*Clostridium Difficile* colitis - We need to get this monkey off our backs!

ECHO-June 15, 2017

Charles Krasner, M.D.

UNSOM, Reno

Sierra NV Veterans Affairs Hospital
Growing
incidence of
C. difficile
Infection (CDAD)

- MMWR- “...incidence, deaths, and excess health care costs are at historic highs” +/- $6.3 billion/yr
- 3x increase in decade- now 500,000 infections and 29,000 deaths per year. More deaths than even MRSA infections.
- **#1 cause** of increase- over use of antibiotics
- **#2 cause** – appearance of a more virulent C. *diff* strain (NAP-1) associated with risk of greater mortality and increased relapse rate – approx. 20% of cases
- **#3 cause**- overdiagnosis
THE IMPACT OF C. difficile Infection (CDI)

**CDI IS SERIOUS, DEADLY, AND EXPENSIVE**

- **29,000 US deaths/year within 30 days of diagnosis**
- **1 in 5 (83,000) recurrences within 2 months**
- **CDI adds up to: 12 days in the hospital and $27,160 per case in direct costs**

**MORE THAN 1/3 OF CDI CASES ARE NOT ASSOCIATED WITH INPATIENT STAY**

- **29%** outpatient healthcare exposures including doctor and dentist offices
- **65%** at least one overnight, INPATIENT hospital stay
- **6%** NOT HEALTHCARE-ASSOCIATED

**EVERYONE CAN HELP REDUCE THE RISK OF CDI**


**PATIENTS**
- Use antibiotics only when necessary
- Don't demand antibiotics for viral infections like colds or flu
  
  *Antibiotics are the single most important risk factor for CDI and should be used only when necessary.*
- Wash your hands thoroughly after using the bathroom

**HEALTHCARE PROFESSIONALS**
- Prescribe antibiotics carefully — change the prescription if needed once you get culture results
- Order a C. difficile test when appropriate
- Promptly identify and isolate infected patients
- Use gloves, wash your hands frequently, and practice good patient contact precautions

**HEALTHCARE ENVIRONMENTS**
- Thoroughly clean using an EPA-approved, spore-killing disinfectant
- Notify other facilities when transferring patients with CDI

[National Foundation for Infectious Diseases]
Antibiotic Rx for Hospitals
Proceed with Caution

If
prescriptions of high-risk antibiotics in hospitals are reduced by 30%

Then
it could lead to 26% fewer cases of deadly diarrhea infections

CDAD is a Clinical Diagnosis

- Watery diarrhea is the cardinal symptom of C. difficile–associated diarrhea (CDAD) with colitis (≥3 loose stools in 24 hours). Other manifestations include lower abdominal pain and cramping, low-grade fever, nausea, anorexia, and leukocytosis.
C. difficile spores germinate in the small bowel upon exposure to bile acids.

Flagellae facilitate C. difficile movement; a polysaccharide capsule discourages phagocytosis.

Facilitates adherence to the colonic epithelium.
Markedly thickened bowel wall in C. diff colitis
C. Diff Lab

Diagnosis-

remember it is the toxin that causes the symptoms

• **Direct culture**- not used - $$$/slow turn around time

• **C. diff PCR**- is there *C. difficle* in the stool? 100% sensitive, but DOES NOT differentiate between those c.diff that are secreting the toxin and those that are not. Whether or not toxin is being secreted, the PCR test will be positive+

• **ELISA** – *Is the C. difficle secreting toxin and causing disease?* detects both the presence of C. difficile bacteria (GDH Ag) as well as detects toxin A +/- toxin B.
Drawback to Molecular (NAT) testing- a positive PCR test does not always mean active infection!

- Toxins cause the disease, so only a test for active Toxin A or B production can help determine if the patient has an active infection or is only a carrier of C. diff
- Colonized carriers (PCR+/toxin -) are 5 to 10 times more common than actively infected patients (PCR+/toxin +) in the hospital
- Diarrhea is common in the hospital – due to laxatives, dietary supplements, medication side-effects and not just colitis
- So assuming a positive PCR test means active disease that needs treatment most of the time will lead to unnecessary treatment
Advantage of ELISA toxin testing

- Can identify both the presence of *C. diff* bacteria (by testing for GDH antigen) and then testing for the disease causing toxins A & B. Neg test result for GDH has same Neg Pred Value as a negative PCR test.

- Based on UC Davis study- allows us to avoid unnecessarily treating patients with PCR+/toxin- test result.
Kaplan-Meier Curves of Time to Resolution of Diarrhea by Clostridium difficile Test Group
The median duration of diarrhea for patients with at least 1 day was 3 days (interquartile range, 1-6 days) for Tox+/PCR+ (121 of 131), 2 days (interquartile range, 1-4 days) for Tox−/PCR+, and 2 days (interquartile range, 1-3 days) for Tox−/PCR− (927 of 1123) (P < .001). Log-rank P values are P < .001 for all groups, P = .003 for Tox+/PCR+ vs Tox−/PCR+, (143 of 162) P < .001 for Tox+/PCR+ vs Tox−/PCR−, and P < .001 for Tox−/PCR+ vs Tox−/PCR−. Tox+/PCR+ indicates C difficile toxin immunoassay positive and polymerase chain reaction positive; Tox−/PCR+, C difficile toxin immunoassay negative and polymerase chain reaction positive; Tox−/PCR−, C difficile toxin immunoassay negative and polymerase chain reaction negative.
NAP-1 *C. diff* strain- nasty super bug now seen throughout Nevada and USA.

- Approx. 1/2 of all cases in NV are NAP-1 positive!!!
- resistant to antibiotics commonly overused in clinic and hospital, particularly fluoroquinolones (Cipro, levofloxacin)
- A genetic mutation allows 10 to 20x more toxin A and B to be secreted, plus it has its own unique binary toxin
- More likely to relapse and progress to fulminant disease and death
- If your micro lab does a PCR test, they are already testing for NAP-1, but you may need to request results
On one end of the spectrum-severe disease: NAP-1+ C. difficile Infection Case

- Spring 2016, 84 year old male receives ciprofloxacin for bacteriuria. Develops C. difficile colitis (PCR+/NAP-1 +). Treated with oral metronidazole.
- Subsequently, has 4 CDI relapses. Treated with oral metronidazole and oral vancomycin
- Undergoes successful stool transplant October, 2016
- Has a fall at home and admitted to hospital January 2017. Given ampicillin for possible cellulitis. In hospital, develops watery diarrhea; within a day progresses to hypotension, lactic acidosis, WBCs 35,000 and renal failure. Abdomen distended, tender no bowel sounds. Stool again shows C. diff PCR+/NAP-1 +
- Day # 3 of illness goes for sub-total colectomy. On pressors, dialysis, respirator
- Day #14- dies
Recurrence of C. diff NAP-1 case

- 75 year old initially admitted to hospital 2/2017 for COPD evaluation. On outpatient PPI, insulin, BP meds

- ICU admit: Given ceftriaxone, azithromycin, steroids, PPI. On ventilator. 2 weeks in hospital

- Goes to SNF for 2 weeks, readmitted 4/2017 with severe abd pain, watery diarrhea, WBC- 24,000, CT scan show colitis. Stool positive for C.diff PCR and NAP-1 PCR positive. No C diff Toxin A&B test available. Treated successfully with oral vancomycin, 10 days in hospital, stools formed by discharge.

- Sent back to same SNF. Remains on PPI. Uh-oh...
C. diff case, cont.

- 10 days prior to discharge home from the SNF, given ceftriaxone for “UTI”. Now with onset of diffuse abd pain, watery diarrhea, severe pan-colitis on CT scan, acute renal failure, WBCs 35,000, lactic acidosis.
- Stool shows same PCR results, but now tested for C.diff toxin A&B: positive. treated with oral/rectal vancomycin and iv tigecycline
- WBCs up to 43,000; condition deteriorates, undergoes total colectomy
On the other end of the spectrum: Asymptomatic *C. diff* Carriers

- 60% of stool carriers in one study also had it on their skin and their surrounding environment
- Spores on the skin of these carriers were easily transferred to others
- Non-poopers are important sources of potential infection to others- everyone should wash with soap and water!
Are we over-diagnosing C. diff infection?

• Careful patient selection is vital
• Up to 50% of tested patients don’t have significant diarrhea (Bristol 7, three or more stools /day)
• Up to 40% are on a laxative regimen when tested
• The PCR test may be 100% sensitive, but only a 45% positive predictive value for CDI- actual disease
• There is no difference in length of diarrhea or mortality in **PCR+/toxin** - or **PCR-/toxin** - patients!
“Diarrhoea in the critically ill is common, associated with poor outcome, and rarely due to Clostridium difficile”
Nikhil Tirlapur, Zudin A. Puthucheary, Jackie A. Cooper, Julie Sanders, Pietro G. Coen, S. Ramani Moonesinghe, A. Peter Wilson, Michael G. Mythen & Hugh E. Montgomery

- Study in ICU patients with diarrhea found 10% were Antigen positive for C. diff, only 1% actually were Toxin positive (study done with ELISA test)
- “A low yield of stool investigations and low prevalence of Clostridium difficile and norovirus suggest a possible pathogenic role for non-infective processes. Several patients received laxatives and enemas before diarrheal episodes suggesting a need for rational intensivist prescribing.”
# Bristol Stool Scale

**Choose your POO!**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rabbit droppings. Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>2</td>
<td>Bunch of grapes. Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>3</td>
<td>Corn on cob. Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>4</td>
<td>Sausage. Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>5</td>
<td>Chicken nuggets. Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>6</td>
<td>Porridge. Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>7</td>
<td>Gravy. Watery, no solid pieces ENTIRELY LIQUID</td>
</tr>
</tbody>
</table>

**Bristol Stool Scale**

| Type 7 | Watery, no solid pieces. Entirely liquid. |
| Type 6 | Fluffy pieces with ragged edges, a mushy stool |
| Type 5 | Soft blobs with clear-cut edges (passed easily) |
| Type 4 | Like a sausage or snake, smooth and soft |
| Type 3 | Like a sausage but with cracks on surface |
| Type 2 | Sausage-shaped but lumpy |
| Type 1 | Separate hard lumps, like nuts (hard to pass) |

Children’s version of the Bristol Stool Chart
Negative consequences of over-treating CDI

• Contact precautions adversely effect the patient- anxiety, depression, isolation
• Receive unnecessary antibiotics that can paradoxically increase risk of actual CDI and select for VRE etc
• Expense of isolation, need for single room
• Adversely effect hospital infection incidence rate
C. diff testing should be restricted only to patients who fit the clinical diagnosis of this colitis

Asymptomatic C. diff colonization and not infection is a common reason for a positive stool PCR test

Stool C. diff testing is not appropriate after treatment of CDI in the absence of symptoms

Postinfectious functional abdominal symptoms occur in 25% of CDI patients and should be differentiated from recurrent CDI with a careful history
Antibiotic Stewardship role: Educate/reinforce this idea at every opportunity

“C. Diff Infection” therapy is based on the principle of:

*treat the symptom, not the test result*

C. diff (as well as UTIs) are not laboratory defined diagnoses, but must be based on clinical signs and symptoms and only then backed up by lab tests if needed.
What else can we do to reduce incidence of C. diff infection?

- Don’t do a “test of cure” PCR test, no matter what the Nursing home requests. Up to 60% of patients remain positive after successful C. diff treatment (no longer Bristol type 7)-they are carriers
- The Micro lab should refuse to test any stool except Bristol 7
- Identify charts of patients that have had C. diff previously – Notification to providers to think twice before prescribing antibiotics
- Review indications for PPIs in the facility- make them opt-in instead of automatic on admit orders. Possibly list indications for PPIs
- Don’t order C.diff tests on patients on stool softeners
What else can we do to reduce incidence of C. diff infection?

Enforce Guidelines for bacteriuria and UTI

• Remove screening u/a’s from pre-op orders
• Educate RNs not to obtain u/a’s from patients with Foley’s unless they have symptoms of burning, etc
• Adopt the guidelines we have talked about for appropriate evaluation of bacteriuria and the primary, short course use of antibiotics that don’t cause c.diff. Avoid Fluoroquinolones whenever possible