Clostridium difficile infections and fecal transplant

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Special thanks to: Sarah Doernberg, MD, MAS

Objectives

- Recognize patients at risk for C. difficile infection (CDI)
- Contrast diagnostic testing for CDI
- Describe treatment strategies for mild, severe, and fulminant CDI
- Devise a treatment approach to recurrent and relapsed CDI
- List current and emerging strategies to prevent CDI

Outline

- Brief background and epidemiology
- Diagnosis
- Management—mild, uncomplicated disease
- Management—moderate-severe disease
- Management—recurrent/relapsed disease
- Management—fulminant disease
- Prevention

One of CDC’s 3 “Urgent Threats”

http://www.cdc.gov/drugresistance/biggest_threats.html

500,000
3.8 billion
EPIDEMIOLOGY

CDI Background

- Anaerobic, spore-forming gram-positive bacillus
- Toxins A + B
- Multiple strains
  - Epidemic strain ID’d 2004
  - 078 strain
- Fecal-oral spread
- 12% of all HAIs
- Carriage of C. difficile

- < 3% for healthy adults in community
- 20% in hospitalized pts
- up to 50% in LTCF
- Risk factors:
  - Antibiotics
  - Age
  - Hospitalization
  - Acid-suppression, IBD, Tube feeds
  - Host immune factors, Chemotherapy

Magill SS et al., NEJM 2014
Epidemiology trends, inpatients
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a7.htm

Duration, number, and intensity of antibiotics affect risk for CDI

Antibiotic use affects the population risk

Spread of CDI in the hospital

Asymptomatic carriers

Endogenous carriage

Symptomatic cases 25–33%

Asians have high CDI-related mortality

Rate of Clostridium difficile Infection by Race

DIAGNOSIS
Diagnostic testing

- Glutamate dehydrogenase Ag (GDH)
  - Bacterial detection
  - Sensitive but not specific

- Polymerase chain reaction (PCR):
  - Toxin-producing gene
  - ↑Sensitivity

- Enzyme immunoassay (EIA)
  - Protein detection
  - ↓Sensitivity
  - ↑Specificity for disease

CDI overdiagnosis

- 21% +PCR
  - Of these, 44% + toxin
  - ↑Sensitivity
  - ↓bacterial load
  - ↓abx
  - ↓diarrhea
  - No CDI-complications

What is wrong with this picture?

- 63 year old Chinese F s/p spinal fusion c/b hardware infection. She received a 6 week course of antibiotics for this and is admitted for redo spinal fusion. She has been constipated and has daily orders for senna, colace and miralax.

- On HD# 8, she develops 2 loose stools and tests positive for C. difficile. She is afebrile with a normal WBC and is started on PO metronidazole. She has no further episodes of loose stools during the remainder of hospitalization.

Overdiagnosis

- 63 year old Chinese F s/p spinal fusion c/b hardware infection. She received a 6 week course of antibiotics for this and is admitted for redo spinal fusion. She has been constipated and has daily orders for senna, colace and miralax.

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TREATMENT

Treatment scenario #1. 73 y/o Filipina recently treated for a UTI with levofloxacin, now having watery stools 4x/day, fever to 38.5, WBC 16K, Cr 1.7 (baseline 0.5), PCR positive for C. difficile toxin. With what should you treat her?

A. Vancomycin 125 mg po qid
B. Vancomycin 500 mg po qid
C. Metronidazole 500 mg po tid
D. Fidaxomicin 200 mg po bid
CDI treatment depends on severity

- Mild to moderate: Does not meet criteria for severe
  - Diarrhea ≥ 3 stools/24 hours
- Severe
  - Not well validated
  - IDSA/SHEA guidelines: Severe disease = Peak WBC > 15K or Cr > 50% above baseline or “advanced age” (65? 75?)
- Severe, complicated
  - Severe plus hypotension, shock, ileus, and/or megacolon

Zar F A et al. Clin Infect Dis. 2007;45:302-307; Cohen et al., Infection Control and Hospital Epidemiology, 2010; 31: 431-455

RCTs metronidazole vs. vancomycin

- Similar findings for recent study of metronidazole vs vancomycin
- Cure not differential with regard to levels of severity
- Higher recurrence across the board (20%)
- Only vancomycin is FDA-approved

New evidence to support vancomycin

- aRR death vanco vs metronidazole, any severity
  - Any severity: 0.86; 95% CI, 0.74 to 0.98;
  - Severe CDI: 0.79; 95% CI, 0.65 to 0.97
  - NNT to prevent 1 death, severe CDI: 25

What about fidaxomicin?

- Bottom line vs. vanco: Similar cure (~88%), lower recurrence (13-15% vs. 25-27%)
- Unclear role in multiply recurrent or severe disease

<table>
<thead>
<tr>
<th>Strain</th>
<th>Cure</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemic</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Non-epidemic</td>
<td>Same</td>
<td>↓</td>
</tr>
<tr>
<td>Concomitant abx</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Prior CDI</td>
<td>Same</td>
<td>E/F</td>
</tr>
</tbody>
</table>

Fidaxomicin | Vancomycin | Metronidazole
$2800 | $250-680 | $22
Additional considerations

- Stop unnecessary antibiotics
- Shorten antibiotic courses
- Narrow antibiotic spectrum
- Stop acid-suppressive medications when possible
  - Esp PPI
  - Do not use anti-peristaltic agents until acute symptoms of CDI improve

Take-home

- For mild-moderate disease, can choose metronidazole, more movement towards PO vancomycin in recent years
- For severe disease, choose vancomycin
  - Higher cure, but same relapse
- Role of fidaxomicin unclear
  - Consider if high risk of relapse or need CA
- ? Use in multiply recurrent disease
- ? Role in severe disease

Treatment scenario #2: 62 y/o Korean male who has takes chronic amoxicillin/clavulanic acid for suppression of *Enterococcal* osteomyelitis and has developed his second bout of *C. difficile* colitis. His WBC count is 9 and Cr is 0.3. What should you treat him with?

A. Metronidazole 500 mg po TID
B. Vancomycin 125 mg PO QID
C. Vancomycin taper

Risk for recurrent CDI

- [Graph showing risk for recurrent CDI](example-graph.png)

References:
Treatment scenario #3. This patient returns one month after you have treated him with a 14-day course of PO metronidazole complaining of ongoing diarrhea. A repeat stool toxin is positive. What do you do?

A. Metronidazole 500 mg po TID x 14 days
B. Vancomycin 125 mg PO QID x 14 days
C. Vancomycin taper
D. Fidaxomicin 200 mg PO BID x 10 days
E. Other

Vancomycin taper

- 125 mg po 4x daily x 14 days
- 125 mg po 2x daily x 7 days
- 125 mg po 1x daily x 7 days
- 125 mg po every other day x 8 days (4 doses)
- 125 mg po every 3 days x 15 days (5 doses)

Fecal diversity with rCDI

FMT basics
- Colonization resistance
- Related donors or banked stool
- Need to screen for transmissible diseases
- Multiple RCTs have now been done
- Guidance document available (Bakken et al)

Fecal diversity ↑ and abxR ↓ post FMT

FMT trial trends

- 6 published
  - 3 vs. abx management
  - 3 vs. FMT refinements
  - Over time, ↓efficacy in RCTs
  - ↑response to comparator abx
  - Might matter whether active recurrence vs. prior recurrence?
  - Might need multiple FMTs
  - Vanco taper might be better than we thought?
  - Commercially-prepared FMT in development

The latest on FMT

- Multiple previous trials supported FMT...
- But comparator group not standard of care
- Phase 2/3 open-label RCT
  - Stopped early for futility
  - FMT by enema
  - Recurrence: 9/16 (56%) FMT vs. 5/12 (42%) taper group
  - 95% CI for Δ CDI with FMT = -2.8% to +47.3%

Poop pill for recurrent CDI?

- Phase 1 study: Open-label, single group feasibility study
  - 14/20 (70%; 95% CI, 47%-85%) had sustained (8 wk) resolution after 1 treatment
    - Nonresponders were re-treated (~7 days later) → Overall response: 90% (95% CI, 68%-98%)
- But, phase 2 study interim analysis: 44% (26/59) recurrences SER-109 vs. 53% (16/30) control patients
- Recent study of purified Firmicutes from healthy donors was safe and resulted in increased diversity

FMT adverse events

Common
- Diarrhea
- Cramping
- Belching
- Nausea
- Bloating

Rare/serious
- Procedure-related harms
  - Perforation
  - Aspiration
  - Norovirus
  - Bacteremia
  - IBD flare
  - Unknown long-term effects
    - Weight changes
    - Chronic disease exacerbation
Take-home

- Recurrent CDI is a challenge
- Treat first episode with same agent, adjust for severity
- Subsequently, use vanco taper
- Primary FMT indications
  - Recurrent or relapsing FMT (usu > 2 episodes)
  - Moderate CDI not responding to Rx
  - More to follow on severe/complicated

Total colectomy with end ileostomy

- Retrospective cohort pts in ICU for CDI
  - N = 161 (38 surgery, 123 medical rx)
- Indications: Shock (40%), megacolon (29%), no response to med rx (26%), perforation (5%)
- aOR death 0.2 (0.1-0.7) colectomy vs. medical rx
  - WBC > 50K and lactate > 5 conferred very poor prognosis
  - More beneficial in age ≥ 65, immunocompetent, WBC ≥ 20, lactate 2.2-4.9
  - 53% died (58% medical rx, 34% surgical)
  - Selection bias likely

Treatment scenario #4: 63 y/o Japanese-American F recently treated for a UTI with levofloxacin, now with profuse diarrhea, T 38.7, BP 79/50, HR 140, WBC 30K, Cr 3.2, and lactate 3.7. What do you treat her with?

A. Vancomycin 125 mg po qid
B. Vancomycin 500 mg po qid
C. Vancomycin 500 mg PR qid
D. Metronidazole 500 mg iv tid
E. Fidaxomicin 200 mg po bid
F. A+C+D
G. B+C+D


Diverting loop ileostomy + colonic lavage

- 3/42 (7%) converted to total colectomy (2 for abd compartment sx)
- 79% had ileostomy reverted
- VS historical colectomy controls, OR for death = 0.24 (0.09-0.63)
- 19% died at 30 days
- 14% more died afterwards, all deemed due to underlying illness
- RCT recruiting (projected end date 2018)

FMT for severe disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cammarota et al., Aliment Pharmacol Ther 2015</td>
<td>Subgroup of RCT w/ recurrent CDI, N = 7 w/ pseudomembranes Single-center</td>
<td>RCT FMT via colo vs vanco Initial 2 pts 1 FMT via colo; remainder FMT q3 days prn</td>
<td>Mortality: 29% (1 FMT) Cure: 71% (≥ 2 FMT)</td>
</tr>
<tr>
<td>Fischer et al, Aliment Pharmacol Ther 2015</td>
<td>Cohort, N = 29 Severe (18) +/-. complicated (10) Single-center</td>
<td>FMT via colo –spk with intermittent vanco</td>
<td>Mortality: 7% (both severe/comp) Success: 93% (≥ 2 FMT in 50%)</td>
</tr>
<tr>
<td>Zainah H et al, Dig Dis Sci 2015</td>
<td>Cohort, N = 14 with severe, refractory CDI (50% in ICU) Single-center</td>
<td>FMT via NGT, pr at 48-72h if not response</td>
<td>Mortality: None d/1 CDI (25% at 100 dd 2/2 underlying dis) Success: 79% (≥ 2 FMT in 21%)</td>
</tr>
<tr>
<td>Aroniadis et al, J Clin Gastroenterol 2015</td>
<td>Multicenter cohort N = 17 70% severe/complicated</td>
<td>FMT mostly via colo</td>
<td>Success: 94% (≥ 2 FMT in 60%)</td>
</tr>
</tbody>
</table>

IVIG in severe disease

- No RCTs
- Retrospective review of 14 patients who received IVIG at one institution
  - 6 refractory
  - 6 recurrent
  - 2 severe IS failing to respond to therapy
- Dose 150 to 400 mg/kg x 1-2
  - 9 (64%) responded fully
  - Of these, 3 (33%) had subsequent recurrences

Take-home for severe, complicated CDI

- Use high-dose oral +/- rectal vancomycin
- Use IV metronidazole
- Consider surgical intervention early
  - Consider diverting loop ileostomy
- FMT is promising
  - Likely, multiple FMTs may be needed
  - Make sure medical therapy has been optimized
- Additional therapies (IVIG, other antibiotics) lack data

Treatment scenario #5. You are starting your 70 y/o South Asian M patient on 4 weeks of ciprofloxacin for prostatitis. He asks you whether he should take probiotics. How do you counsel him?

A. Probiotics will prevent antibiotic-associated diarrhea, including CDI
B. Probiotics will prevent antibiotic-associated diarrhea but not CDI
C. Probiotics are useless
RCT of probiotics for CDI

<table>
<thead>
<tr>
<th>Diarrhea class</th>
<th>Probiotic</th>
<th>Placebo</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAD</td>
<td>159/1470 (11%)</td>
<td>153/1471 (10%)</td>
<td>1.04 (0.83–1.32)</td>
</tr>
<tr>
<td>CDI</td>
<td>12/1470 (0.9%)</td>
<td>17/1471 (1.2%)</td>
<td>0.70 (0.34–1.46)</td>
</tr>
</tbody>
</table>

- No benefit for probiotic
- Very low rates of CDI in this population
- Majority of patients were receiving amoxicillin/ampicillin or second-generation cephalosporins (UK study)
- Likely underpowered for the CDI outcome

Allen SJ et al., Lancet 2013 Oct 12;382(9900):1249-57

Meta-analysis + PLACIDE trial

PREVENTION
**Infection control**

- Gloves + gowns for duration of diarrhea
- Wash with soap and water
- Private rooms
  - Dedicated commode
  - Bleach cleaning
  - Antimicrobial stewardship

**Identification and isolation of carriers**

![Graph showing CBIs per 1000 patient days]

Cohen et al., Infection Control and Hospital Epidemiology, 2010; 31: 431-455

**Non-toxigenic C. diff for secondary prevention**

- 173 patients with 1st or 2nd episode of CDI w/ 28 days (phase II)
  - 1-2 days after stopping CDI treatment randomized to non-toxigenic C diff (NTCD-M3) vs. placebo

**Secondary prophylaxis?**

1. Retrospective cohort at two hospitals in Quebec
   - aHR 0.59 (0.43-0.80)
   - aHR 1st CDI 0.91 (0.57-1.45)
   - aHR recurrence 0.47 (0.32-0.69)

   ![Graph showing recurrence rate]

   Gerding DN et al., JAMA 2015; 313(17):1719-1727

2. Retrospective cohort St. Louis
   - OR 0.12 (0.04-0.4)
   - No multivariate analysis

   ![Graph showing recurrence rate]


Adult w/ CDI Rx'd non-CDI abx within 90 d (in or outpt)

Recurrence w/i 6 mo

aHR 0.59 (0.43-0.80)

Recurrence w/i 4 weeks

OR 0.12 (0.04-0.4)
Host protection

Actoxumab  Bezlotoxumab

Monoclonal Abs for secondary prevention MODIFY I and II trials

- NNT = 10
- No clear subgroup benefited
- Cost may be an issue
- Δ sustained cure Bezlotux vs. SOC: 9.7% (4.8-14.5)

CDI prevention summary

- Remember infection control basics
- Role of isolation of carriers evolving
- Unclear role for probiotics, unlikely to be a game-changer
- Non-toxigenic C. diff is promising
- Passive immunity is effective but costly
- There may be a role for vaccine in the future
- Do not forget good infection control and antimicrobial stewardship practices!
## CDI strategies: Bringing it all together

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary Prevention</th>
<th>Secondary Prevention (if necessary)</th>
<th>Result</th>
<th>Therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>In widespread routine use</td>
<td>Smallest factor</td>
<td>Phase II</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Metronidazol</td>
<td>In widespread routine use</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Florfenicol</td>
<td>Large variable by region/ healthcare provider</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Large variable by region/ healthcare provider</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Bacteriostatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New antimicrobial</th>
<th>Stage of Development</th>
<th>Same as treatment</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>Phase II (ongoing)</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>(various)</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

**THANK YOU!**