cases of IBD flares


Safety of FMT for Immune Compromised Patients?

- 66 Patients (16 centers)
- Retrospective survey
- Minimum 12 week follow up

Inunnah et al. ACG meeting, October 2013
Results

- Overall, 89% cure of CDI with FMT
- 9 Serious adverse effects
  - 3 IBD flares (9% of IBD patients)
- 2 Deaths
  - Aspiration during colonoscopy
  - Worsening PNA
- No infectious complications of the FMT itself

FMT - The Future

- In 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

**RCDI – Recent Meeting Update**

- Donor stool in gel capsules – 27 patients
  
  Louie et al, ID Week, October 2013

- FMT by colonoscopy most cost effective using decision analysis
  
  Konijetti et al, ACG, October 2013
RCDI Treatment

• 1\textsuperscript{st} recurrence
  – Repeat initial regimen
• 2\textsuperscript{nd} recurrence
  – Vancomycin pulse regimen
• 3\textsuperscript{rd} 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
• Test any diarrheal illness in immune compromised patients
• Recurrent CDI – a treatment challenge
Question 1

A 42-year-old man presents with severe diarrhea 2 weeks after receiving a course of antibiotics. On exam, there is mild abdominal tenderness, and an abdominal CT scan done in the emergency room shows colon wall thickening in the left colon. Stool for *C. difficile* toxin by PCR is positive. He is started on vancomycin 125 mg four times a day. Two days later he has abdominal distension, and the serum albumin has dropped. Which is the most appropriate next step?
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A. Oral metronidazole should be added.
B. IV vancomycin should be given with IV metronidazole.
C. IV metronidazole should be given and vancomycin can be increased
D. Rifaximin should be added to the metronidazole.
E. Metronidazole enemas should be given.

---

**Answer**

Answer: C

This is severe *C. difficile* disease that is not responding to vancomycin. He should be given oral vancomycin at a higher dose, and metronidazole should be given intravenously. He needs to be watched closely with early surgical consultation. There is no role for IV vancomycin as it does not reach the colon lumen. There is no role for rifaximin in severe disease. Metronidazole enemas have not been tested; vancomycin enemas have been used.
A 50-year-old woman has had two episodes of *C. difficile* infection. Each time she was retreated with antibiotics, first with 2 weeks of metronidazole and then with 2 weeks of vancomycin. The diarrhea resolved with treatment, but symptoms recurred within 5-7 days after antibiotics are discontinued and stool test is positive for *C. difficile*. Which is the most appropriate management strategy?

A. Six weeks of high-dose metronidazole, followed by a tapering dose  
B. Ten days of vancomycin followed by a pulse regimen  
C. Cholestyramine powder given with antibiotics  
D. A probiotic such as VSL #3 as an adjunct to metronidazole  
E. Rifampin monotherapy
Answer

• Answer: B

• A pulse regimen of vancomycin should be given next. 125 mg q I d x 10 days, then one dose a day every 3 days for ten more doses is an excellent regimen. Metronidazole should not be used long term as it can cause irreversible peripheral neuropathy. Cholestyramine will bind antibiotics and should be given several hours before or after antibiotics, if it is used but it does not bind *C. difficile* toxins. Probiotics may have a role as an adjunct with antibiotics; There is evidence for *S. boulardii* but not VSL #3 to decrease recurrences when given as adjunct with antibiotics. *Lactobacillus GG* has also been used. Rifampin has not been shown to be effective. Rifaximin has been successful following vancomycin in 2 small case series.

Question 3

A 65-year old man presents with severe diarrhea 2 weeks after receiving a course of antibiotics for hip osteomyelitis. On exam, there is moderate abdominal tenderness and WBC 16,000. Stool for *C. difficile* toxin by PCR is positive. He is started on high dose vancomycin and IV metronidazole. Two days later he has more abdominal distension, a CT scan shows colon wall thickening. The serum lactate is 3.4. Which is the most appropriate next step?
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B. The antibiotic for osteomyelitis should be stopped.  
C. Oral vancomycin should be stopped and IV metronidazole should be increased  
D. A surgery consult is indicated.

**Answer**

Answer: D

This is severe *C. difficile* disease that is not responding to maximal therapy and may need a colectomy, thus early surgical consultation is indicated.