Guidelines for Treatment and Prevention of *Clostridium difficile* Infection

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Disclosure of Financial Relationships

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Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.
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?
5. How do we prevent 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
Diagnostic Testing

- Tissue culture toxin B
  Old gold standard
- Toxigenic Culture
- GDH (glutamate dehydrogenase antigen)
- Enzyme Immune Assays (EIA)
- Polymerase Chain Reaction (PCR)
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
EIA Tests

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

Toxins A + B - better
  Specific but not sensitive

Should not be stand alone tests
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
Can now use rectal swabs for PCR
  Useful if patient has ileus
PCR is probably the new gold standard
C. difficile Tests

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

BUT diagnostic tests are imperfect

If you think your patient has *C. difficile* and is sick, start empiric therapy
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
  Detected 25 of 30 cases
  265 of 270 negatives
Sits next to bed
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?

Macrocyclic 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

Louie et al, NEJM 2011; 364:422
## 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>$1,800</td>
</tr>
<tr>
<td>Vancomycin generic</td>
<td>$106</td>
</tr>
<tr>
<td>IV vancomycin given orally</td>
<td>$400</td>
</tr>
<tr>
<td>Fidaxomicin (200mg)</td>
<td>$2,700</td>
</tr>
</tbody>
</table>
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

IDSA definition:
- WBC > 15,000 or
- Creatinine ↑ 1.5 x baseline
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 poor outcome:
- 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
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
Unproven Therapies

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

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
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; 254:423
## 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 2009</td>
<td>42</td>
<td>21/42 (50%)</td>
</tr>
</tbody>
</table>
4. How do I treat patients with recurrent CDI?
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

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

Colon Microbiota

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 Dis 2000; 31;1012
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

Monoclonal antibody to toxin A and B as adjunct to antibiotics promising but still in trials – phase 3 trials

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
“Human stool is the ultimate probiotic”

Lawrence Brandt, MD
Albert Einstein College of Medicine
Bronx, NY, 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?
1700 years ago in China, the 4th Century used human feces to treat severe diarrhea; the 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)
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
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
Tvede, Rask-Madsen, Lancet, 1989; 1:1156-60
Terminology – Restoring the Normal Microbiota

Fecal bacteriotherapy
Fecal enemas
Fecal flora reconstitution
Stool transplant

Fecal microbiota transplant (FMT) = now the new accepted terminology
FMT – Methods

Colonoscopic route – healthy spouse donor stool to right colon via colonoscopy

Stool Per NG tube

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
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
FMT - Unanswered Questions

Does it work?

Why does it work?

Is it safe?

What’s the best method?
Does it Work?

Duodenal Infusion of Donor Feces for Recurrent *C. difficile*

Van Nood E, et al
# 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
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
Is it Safe?

Long Term Follow Up Study- FMT via Colonoscopy

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawrence Brandt</td>
<td>Bronx, NY</td>
</tr>
<tr>
<td>Colleen Kelly</td>
<td>Providence, RI</td>
</tr>
<tr>
<td>Mark Mellow</td>
<td>Oklahoma City, OK</td>
</tr>
<tr>
<td>Neil Stollman</td>
<td>Oakland, CA</td>
</tr>
<tr>
<td>Christina Surawicz</td>
<td>Seattle, WA</td>
</tr>
</tbody>
</table>

(Brandt et al, Am J Gastro 2012; 107:1079)
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
Long Term Safety

- 4 had a new medical condition
  - Peripheral neuropathy
  - Sjögren syndrome
  - ITP
  - Rheumatoid arthritis
- No infections or deaths related
  - 1 sepsis – 6 months later in Crohn’s pt.
  - 1 pneumonia
In US,
FDA no longer requires
Investigational New Drug Application (IND) for FMT

Trials ongoing in Canada
What’s the Best Method - Is Colonoscopy Better?

• NIH funded RCT - Drs. Colleen Kelly (Brown University) and Lawrence Brandt (A Einstein University)

• Control – colonoscopy with the patients own stool
RCDI – Recent Meeting Updates

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

• FMT cost effective
  • By colonoscopy
  • By decision analysis
    Konijetti et al, ACG, October 2013

• FMT appears safe in immune suppressed patients – 83 patients
  Ilhunnah, ACG, October 2013
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, Allen-Vercoe et al, Microbiome 2013; 1:3
RCDI Treatment

1\textsuperscript{st} recurrence
  Repeat initial regimen
2\textsuperscript{nd} recurrence
  Vancomycin pulse regimen
3\textsuperscript{rd} recurrence
  Consider FMT
A bit of kindness at just the right time can make all the difference.
Prevention

• Wise antibiotic policies
• Hand hygiene + barrier
• Screen patients at admission to hospital (Montreal Heart Institute)
• Bleach cleaning at home
• Probiotics?
Diverse Sources of CDI

Whole genome sequencing

Symptomatic CDI

Oxford community, UK

(Eyre et al NEJM 2013; 369:1195-1205)
Results

• 1223 cases (2007-2011)
• Hospital based transmission or related to another case – only 35%
• Most was not patient-to-patient transmission
• Other sources:
  Asymptomatic people
  Environment
    Meat
    Pets
Disinfection

• Bleach – 1 cup in 9 cups water

• Spray over kitchen, bathroom, cell phone

• Leave wet – spray x 10 minutes then rinse off

• Toss soiled underwear or launder repeatedly
Probiotics - Prevention

AAD  • Good data

*Lactobacillus GG*

Saccharomyces boulardii

CDI  • Recent meta-analysis favored use

Multiple agents


• Health Canada – approved Bio-K⁺ (L. acidophilus, CL1285, L. casei, LBC80R) in 2013

(Gao et al, Am J Gastroenterol 2010)
Prevention

Wise antibiotic policies

Hand hygiene

Barrier

Bleach cleaning at home
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