The New C. Difficile: Diagnosis, Prevention & Treatment

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Clostridium difficile

- Organism first described in 1935
  - in stool of healthy newborn infants
- Anaerobic spore-forming bacillus
- Fecal-oral transmission
  - contaminated environment
  - hands of healthcare personnel

Clostridium difficile Associated Diarrhea

- Clostridium difficile-associated disease (CDAD)
  - First described in 1978 by Bartlett
  - Most common cause of health care-associated infectious diarrhea in adults
  - Most common cause of antibiotic-associated diarrhea (15-25%)

**Clostridium difficile Associated Disease**

- Spectrum of infection
  - Asymptomatic carrier
  - Mild disease
  - Severe disease
  - Fulminant infection
    - Toxic megacolon and perforation
    - Diarrhea may be absent with dysmotility

**Pathogenesis of CDAD**

Antibiotic therapy

Alteration of colonic microflora

C. difficile exposure and colonization

Release of toxin A and toxin B

Colonic mucosal injury and inflammation


**Clostridium difficile Associated Diarrhea**

- Antimicrobial exposure is major risk factor for disease
  - Acquisition and growth of *C. difficile*
  - Suppression of normal flora of the colon
    - Clindamycin, penicillins, cephalosporins, fluoroquinolones
    - Judicious antibiotic use decreases incidence of CDAD

**Epidemiology of CDAD**

- Health care–associated infection prevalence (non-epidemic)
  - 0.1 to 30 per 1,000 patients
  - Marked increase in last 10 yrs
- Community incidence
  - 8 to 12 per 100,000 person-years

**Antimicrobial Use as a Risk Factor for CDI**

- Most important modifiable risk factor
  - Suppresses normal flora providing a “niche” for *C. difficile* to flourish
- Virtually every antimicrobial has been associated with CDI
- Longer and multiple antimicrobial exposures increases risk

**Impact of CDAD on Cost and Length of Stay**

- Independent predictors of ↑ hospital costs
  - Disease severity
  - Course complicated by *C. difficile* diarrhea
- Cost of $10,488 for patient with CDAD
  - 54% (95% CI, 17%–103%) higher than typical patient
- CDAD is an independent predictor of increased length of stay
  - 3.6 days (95% CI, 1.5–6.2)
  - 55% (95% CI, 23%–94%) longer than typical patient

*Infect Control Hosp Epidemiol 2010*
Adjusted hazard ratios for CDI by antibiotic received

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>AHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>3.44*</td>
</tr>
<tr>
<td>1st generation cephalosporins</td>
<td>1.78*</td>
</tr>
<tr>
<td>2nd generation cephalosporins</td>
<td>1.89*</td>
</tr>
<tr>
<td>3rd generation cephalosporins</td>
<td>1.56*</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.77*</td>
</tr>
<tr>
<td>β-lactam/β-lactamase inhibitors</td>
<td>1.88*</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1.65*</td>
</tr>
<tr>
<td>Narrow spectrum penicillins</td>
<td>1.37</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>1.34</td>
</tr>
</tbody>
</table>

* p<0.05

Pepin et al., CID, 2005

Outbreak Associated With Increased Death and Colectomies

- Outbreak of nosocomial C. difficile infection
  - 253 infections during first 2 years
- Increase from 2.7 to 6.8 cases per 1,000 discharges (P<0.001)
  - 26 colectomies
  - 18 deaths
- Fluoroquinolone use increased prior to outbreak


Outbreak Associated With Increased Death and Colectomies

- Antibiotics independently associated from multivariate analysis
  - Clindamycin (OR, 4.6; 95% CI, 1.9-12.8)
  - Ceftriaxone (OR, 5.4; 95% CI, 1.8-15.8)
  - Levofloxacin (OR, 2.6; 95% CI, 1.2-3.3)
- Other drugs independently associated
  - Immunosuppressives (OR, 3.2; 95% CI, 1.7-6.1)
  - Proton pump inhibitors (OR, 1.8; 95% CI, 1.2-2.9)
  - H2 blockers (OR, 1.6; 95% CI, 1.0-2.5)

Other Risk Factors for CDI

• Advanced age
• Increased hospitalization duration
• Chemotherapy
• Immunosuppression
  – Evidence suggests that *C. difficile* has become the most important pathogen causing bacterial diarrhea in US pts with HIV

Infect Control Hosp Epidemiol 2010

Other Risk Factors for CDI

• Gastrointestinal surgery
• Manipulation of GI tract
  – including tube feeding
• Probable, although controversial
   use of acid-suppressing medications

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DIAGNOSIS OF C. DIFF DISEASE
SPECIMEN

• Send only unformed stool

DIAGNOSTIC CHALLENGES

• Tissue cytotoxic assay
  – “Gold standard”
  – Not used by clinical labs because of need for technical expertise and 48 hour turn-around time
Types of commercial toxin detection assay

- Enzyme immunoassay (EIA)
  - 96-well format
  - manual
  - Semi-automated
- Enzyme-linked Fluorescence Assay
  - Automated
- Lateral flow assay
  - Rapid

Enzyme Immunoassay for Toxins A and B

Positive control

- - +

Negative control

Sensitivity: manufacturer states 95% compared to cytotoxic assay
Glutamate dehydrogenase test (GDH)

DIAGNOSTIC CHALLENGES

- EIA
  - Results in 2 hours
  - Sensitivity 60-95%; Specificity 75-100%
  - Repeat testing not warranted
    - Changes diagnosis in <1% of cases
    - Increases rate of false positive test


DIAGNOSTIC CHALLENGES

- EIA
- Tissue cytotoxic assay
- Culture
  - Very sensitive
  - Difficulty in differentiating toxin-producing from non-toxin producing strains
### Summary: Diagnostic Tools

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin testing (EIA)</td>
<td>Rapid/cheap/easy to use</td>
<td>Sensitivity: 63-94% Specificity: 75-100%</td>
</tr>
<tr>
<td>Toxigenic culture</td>
<td>High sensitivity High specificity</td>
<td>Labor intensive/Slow TAT</td>
</tr>
<tr>
<td>GDH</td>
<td>Sens: 83-95%; Specificity: 89-99%</td>
<td>Rapid; Inexpensive</td>
</tr>
<tr>
<td>Cell cytotoxicity assay</td>
<td>Sensitivity: 67%</td>
<td>Labor intensive/Slow TAT</td>
</tr>
<tr>
<td>PCR</td>
<td>Rapid; stand alone test Sens: 94.4%; Specific: 96.3%</td>
<td>Expensive</td>
</tr>
</tbody>
</table>

### THERAPY

**STANDARD THERAPY**

- Withdrawal of inducing agent
- Avoid drugs with antiperistaltic activity
- Oral metronidazole
  - 250 mg qid or 500 mg tid x 10 d
  - First line therapy since 1980’s
  - CDC preferred therapy
  - New reports of failure rates of 16-38%

Bartlett, Ann Int Med 2006;145:758-764
STANDARD THERAPY

- Withdrawal of inducing agent
- Avoid drugs with antiperistaltic activity
- Oral metronidazole
- Oral vancomycin
  - 125 mg-250 mg po qid x 10 d
  - Probably more effective, esp. in seriously ill patients

Bartlett, Ann Int Med 2006;145:758-764

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### Treatment guidelines

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Recommended Treatment</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Episode: Mild or Moderate</td>
<td>metronidazole 500 mg po tid x 10-14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial Episode: Severe</td>
<td>vancomycin 125 mg po qid x 10-14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial Episode: Severe, Complicated</td>
<td>vancomycin 500 mg po/NGT qid + metronidazole 500 mg iv qd (if complete ileus, consider rectal vancomycin)</td>
<td>C-III</td>
</tr>
<tr>
<td>First Recurrence</td>
<td>same as for initial episode</td>
<td>A-II</td>
</tr>
<tr>
<td>Second Recurrence</td>
<td>vancomycin in a tapered/pulsed regimen</td>
<td>B-III</td>
</tr>
</tbody>
</table>

Adapted from practice guidelines: Infection Control and Hospital Epidemiology, May 2010

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### RECURRENT CDI

- Either relapse of infection of the original strain or re-infection after exposure to new strain
- Historically 6-25% have at least one recurrence
- Recent reports show an increase in frequency of recurrences after metronidazole therapy, especially in patients aged 65 years or more
**Multiple recurrence treatment**

- **Vancomycin**
  - 125 mg qid x 10-14 days
  - 125 mg bid x 7 days
  - 125 mg daily x 7 days
  - 125 mg q2-3 days x 2-8 wks

- Metronidazole shouldn’t be used beyond the first recurrence or long-term given the cumulative risk of neurotoxicity

**OTHER DRUGS**

- **Fidaxomicin**

**FIDAXOMICIN**

- Macrocyclic antibiotic
- More active *in vitro* than vancomycin by factor of 8
- Minimal systemic absorption
- High fecal concentrations
- Limited activity *in vitro/in vivo* against components of normal gut flora
Fidaxomicin vs. Vancomycin

• Phase 3 clinical trial comparing efficacy and safety of fidaxomicin vs. vancomycin
• 629 adults with acute *C. difficile* infection and + toxin were randomly assigned to fidaxomicin 200 mg bid or vanco 125 mg po qid

*N Engl J Med, 2011*

Fidaxomicin vs. Vancomycin

• Primary end point
  – clinical cure (resolution of symptoms and no need for further treatment as of the 2nd day after therapy ended)
• Secondary end points
  – recurrence of *C. difficile* infection (diarrhea and + toxin within 4 wks)
  – global cure (cure with no recurrence)

*N Engl J Med, 2011*

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Figure 2. Rates of Primary and Secondary End Points.

For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was ≥3 percentage points in the modified intention-to-treat (mITT) analysis and ≥2 percentage points in the per-protocol (PP) analysis.

*N Engl J Med, 2011*
OTHER DRUGS

• Fidaxomicin
• Rifaximin

Rifaximin

• Comparable cure rates with vancomycin in small study (n=20)

• Used as adjunct in pts with multiple recurrences
  • Rifaximin x 4 wks (400mg tid x 2 wks + 200mg tid x 2 wks)
  • In 5 of 6 resulted in no additional episodes
  • “Rifaximin chaser”: 2 wk course (usually 400mg bid) following last course of vancomycin treatment
  • In group of pts with mean of 6 recurrences, there were no additional recurrences in 11 (75%) of 14
  • Resistance is an issue with 2 of 3 failures showing high-level resistance (MIC >256 µg/mL)
OTHER DRUGS

• Nitazoxanide
• Bacitracin
• Teicoplanin
• Fusidic acid

No advantage over vancomycin and metronidazole or are currently unavailable

What else is available?

Non-Antimicrobial Treatments

• Intraluminal toxin neutralizing agents
  – Bovine whey protein
  – Tolevamer
Intraluminal toxin neutralization

- Tolevamer
  - High molecular weight anionic polymer
  - Toxin neutralization (including against BI/NAP1/027) demonstrated in vitro
    - Affinity for toxin A higher than for toxin B
  - In 2 phase 3 trials markedly inferior to both metronidazole and vancomycin in treatment response

CID, 2010

Intraluminal toxin neutralization

- Whey protein in immunized cow’s milk (contains high levels of secretory IgA)
  - Primary treatment trial
    - Randomized, double blinded comparing immune whey 200 mL tid to metronidazole 400mg tid x 14D
    - Treatment response in 100% treated with metronidazole and 89% treated with whey
  - Recurrence prevention trial
    - Open label and uncontrolled
    - Recurrence rate of 10% (11 of 109)

CID, 2010

Non-Antimicrobial Treatments

- Intraluminal toxin neutralizing agents
- Biotherapeutic agents
  - Probiotics
  - Fecal transplants
  - Nontoxigenic C. difficile
PROBIOTICS

- Organisms
  - Lactobacillus
  - Saccharomyces boulardii
  - Yogurt (Streptococcus thermophilus)
- Insufficient evidence to recommend
- Concern over safety
  - Bacteremia/fungemia in immunocompromised patients

Fecal Donor Instillation Therapy

- Retrospective study of 40 pts with recurrent CDAD treated at a medium-sized Norwegian hospital from 1994 through 2008
- Close relatives or other household members selected as stool donors
  - Individuals without symptoms of GI disease or a hx of chronic infectious disease were considered suitable
  - Donors were screened for Hep A/B/C and hiv as well as enteric bacterial pathogens (Salmonella, Shigella, Campylobacter, Yersinia)

Scandinavian Journal of Infectious Diseases, 2010

Fecal Donor Instillation Therapy

- FDIT Protocol
  - All antimicrobial therapy stopped evening prior to stool transplantation and pts were NPO from midnight
  - Fresh stool sample of 50-100g obtained on day of instillation procedure
  - Stool sample was spread out onto a gauze pad which was then placed in a strainer
  - The gauze was flushed with 250 ml sterile 0.9% NaCl
  - The resulting suspension was collected and aspirated into syringes
  - ~200 cc was introduced through the instrument canal of the gastroscope with a small amount of sterile 0.9% NaCl

Scandinavian Journal of Infectious Diseases, 2010
Fecal Donor Instillation Therapy

- 83% success rate reported (33 patients)
  - In 73% first treatment successful (no recurrence within 80 days)
  - Of the 11 patients failing to respond to the first instillation treatment, 6 patients received a second instillation, 4 of which were successful
  - Of the 7 non-responders, 5 were seriously ill due to long lasting diarrheal disease and comorbidity and died within 80 days and 2 were believed to have IBD who responded to steroids
- No adverse effects of FDIT observed

Scandinavian Journal of Infectious Diseases, 2010

NON-TOXIGENIC C. DIFFICILE

- When given to hamsters during or after antibiotic treatment able to harmlessly colonize the gut and prevent subsequent infection challenge with toxigenic strains of C. difficile

CID, 2010

NON-TOXIGENIC C. DIFFICILE

- In patients with natural asymptomatic colonization with C. difficile there is an associated decreased risk in CDI
- Human safety trials of nontoxigenic C. difficile were completed in early 2010

CID, 2010
Non-Antimicrobial Treatments

- Intraluminal toxin neutralizing agents
- Biotherapeutic agents
- Systemic antibody approaches
  - IVIG
  - Monoclonal antibodies
  - Active vaccines

CID, 2010

IVIG

- IVIG preparations contain neutralizing levels of IgG antibody to toxin A and toxin B
- In 1991 IVIG was reported to be effective for immunoglobulin-deficient children with chronic recurrent CDI

CID, 2010

IVIG

- Only retrospective studies are available and there's no conclusive evidence of benefit, nor has an effective dose been established
  - One study compared 18 pts who received IVIG (200-300 mg/kg) compared with a group of patients with similar CDI severity found no difference in mortality, colectomy rate, or length of stay

CID, 2010
Monoclonal Antibodies

- Randomized, double-blind, placebo-controlled study of 200 patients
- Two neutralizing, fully human monoclonal antibodies administered together as a single infusion (each 10 mg/kg) to patients with symptomatic *C. difficile* infection who were receiving either metronidazole or vancomycin
- Primary outcome was laboratory-documented recurrence of infection during the 84 days after

*From N Engl J Med, 2010*

Antibody vs. placebo

![Graph showing antibody vs. placebo](image)

*From N Engl J Med, 2010*

VACCINES

- Focused on developing immunity to the *C. difficile* toxins
  - based on studies showing serum IgG antibody to toxins A and B correlated with protection
- In humans, preliminary trials of a parenteral vaccine containing toxoids A and B have shown that the product is safe and induces a vigorous antibody response

*From CID, 2010*
VACCINES

- Questions arise regarding response to vaccine in elderly population, magnitude and duration of protection and selection of an appropriate at-risk population

PREVENTION

Infection Control and Prevention

- Gloves and gowns on entry to room of patient with CDI
- Compliance with hand hygiene
- Soap and water
Infection Control and Prevention

• Identification and removal of environmental sources (i.e. replacement of electronic rectal thermometers with disposables)
• Use chlorine-containing agents or other sporicidal agents to address environmental contamination
• Spore form of *C. difficile* is highly resistant to killing by alcohol

Infect Control Hosp Epidemiol 2010

Infection Control and Prevention

• Accommodate pts with CDI in private rooms
• If single rooms not available, cohort patients
• Minimize frequency and duration of antimicrobial therapy

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Infection Control and Prevention

• There is NO need for:
  – Routine identification of asymptomatic carriers for infection control purposes
  • Treatment of such identified patients is not effective
  – Routine environmental screening for *C. difficile*
  – Administration of probiotics to prevent primary CDI
  • Limited data to support this approach and potential risk of bloodstream infection

Infect Control Hosp Epidemiol 2010
SUMMARY

• CDI rates are increasing nationally
• More severe strains are being seen, leading to increased morbidity and mortality
• Current therapies are not optimal
• Prevention is paramount:
  – Hand hygiene, environment, ASP

Prediction is very difficult, especially about the future.

Niels Bohr

THANK YOU