What’s New in the Management of *Clostridium difficile* Infection (CDI)?

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Notice!

This is a presentation on *Clostridium difficile* infection (CDI), not the presentation on CDI, which will be completed closer to the meeting date....

Objectives

Recognize the general mechanisms of CDI pathogenesis and be able to differentiate the clinical presentation of antibiotic association diarrhea from CDI.

Describe the epidemiology and recognize the risk factors for CDI acquisition and summarize the CDC initiative for facility-level reporting of CDI events.

Recognize the current treatment standards for CDI and review the literature regarding newer CDI therapies.

Identify established strategies for prevention of CDI including the role of antibiotic stewardship and employ relevant prevention strategies to your practice setting.
AAD and CDAD

Objectives

• Differentiate between Antibiotic Associated Diarrhea (AAD) and Clostridium difficile Associated diarrhea (CDAD)
• Describe the pathogenesis and transmission cascade that causes CDAD
• Describe the epidemiology and recognize the risk factors for CDAD acquisition
• Recognize the treatment alternatives for initial and relapsing CDAD
• Describe interventions for reducing the incidence of CDAD and AAD including the current available data relative to probiotics

Antibiotic Associated Diarrhea (AAD)

Introduction

• Diarrhea or loose stools is a common side effect of antibiotic therapy (~ 5-20%)
• Diarrhea is also a common condition in hospitalized patients (osmotic load, other drugs) and some studies suggest 80% of diarrhea in hospitalized patients may be due to non-CDAD causes
• Mechanisms of AAD: not completely understood > disruption in normal bowel flora (Bifidobacterium, Sacchromyces, Lactobacillus, etc.) that aid in digestion of CHO and bile acids, and maintain balance between pathogenic and non-pathogenic bacteria
• AAD: Diarrhea is watery, +/- mucus but no blood, colonic mucosa is normal - No systemic symptoms of infection other than dehydration. Contrast to CDAD

AAD Diagnostic Considerations


• Swedish prospective study 5 centers
• Antibiotic associated diarrhea 4.9% of all patients
• In the elderly AAD > 7.1%
• Abx duration more than 3 days greatly increased risk
• Broad-spectrum and anti-anaerobic antibiotics more at risk for AAD (cephs, clinda, FQ, etc.)

Key Point: AAD common, many ABX risk factors are same as CDAD risk factors
**Clostridium difficile**

**Introduction**

- Discovered in 1935
- Named *difficile* because it’s quite difficult to grow in the lab
- Gram-positive rod
- Spore-forming
- Obligate anaerobe

**CDAD Infection**

**Introduction**

- Most common cause of nosocomial infectious diarrhea in adults
- Significant morbidity and mortality
- Antibiotic use is strongly associated with CDAD (~90% of cases have antecedent ABX exposure)
- Major increase in incidence and disease severity in past 5-7 years

**CDAD Pathogenesis**
CDAD Infection

Pathogenesis

- Pathogenic C. difficile produces cytotoxins: A+B
  - Toxin B: cytotoxin
  - Toxin A: enterotoxin
  - Internalization of toxin
  - Epithelial mucosa
  - Destruction of actin regulation
  - Inflammatory response
  - Secretory diarrhea

Sunenshine, Cleve Clin Med, 2006

CDAD Pathogenesis

The role of immunity

- Humoral immunity primary defense
- Colonic IgA can neutralize the toxin
- Patients with high levels of antibody are typically asymptomatic – those with low levels develop severe and recurrent infections
- Elderly and immunocompromised more likely to develop recurrent CDAD

CDAD Infection

Clinical Presentation:

Spectrum of disease

- Asymptomatic
- Watery diarrhea
- Colitis/Pseudomembranous colitis
- Fulminant colitis
CDAD Presentation

Asymptomatic

- Most patients are asymptomatic
- Some surveillance studies suggest that up to 50% of patients will be colonized after 14 days hospitalization
- Reservoir for infection
- 80% of CDAD is still HC associated but 3-5% of the pop may harbor toxigenic strains wo/ HC exposure
- Do not treat asymptomatic carriage, prolongs carriage state
- Infection Control


CDAD Presentation

Watery diarrhea

- Diarrhea is watery, with mucus but no blood
- Colonic mucosa is normal
- No systemic symptoms
- Difficult to determine if this is clinical presentation is CDAD or merely AAD with positive test for CDAD
- Diarrhea may resolve in these cases / WO treatment by discontinuation of offending antibiotics

CDAD Presentation

Colitis

- Watery diarrhea (multiple times/day)
- Dehydration
- Malaise, abdominal pain, fever
- Mild leukocytosis
- Fecal leukocytes or blood present
- Sigmoidoscopy shows patchy erythema
**CDAD Presentation**

**Pseudomembranous colitis**

- Similar to colitis, but more severe
- Sigmoidoscopy shows classic pseudomembranes, yellow plaques colonic mucosa
- Colonic wall thickening

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**CDAD Presentation**

**Fulminant colitis**

- 3-7% of symptomatic infections
- High fever, chills, marked leukocytosis
- Profound leukocytosis (>20 K, Scr > 2.5 mg/dl) bad prognostic sign
- Severe cases may occur without diarrhea (obstruction)
- Complications
  - Perforation
  - Prolonged ileus
  - Megacolon
  - Death

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**CDAD Infection**

**Diagnosis**

- History and risk factors
  - Antibiotic or chemo exposures, other RF
- Physical findings and presentation
  - 3 or greater loose watery stools in 24 hours
- Laboratory diagnosis
  - Fecal leukocytes or occult blood, + CDAD test
- Colonoscopy for more severe cases
  - Patients with systemic S/S infection (leukocytosis >15K, inc SCR >50% over baseline), diminished bowel sounds, thickened colon wall via CT. Shock!
**CDAD Infection**

Key Point

- Most labs utilize some rapid test +/- confirmatory culture. May ELISA have false negatives and may need to submit an additional specimen if negative and high probability of CDAD.

E. coli, Cleve Clin Med, 2006

**CDAD Epidemiology**

**Epidemiology**
- Incidence has increased significantly over time in all settings.
- Most commonly dx Health Care associated rather than nosocomial.
- Increasingly CDAD WO HC exposure even WO/antibiotic exposure.

**Classic Risk Fx**
- Antibiotic therapy (esp. clinda, aminoPCN, cephs, and FQ)
- Neoplastic therapy.
- Old age.
- Severity of chronic disease.
- GI procedures.
- Acid anti-secretory medications (PPI).
- ICU stay.
- Duration of hospital stay.

**Changing Epidemiology of CDAD**


Changing Epidemiology of CDAD

- Epidemics of Diarrhea Caused by a Clindamycin-Resistant Strain of C. difficile in Four Hospitals.
- "J" Strain of C. difficile
- Late 1980s - 2000
- Same strain that possessed erm B gene that codes for ribosomal methylase (high level erythromycin resistance)
- Clindamycin OR 4.35 for J strain CDAD
- Multiple studies demonstrate reduction in clindamycin use implies reduction in CDAD.

Changing Epidemiology of CDAD


- Outbreak in late 2002 (n=1721 cases)
- Incidence quadrupled relative to early 90s
- Proportion of severe cases 7.1%>>>18.2%
- 30 day mortality 4.7%>>>13.8%
- Subsequently identified as BI/NAP1 strain. (Binary Toxin)
- Deletion of gene(tcdC) that is a negative regulator for production of C. difficile toxins A and B.
- Key Point!!! BI/NAP1 isolates produce 16 and 23 times more A and B toxins in vitro than previous epidemic strains, respectively

Changing Epidemiology of CDAD

An Epidemic, Toxin Gene Variant Strain of Clostridium difficile. NEJM, 2005, 353, 2433-41

- 187 Clostridium difficile isolates from 8 states compared to library of isolates from 1990s
- 47% BI/NAP1 strains vs. 17% historical
- 100% FQ resistant, 80% Clindamycin resistant

<table>
<thead>
<tr>
<th>Agent</th>
<th>BI/NAP1 (n=187)</th>
<th>BI/NAP1 (n=187)</th>
<th>BI/NAP1 (n=187)</th>
<th>BI/NAP1 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>20 (10.8)</td>
<td>31 (16.6)</td>
<td>10 (5.4)</td>
<td>30 (16.1)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>78 (41.9)</td>
<td>4 (2.1)</td>
<td>9 (4.8)</td>
<td>8 (4.3)</td>
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<tr>
<td>Vancomycin</td>
<td>151 (80.7)</td>
<td>11 (5.9)</td>
<td>12 (6.4)</td>
<td>22 (11.8)</td>
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<tr>
<td>Metronidazole</td>
<td>167 (88.9)</td>
<td>12 (6.4)</td>
<td>12 (6.4)</td>
<td>21 (10.9)</td>
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<tr>
<td>N/A</td>
<td>4 (2.1)</td>
<td>6 (3.2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: BI/NAP1 isolates were compared against BI/NAP5 isolates from a historical cohort.
CDAD Summary

- AAD vs CDAD
- Compare types of CDAD presentations
- Diagnosis of CDAD
- Risk factors for CDAD
- Pair, share, discuss

AAD and CDAD Treatment

General Principles

- Graded response based on severity of disease
- AAD may be treated with, changing or D/Cing, unnecessary antibiotics, probiotic, or anti-diarrheal co-administration
- Important to differentiate AAD from CDAD and understand caveats!
- Antibiotic “prophylaxis” in asymptomatic carriers of CDAD not appropriate!
- Watery diarrhea in a CDAD+ patient without S/S of local (focal WBC) or systemic S/S may respond to D/C of antibiotics alone.
- Avoid anti-diarrheals for any CDAD+ patient
- Antibiotic therapy +/- surgery is likely necessary for patients with CDAD colitis, pseudo-membranous colitis, or fulminate colitis

AAD and CDAD Treatment

Probiotic definition:

- Live microbes that beneficially affect the host by improving intestinal microbial balance
- Common organisms found in the gut and used as probiotics
- Lactobacillus
  - acidophilus, casei, rhaminosum GC, bulgaris
- Saccharomyces boulardii-yeast
- Bifidobacterium
- Unregulated as drugs – nutritional supplements
Probiotics and AAD/CDAD

Meta-analysis:
- Probiotic data suggest benefit for prevention of AAD
- Probiotic data for treatment of AAD and CDAD less clear/controversial
- Studies for RX of CDAD w probiotics
- Heterogeneous populations, agents, and studies
- All benefit from 2 studies w/ S. boulardii in severely ill patients RXd w/ high dose vanco
- S. Boulardii unique: yeast that produces a protease that neutralizes toxins A+B

“CDC is currently monitoring research on probiotic use, but cannot make any recommendations at this time.”

Reports of Saccharomyces fungemia in immunocompromised

“Administration of probiotics for primary prevention of CDAD not recommended at this time D/T limited data and bacteremia potential”

McFarland LV, AmJ Gastroenterol,2007
Shea CDAD Guidelines, ICHE 2010

AAD Treatment

- Probiotics:
  - Product selection: Recommend organisms and formulations that have been utilized in clinical studies whenever possible
  - Dose: Formal dose ranging studies have not been conducted. Recommend doses and regimens most frequently associated with clinical trials(doses varied considerably)
    - S. boulardii: 500 mg BID if standardized to 3 X 10^10 CFU/gm
    - Lactobacillus spp. 3 X 10^8 – 20 X 10^8 CFU BID-QID – Most studies conducted with 3-5 billion CFU/day BID
  - As these are food supplements concerns for potency, organism, viability, etc.

AAD Treatment

- Triage: Puss/blood in stool, fever, severe diarrhea or abd pain, elderly >>> medical evaluation
- Instruct on maintaining hydration
- Consider anti-motility agents only if CDAD negative
- May be able to DC or switch abx
- Probiotics may be considered at abx initiation or when diarrhea occurs and continued for several weeks after
- Avoid in: immunesuppressed and children < 2( not fully developed immune systems)!
CDAD Infection

Treatment

- Stop the offending antibiotic if possible (20-25% of cases will resolve if antibiotic is stopped—mild cases). Continued abx after dx and CDAD RX >>> increases risk for recurrence 10-fold!
- Avoid antimotility agents (slow toxin transit time)
- Maintain adequate hydration
- Start anti-Clostridial therapy

Gerding CID, 2008;46:S32-42

CDAD Infection

Treatment

Shea CDAD Guidelines, ICHE 2010

CDAD Treatment

Clin Inf Dis, 2007 Zar et al.

RCT of Vanco vs Metro

172 patients stratified by disease severity

Metro = Vanco overall
Metro < Vanco severe
Recurrence in 14 vs 15%

Vanco superior for SEVERE disease
CDAD Treatment


Quebec Group: Retrospective observational cohort of 165 cases severe CDAD
53% 30 day mortality (44% in first 48h)
After correction for predictors of survival AOR 0.22 95% CI 0.07-0.67, p=0.008
Beneficial inc>65 yo, WBC>20, or lactate 2.2-4.9

• If too ill and NPO >>>
• Cannot use PO meds>>>
• IV metronidazole + vancomycin enema may be used along w/surgery

CDAD Treatment

Treatment response and reoccurrence

• 85-90% of cases will initially respond to either metronidazole or vancomycin
• Surveillance data suggest resistance to either agent is low (0-5%) - rarely cause of failure
• 20-25% of patients will have a recurrent episode
• Persistent abnormal flora is considered the primary abnormality
• Re-challenge with antibiotics also a problem
• Treat first recurrence with same agent as previous treatment unless severe

Gerdning CID, 2008;46:S32-42

CDAD Infection

Fidaxomicin

• New macroyclic antibiotic approved in May, 2011 for treatment of CDAD
• Narrow spectrum – new MOA

• Phase 3 study:
• Fidaxomicin 200 mg QD vs Vancomycin 125 QID
  – Study 40% outpatient with moderate disease
  – Clinical cure 92.1% vs 89.8% (non-inferiority)
  – Recurrence of infection 13.3% vs. 24.0% (p=0.005)
  – Difference in recurrence rate occurred only in non-BINAP1 strains.
• Cost ~ $3,000 / treatment course and cost benefit yet to be determined...

NEJM, 2011;364:422-31
CDAD Infection

**Treatment: Multiple recurrences**

- Higher likelihood of RX failure (30-60%)
- Vancomycin preferred to metronidazole
- Big problem, lots of solutions few of them tested in RCT or not beneficial!!!!
- Higher dose vancomycin (500 mg QID) superior to low dose vancomycin
- Vancomycin taper (treat 10 days) then taper dose every few days until off (3-4 additional weeks)
- Vancomycin pulse dose (treat 10 days) then give every 3 days for 3-4 additional weeks
- Pulse dose and taper possibly effective

Gerding CID, 2008;46:S32-42

**CDAD: Alternative Treatments**

- Big problem, lots of solutions few of them tested in RCT or not beneficial!!!!
- Tolevamer: soluble non-antibiotic polymer binds toxin: RCT non-inferior to vanco > strong trend in favor of vanco not approved yet
- Other binding resins (cholestopol, etc.) NOT effective or recommended
- Nitazoxanide: Non-inferior to metronidazole. Promising open label data for salvage
- Rifaximin: limited data – no major trial data yet
- IVIG: not effective for salvage
- Stool transplant effective in case reports but no RCT

Gerding CID, 2008:46:S32-42

**CDAD Infection**

**Prevention**

- Contact isolation procedures effectively reduce transmission
  - Randomized trial of increased glove use decreased incidence from 7.7 to 1.5 cases/1000 patient/days
  - Careful attention to hand-cleansing is critical
  - Alcohol foam does not kill spores, less effects than soap and water
- Cohorting or isolation symptomatic patients
CDAD Infection

Prevention

• Environmental: Cleaning of environmental surfaces with sporicidal agent (chlorine-based)

• Antibiotic Stewardship:
  – Minimizing use of broad spectrum agents or narrow antibiotic spectrum (de-escalation)
  – Studies support restricting specific antibiotics associated with outbreaks associated w/ reductions
  – Per SHEA guidelines: Implement antibiotic stewardship program (A-II evidence)

CDAD Summary

• CDAD is a serious infection

• The incidence of CDAD infection has increased

• Most patients respond to antibiotic discontinuation, or RX with metronidazole or vancomycin treatment

• CDAD is associated with higher mortality in older debilitated patients

• Recurrent disease is common and difficult to treat

• There are effective strategies to prevent CDAD infection