Management of *C. difficile* Colitis

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Why even talk about *C. difficile*?

Epidemic since year 2000
US, Canada and Europe
Increased severity and mortality
Elderly patients at increased risk
CDI cases by age-frequency

CDI Mortality and age-severity

CDC data 2007
Today

1. best diagnostic tests
2. appropriate therapy
3. surgery consult
4. recurrent CDI
5. prevention

Treatment: Practice Guidelines

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Surawicz CM, Brandt LJ, Binion DG et al
What are the best diagnostic tests for CDI?

Diagnostic Testing

- Polymerase Chain Reaction (PCR)
  - Detects gene for Toxin B
  - New gold standard
- GDH (glutamate dehydrogenase antigen)
  - Very sensitive but not specific
  - If positive, needs confirmatory test
- Enzyme Immune Assays (EIA)
  - Not good stand alone tests
**C. difficile Tests**

Test only patients with diarrhea since 80% of infants and 5-15% of adults are carriers

Do not routinely test 3 stools--Low yield

Don’t test for cure (usually)

Culture and toxin can stay positive for a month


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**Flex sigmoidoscopy- can be useful**
Pseudomembranes - not always C difficile?

Ischemia
Shiga toxin E coli
Klebsiella oxytoca
Staphylococcus enterocolitis (if it exists)

The Future? – Cliff and C. diff

A Beagle that can detect C. difficile
Cliff

Cliff – 2 year old beagle
Trained at Vrije U. in Amsterdam
Hospital- he sits next to bed when positive
Detected 25 of 30 cases
265 of 270 negatives
Almost as good as PCR!
You tube video interesting

Take Home Points

Diagnostic tests are imperfect

Even PCR can be negative with pseudomembranous colitis

If you think your patient has *C. difficile* and is sick, start empiric therapy with vancomycin
Appropriate therapy—stratify by severity

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
Case

A 52-year old woman with stage IV cervical cancer is undergoing chemotherapy with cisplatin. She develops acute diarrhea and abdominal pain. On exam, she is tender in the left lower quadrant with abdominal distension and has a low grade fever. Hct 38, WBC 17,000, electrolytes are normal but the potassium is a little low. Albumin is 3.5; Stool test for C difficile toxin B by PCR is positive.

What is the most appropriate initial therapy?

A. Metronidazole 500 mg q 8 hrs orally
B. Metronidazole 500 mg q 8 hrs intravenously
C. Vancomycin 125 mg q 6 hrs orally
D. Vancomycin 500 mg in 100 ml saline per rectum
Answer C: Vancomycin 125 mg q 6 hrs orally

This is severe CDI given her distension and elevated white blood cell count, so vancomycin 125 mg qid is indicated as initial therapy rather than metronidazole which is fine for mild to moderate CDI. The higher dose of vanco is not needed, nor is IV metronidazole.

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 \text{ 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)
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

Case cont’d

Over the next 2 days, she continues to have diarrhea and abdominal pain. The WBC has risen to 35,000 and the albumin is now 2.7. A CT scan shows colon wall thickening in the right colon.
What changes should you make to her therapy?

A. Add metronidazole, 500 mg IV every 8 hours
B. Continue vancomycin 125 mg p o every 6 hours and watch for 2 more days
C. Vancomycin 500 mg p o every 6 hours and IV metronidazole 500 mg IV every 8 hours
D. Add immune globulin IV

Answer C: Vancomycin 500 mg p o every 6 hours and metronidazole 500 mg IV every 8 hours

This patient meets criteria for severe and complicated CDI, thus therapy with highest doses (500 mg q i d) vancomycin and IV metronidazole is indicated. There is no data to support use of IVIG.
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.
- Metronidazole 500 mg tid IV
- Consider vancomycin enemas 500 mg IV
- vancomycin in 100 ml NS via rectal tube, clamp 60 min. Repeat qid

CDI and IBD

- Higher morbidity and mortality (4 -6x)
- ↑ colectomy rates
- Risks: Colon disease
- Severe disease
- Immune suppression
  - Especially steroids

Ananthakrishnan et al, IBD 2011; 17:976-83
**CDI - IBD**

Test all flares  
Inpatient  
Outpatient  

Test pouchitis

Test unexplained increase ileostomy output

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**Treatment – CDI and IBD**

Treat CDI first

If severe, treat both CDI and IBD

Keep immune suppression going
Don’t escalate for 3 days?
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>

Case cont’d

Over the next 24 hours she continues to decline with respiratory compromise and increasing abdominal distension. You ask for a surgery consult; the surgeon does not think she can tolerate a colectomy.
What is the next best step?

A. Add immune globulin and a probiotic
B. Consider loop ileostomy done laparoscopically
C. Transfer to comfort care
D. Consider fecal microbiota transplant

Answer C: Consider loop ileostomy done laparoscopically

This patient has severe and complicated CDI that is not responding to maximal therapy. A surgical consult is indicated to evaluate for possible colectomy or loop ileostomy. There is not enough data to support FMT although there are anecdotal cases of success.
Impact of Emergency Colectomy for Fulminant C. difficile Colitis

January 2003 – June 2005, retrospective series of 161 patients

Surgery – 38 ; mortality 34%
Medical Rx– 123 ; mortality 58%

Outcome 30 Day mortality

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

No response to maximal medical therapy in 3-5 days in severe/complicated
Hypotension/shock/sepsis
Renal or pulmonary decline
Rising wbc and creatinine/dropping albumin
Progressive abdominal distension
Diverting Loop Ileostomy – Another Option

Loop ileostomy with PEG + vancomycin colon lavage
mortality 19% c/w 50% colectomy
Laparoscopic in most
Colon preserved in most
80% hooked back up

Neal et al, Ann Surg 2011; 254:423

Case

A 75-year old woman is referred to you for recurrent *Clostridium difficile* infection. She has had 4 recurrences. She has had 2 courses of metronidazole, one of fidaxomicin and one with vancomycin- and a pulsed regimen. She is very frustrated. She is fine while on treatment, but develops symptoms within 1 to 2 weeks of ending the treatment regimen. She has had a recent colonoscopy which was normal. She lives independently.
Which is the next best choice for therapy?

A. Cholestyramine daily
B. Fidaxomicin taper
C. Fecal microbiota transplant
D. Saccharomyces boulardii

Answer: C Fecal microbiota transplant

With so many recurrences FMT is the next best step with 90% response rate. Cholestyramine is a binder but there is no evidence that it actually binds C. difficile toxin. Fidaxomicin has already failed, so no benefit for a repeat course with a taper. S. boulardii decreases recurrences as an adjunct to vancomycin, but is not useful as monotherapy.

Recurrent CDI

Pathophysiology

Impaired immune response

Altered colonic microbiota
**Impaired Immune Response**

Patients with RCDI had lower levels of IgG antibody to Toxin A

Lower levels of anti-toxin B Ab were associated with recurrence in a vaccine trial


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**Altered colon microbiome-dysbiosis**

Stable microbiota is perturbed by antibiotics

Susceptible bacteria killed; less diversity and loss of colonization resistance (dysbiosis)

Exposure to *C difficile*: spores germinate, bacterial toxins cause disease

More antibiotic treatment- persistent dysbiosis
Altered Colonic Microbiome

_Bacteroidetes_ and _Firmicutes_ = majority of normal

Evaluated microbiome in 7 pts with CDI and 3 controls
3 developed RCDI cases.
- microbiota very different
- significant decrease in phylogenetic richness


Decreased Microbial Diversity in _C. difficile_

Recommendation: Treatment of first CDI Recurrence

The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used.

Treatment of 2d recurrence

The second recurrence should be treated with a pulsed vancomycin regimen.
RCDI – Vancomycin Regimen

Vancomycin 125 mg qid x 10 days,
then Vancomycin 125 mg a day every
3 days x 10 more doses

Simple and not too expensive

Courtesy of Dr. Scott Curry, U. of Pittsburgh

Other therapies?

Rifaximin “chaser”- 2 wk vanco, then 2 wk rifax; small trial, small neg RCT
Fidaxomicin- not studied in RCDI
Neither drug FDA approved for CDI.

IVIG- case reports
Monoclonal antibody to Toxins A + B in phase 3 trials
Vaccines in development
Recommendation: Other Investigational Treatment

There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI.

Probiotics

Saccharomyces boulardii – 2 RCT
Decreased recurrences by 50% with adjunct antibiotics

Recurrences with high dose vancomycin
(15.7% vs 50%) but not with low dose vancomycin or metronidazole

McFarland et al, JAMA 1994; 271:1913,
Surawicz et al, Clin Infect Dis 2000; 31:1012
Recommendation: Treatment of 3 or more CDI Recurrences

If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered.

Fecal Microbiota Transplant

Multiple systematic reviews show efficacy, around 90%
Nothing else nearly this good
RCT from Netherlands showed efficacy in RCDI pts via nasoduodenal route

Guo et al, APT 2012; van Nood et al NEJM 2013
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

Zhang et al, Am J Gastroenterol 2012; 107:1755 (letter)
What Do I Do?

Make sure it is RCDI – post infectious IBS common after CDI

Make sure not it is recurrent, not refractory
Refractory disease needs more aggressive therapy

Vancomycin pulse – works sometimes

What do I do?

Sometimes I offer rifaximin and/or fidaxomicin

Vancomycin pills vs. IV form orally

Usually FMT
RCDI Treatment

1\textsuperscript{st} recurrence
   Repeat initial regimen
2\textsuperscript{nd} recurrence
   Vancomycin pulse regimen
3\textsuperscript{rd} recurrence
   Consider FMT

What if They Need Antibiotics Again?

Reassure: recurrence unlikely especially post FMT
Suggest most narrow spectrum antibiotics that is appropriate
I do not give prophylactic metro or vanco
Consider probiotics but which ones?
   Single agents or mixtures?
   Kefir?
Prevention of CDI

How do we prevent CDI?

• Wise antibiotic policies
  • Clindamycin, cephalosporins, quinolones
• Hand hygiene (soap and water), barrier and isolation
• Screen patients at admission to hospital?
  (Montreal Heart Institute does this; isolate those pts)
What about cleaning the hospital and home?

In hospitals need EPA approved sporicidal cleaners (5000 ppm chlorine containing)

At home: spray bottle mixture of 1 cup bleach to 9 cups water

1. Spray surfaces
2. Sit 10 minutes
3. Rinse off

Probiotics - Prevention

Antibiotic Associated Diarrhea (AAD) –

Good data for *Lactobacillus* GG and *Saccharomyces boulardii*

CDI –

Two meta-analyses moderate evidence for prevention of diarrhea and CDI

Moderate quality evidence

Negative trial of *Lactobacillus* and *Bifidobacter* to prevent AAD and CDI in elderly patients on abx

Probiotics - bottom line

Limited role in treatment of RCDI
May have a role in prevention of AAD
Not clear if can really prevent CDI
Which ones? What doses? Single or combinations?
Really need better data

Summary

• PCR for Toxin B likely new gold standard stool test
• Stratify disease severity and treat appropriately with metronidazole or vancomycin
• For severe and complicated disease
  - Vancomycin and IV Metronidazole
  - Surgery consult
• Recurrent CDI – consider FMT for worst cases
• Prevention, especially in the hospital setting, is key