C. Difficile Associated Diarrhea Overview & Management

Sajal Chopra
Pharm D. Candidate
Learning Objectives

1. Recognize the increasing incidence of C. difficile associated diarrhea (CDAD) and its risk factors

2. Recognize the severity of disease associated with the NAP1 strain and its risk factors

3. Describe severity criteria useful in choosing appropriate empiric therapy

4. Describe the appropriate monitoring parameters and strategies for management of patients with C. difficile

5. Address commonly asked questions encountered by pharmacists regarding CDAD
Definition

According to the IDSA guidelines, a case definition of CDI includes:

1) Presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours

2) A stool test result positive for the presence of toxigenic C. difficile or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis

Rarely (<1%) a symptomatic patient will present with ileus and colonic distension with minimal or no diarrhea.
BACKGROUND

Epidemiology
Pathogenesis
Risk Factors
Epidemiology

- 400% higher incidence in the US between 2004-2014 compared to the previous decade.\(^1\)

- In Canada, the rate per 1000 patient admissions has gone up from 4.51 in 2007 to 5.35 in 2011.\(^2\)

- Higher incidence has been seen in the elderly population (close to 10x more)\(^3\)

- Mortality rate for HA-CDI was 5.3% in 2011.\(^2\)
  - Includes directly and indirectly related death, 30 days after Hospital acquired C.Diff infection (HA-CDI)

Comparing Provincial & HSN average annual C.difficile rates

Pathogenesis

Exposure to *Clostridium difficile*
- Contaminated HCW hands
- Contaminated environment

Acquisition of *Clostridium difficile*

Clinical risk factors
- Insufficient immune response

Hospitalized patient

Alteration of gut flora (antibiotics)

CDAD

Asymptomatic colonization

Risk Factors

- Age greater than 65
- Recent antibiotic use
  - As far back as last 2-3 months
- Recent hospitalization
  - Along with length of stay
- Gastric acid suppression
  - PPIs, Antacids, H2RAs
- Immunosuppression
  - Steroid use, Chemotherapy, HIV
- Inflammatory bowel disease
  - Higher incidence in Ulcerative Colitis vs Crohn’s Disease
- Manipulation of GI tract (surgery), including tube feeding

NAP1/BI/027 Strain

- Hypervirulent strain that has up to 20 times more toxin production than normal due to a gene mutation

- Found to be resistant to Fluoroquinolones, which has led to it’s correlation with Fluoroquinolone use

- Led to an outbreak in Quebec in the early 2000s, with an overall mortality rate of 16%.\(^1\)

- Subgroup analysis showed no difference in outcomes for those aged less than 60 but more severe outcomes in older patients.\(^1\)

# NAP1 and Mortality

<table>
<thead>
<tr>
<th></th>
<th>NAP1/027</th>
<th>Other types</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death and ICU admissions</td>
<td>39 (12.5%)</td>
<td>41 (5.9%)</td>
<td>80</td>
</tr>
<tr>
<td>No severe outcomes</td>
<td>272 (87.5%)</td>
<td>656 (94.1%)</td>
<td>928</td>
</tr>
<tr>
<td>Total</td>
<td>311</td>
<td>697</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.0003 (Chi-Square test)

DIAGNOSIS/MANAGEMENT
## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR toxin gene detection</td>
<td>92-97</td>
<td>100</td>
<td>• Highly sensitive and specific</td>
<td>• Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fast (1-2 hours)</td>
<td></td>
</tr>
<tr>
<td>ELISA toxin test</td>
<td>65-85</td>
<td>95-100</td>
<td>• Fast (2-6h)</td>
<td>• Not very sensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Easy to do</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• High specificity</td>
<td></td>
</tr>
<tr>
<td>Cytotoxin assay</td>
<td>80-90</td>
<td>99-100</td>
<td>• High sensitivity &amp; specificity</td>
<td>• Takes 24-48h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Needs tissue culture facility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Only detects toxin B</td>
</tr>
<tr>
<td>Stool Culture</td>
<td>90-100</td>
<td>98-100</td>
<td>• Allows strain typing</td>
<td>• 2-5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Labor intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Non-specific</td>
</tr>
</tbody>
</table>

C. Difficile toxin is very unstable at room temperature and may be undetectable within 2 hours of collection if not promptly refrigerated or tested, giving a false negative.³

---

Diagnosis

- Patient must have unformed stools (symptomatic) for it to be sent for culturing
  - a stool specimen that takes the shape of the container it is put in and is equivalent to types 5-7 on the Bristol stool chart.

- Asymptomatic patients should not be tested because as many as 20-50% of adults in a healthcare environment can be carriers.

- Test of cure should not be performed as a successfully treated patient can still shed toxin in the stool for many weeks.

---

Percentage of stool, skin and environmental cultures positive for C. difficile among 52 patients with C.diff infection. The numbers of patients who had samples cultured at each time point were 52 before treatment, 48 on day 3 of treatment, 43 after resolution of diarrhea, 28 at the end of treatment, 22 at 1–2 weeks after treatment, 15 at 3–4 weeks after treatment, and 8 at 5–6 weeks after treatment.

Determining severity

As per the 2010 IDSA guidelines:

- Mild to moderate if WBC 15,000 cells/µL or lower AND SCr level less than 1.5x baseline

- Severe if WBC >15,000 cells/µL OR SCr level greater than or equal to 1.5x baseline

- Severe, complicated if presence of hypotension/shock, ileus, megacolon

**Criteria based on expert opinion.**

Since then..


Severity Criteria

- Age greater than 65
- Immunosuppression (HIV with CD4 less than $50 \times 10^6$, solid organ or stem cell transplant, neutropenia, systemic steroids equivalent to prednisone 20 mg daily)
- Temperature greater than 38°C
- Increase in SCr greater than 50% from baseline or significantly decreased urine output
- WBC greater than $15 \times 10^9$/L
- Albumin less than 30 g/dL
- Abdominal examination consistent with peritonitis

Mild to Moderate Disease
- Patient meets less than 2 severity criteria
  + Patient is stable with no signs of shock*

Severe Disease
- Patient meets 2 or more severity criteria
  + Patient is stable with no signs of shock*

Complicated/Fulminant Disease
- Patient is hemodynamically unstable or has signs of shock*
  OR
- Patient has ileus or toxic megacolon

*Shock: SBP less than 90 mm Hg or SBP decrease greater than 40 mm Hg from baseline, urine output less than 0.5 mL/kg/h, decreased level of consciousness, serum lactate greater than 2 mmol/L

Available at:
Treatment

Mild/Moderate Disease

- **Metronidazole 500 mg** PO/NG three times daily for 10-14 days
  *IV if unable to take enteral medication, PO/NG preferred

Severe Disease

- **Vancomycin 125 mg** PO/NG four times daily for 10-14 days
  **Metronidazole 500 mg** IV three times daily for 1-14 days
  +/-

Complicated/ Fulminant Disease

- **Vancomycin 125 mg** PO/NG four times daily for 14 days
  **Metronidazole 500 mg** IV three times daily for up to 14 days
  +/-

- **Vancomycin 500 mg** in approximately 100 mL NS per rectum four times daily as retention enema, retain for 60 minutes
Monitoring

☐ Vital signs (Temp, BP) ☐ Creatinine ☐ Frequency of bowel movements
☐ Electrolytes ☐ Albumin
☐ CBC ☐ Lactate

Reassess the need for following therapies:

- Concurrent antibiotics for active infection. If required, possible to switch to lower risk antibiotics?

- Concurrent acid suppression (PPIs, H2RAs, Antacids)

- Discontinue antidiarrheal/antiperistaltic agents
  - Want the toxin to be flushed out of the colon
  - Metronidazole achieves higher concentration in the colon in presence of diarrhea

- Discontinue/reassess narcotics and bowel regimens
Response to Treatment

Is patient responding to treatment?

Yes
- Continue current treatment
  - Ongoing monitoring

No
- Patient deteriorating at any time
- OR
  - Failing to respond to therapy by end of day 4*, if any of the following:
    - Frequency and volume of loose bowel movements not improved
    - Fever greater than 38°C by the end of day 2
    - White blood cell count greater than 15 x 10^9/L
    - Worsening symptoms/deteriorating at any point

Reassess severity/treatment

Available at:
Treatment for recurrence

- First recurrence is treated with the same regimen as the initial episode but stratified by disease severity. \(\text{(C-III)}\)

- Do not use Metronidazole beyond first recurrence or for long term chronic therapy due to risk for cumulative neurotoxicity. \(\text{(B-II)}\)

- For second or later recurrence, use Vancomycin therapy using a tapered and/or pulse regimen as the preferred strategy. \(\text{(B-III)}\)

Pulse regimen

- Vancomycin 125 mg PO q6h for 10-14 days then, 125 mg PO BID for 7 days followed by 125 mg PO daily for 7 days, and then 125 mg every 2-3 days for 2-8 weeks.¹

- Vancomycin 125 mg PO q6h for 10 days, followed by 125 mg PO daily pulsed every 3 days for 10 doses.²

Purpose of the pulse regimen is to allow the spores to germinate and then kill the vegetative form of C. difficile as spores are not eradicated by antibiotics.

APPLYING THE ALGORITHM

Intervention Template

Purpose

APPLYING THE ALGORITHM
Intervention Template

Intervention name: FNA

Date:

Current treatment:

C diff PCR:

a) Age > 65?

b) Immunocompromised?

c) Fever (> 38)?

d) SCr increased more than 50% from baseline or reduced urine output?

e) WBC > 15?

f) Albumin < 30?

g) Peritonitis?

1 point for each of above AND positive PCR:

Score 0-1 = Mild/mod = Flagyl 500 mg PO q8h x 10-14 days.

Score 2+ = Severe = Vanco 125 mg PO q6h x 14 days +/- Flagyl 500 mg IV q8hr x 1-14 days.

Ileus/toxic megacolon/shock = Complicated = Vanco 125 mg PO q6h x 14 days AND Flagyl 500 mg IV up to 14 days +/- vanco retention enema 500 mg in 100 mL NS PR QID (retain for 60 mins)

Suggestions:

Plan/FU:
Purpose

- Pharmacist’s involvement early in the CDI process is critical for timely interventions on medication related issues.

- We want to be able to gather stats on the number of patients we intervene on to change therapy.

- Also how many patients are started on the correct regimen according to severity.

- Ultimately want to transition this into a pre printed order or an automatic substitution.

Available at:
FREQUENTLY ENCOUNTERED QUESTIONS BY PHARMACISTS
Questions

1. Are certain antibiotics more likely to cause C. difficile infection?

2. How soon can we repeat PCR testing after a negative test result?

3. Do probiotics have any role for treatment or prevention of C. difficile infection?
Antibiotics and C. difficile Risk

- Any antibiotic can potentially cause a C. difficile infection
- No head to head RCTs out there comparing antibiotics and their risk for C. difficile infection
- Most if not all data comes from retrospective or observational studies, thus lots of confounders
- Highly dependent on prescribing trends! More you use, more likely to see CDI

**Frequently associated**
- Fluoroquinolones
- Clindamycin
- Cephalosporins
- Penicillins (broad spectrum)

**Occasionally associated**
- Macrolides
- Septra

**Rarely associated**
- Aminoglycosides
- Tetracyclines
- Metronidazole
- Vancomycin

Table adapted from UptoDate
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description of Meta-analysis</strong></td>
<td>13 Case control studies and 1 cohort study</td>
<td>6 Case control studies and 1 cohort study</td>
<td>8 case control studies Cases not reported</td>
</tr>
<tr>
<td></td>
<td>3202 cases</td>
<td>2578 cases</td>
<td>30,184 patients</td>
</tr>
<tr>
<td></td>
<td>15,938 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>OR: 1.57 (CI: 2.04-4.02)</td>
<td>OR: 16.8 (CI: 7.48-37.76)</td>
<td>OR 20.43 (CI: 8.50-49.09)</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td>OR: 1.97 (CI: 1.21-3.23)</td>
<td>OR: 5.68 (CI: 2.12-15.23)</td>
<td>OR: 4.47 (CI: 1.60-12.50)</td>
</tr>
<tr>
<td></td>
<td><strong>Subgroup</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; gen – OR 1.36 (CI 0.92-2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; gen – OR 2.23 (CI 1.47-3.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; gen – OR 3.20 (CI 1.80-5.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
<td>OR: 1.66 (CI: 1.17-2.35)</td>
<td>OR: 5.50 (CI: 4.26-7.11)</td>
<td>OR: 5.65 (CI: 4.38-7.28)</td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td>No significant association seen</td>
<td>OR: 2.71 (CI: 1.75-4.21)</td>
<td>OR: 3.25 (CI: 1.89-5.57)</td>
</tr>
<tr>
<td></td>
<td><strong>Pip-Taz/Amoxi-clav subgroup</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR 1.54 (CI 1.05-2.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td>No significant association seen</td>
<td>OR: 2.65 (CI: 1.92-3.64)</td>
<td>OR: 2.55 (CI: 1.91-3.39)</td>
</tr>
<tr>
<td><strong>Septra</strong></td>
<td>OR: 1.78 (CI: 1.04-3.05)</td>
<td>OR: 1.81 (CI: 1.34-2.43)</td>
<td>OR: 1.84 (CI: 1.48-2.29)</td>
</tr>
<tr>
<td><strong>Carbapenemems</strong></td>
<td>OR: 1.84 (CI: 1.26-2.68)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>No significant association seen</td>
<td>No significant association seen</td>
<td>No significant association seen</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>No significant association seen</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

Abbreviations: Odds Ratio (OR), 95% Confidence interval (CI)

Available at: https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence
Does Doxycycline Protect Against Development of Clostridium difficile Infection?

Sarah B. Doernberg,1 Lisa G. Winston,1 Daniel H. Deck,2 and Henry F. Chambers1

1Department of Internal Medicine, Division of Infectious Diseases, University of California, San Francisco, and 2Department of Pharmaceutical Sciences, San Francisco General Hospital, California

Background. Receipt of antibiotics is a major risk factor for Clostridium difficile infection (CDI). Doxycycline has been associated with a lower risk for CDI than other antibiotics. We investigated whether doxycycline protected against development of CDI in hospitalized patients receiving ceftriaxone, a high-risk antibiotic for CDI.

Methods. We studied adults admitted to an academic county hospital between 1 June 2005 and 31 December 2010 who received ceftriaxone to determine whether the additional receipt of doxycycline decreased the risk of CDI. Patients were followed from first administration of ceftriaxone to occurrence of CDI or administrative closure 30 days later.

Results. Two thousand three hundred five unique patients comprising 2734 hospitalizations were studied. Overall, 43 patients developed CDI within 30 days of ceftriaxone receipt, an incidence of 5.60 cases per 10,000 patient-days. The incidence of CDI was 1.67 cases per 10,000 patient-days in those receiving doxycycline, compared to 8.11 per 10,000 patient-days in those who did not receive doxycycline. In a multivariable model adjusted for age, gender, race, comorbidities, hospital duration, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics, for each day of doxycycline receipt the rate of CDI was 27% lower than a patient who did not receive doxycycline (hazard ratio, 0.73; 95% confidence interval, .56-.96).

Conclusions. In this cohort of patients receiving ceftriaxone, doxycycline was associated with lower risk of CDI. Guidelines recommend this combination as a second-line regimen for some patients with community-acquired pneumonia (CAP). Further clinical studies would help define whether doxycycline-containing regimens should be a preferred therapy for CAP.

References:

Repeat PCR Testing

- Micro policy: You must wait a week before you can repeat a C. diff toxin PCR after it comes back negative.

- Retrospective cohort study looked at 406 repeat tests in the two weeks after the initial negative.

- Only 10 of 406 tests came back positive (2.5%) in the two weeks.

- Rate of positives within 1 week was 1.1% while after the 1 week mark it was 5%.

Repeat testing within a week after a negative result is of little to no clinical value.

Luo RF, Banaei N. Is repeat PCR needed for diagnosis of Clostridium difficile infection?. J Clin Microbiol. 2010;48(10):3738-41
Probiotics

- Limited data out there for treatment, more data pertaining to prevention

- 2012 Meta analysis looking at 20 randomized trials with a total of 3818 patients, concluded probiotics reduce incidence of C. difficile associated diarrhea (CDAD) by 66%¹

- Common problem with these meta analyses is the heterogeneity between studies as not all studies use the same strain/formulation or dose

- Probiotics are not regulated as tightly as drugs, which makes them more susceptible to manufacturing inconsistencies

- PLACIDE study published in 2013 was a large, well designed RCT with 2941 patients over the age of 65, looking at CDAD prevention using a multistrain preparation of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*²
  - Found no significant reduction in CDAD (RR 0.71; 95% CI 0.34-1.47)

- Risks of probiotics include bacteremia/fungemia in severely ill or immunocompromised patients

- Overall, no good data to support use of probiotics in treatment or prevention of CDAD but is an option for patients who can afford it and have no contraindications

---


Questions?