Clostridium Difficile colitis - Treat the Patient, not the Test!
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Growing incidence of *C. difficile* Infection (CDI)

- 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 associated with risk of greater mortality and increased relapse rate – approx. 20% of cases
  - **#3 cause**- overdiagnosis???
Pathogenesis of *C. difficile*-associated Disease

From Shim et al. *Lancet* 1998
Pathogenesis of C difficile-associated Disease

From Shim et al. Lancet 1998
Pathogenesis of
C difficile-associated Disease

From Shim et al. Lancet 1998
Clinical Diagnosis of CDI

• 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.
Clostridium difficile
spores and vegetative
cells are ingested

- Spores
- Vegetative cells

Most vegetative cells are
killed in the stomach, but
spores can survive the acid
environment

C. difficile spores germinate
in the small bowel upon
exposure to bile acids

Flagellae facilitate C. difficile
movement; polysaccharide
capsule discourages phagocytosis

C. difficile multiplies in the colon

Gut mucosa facilitates
adherence to the colonic
epithelium

C. difficile vegetative cells produce toxins A and B and
hydrolytic enzymes (1). Local production of toxins A and
B leads to production of tumour necrosis factor-alpha
and proinflammatory interleukins, increased vascular
permeability, neutrophil and monocyte recruitment (2),
opening of epithelial cell junctions (3) and epithelial cell
apoptosis (4). Local production of hydrolytic enzymes
leads to connective tissue degradation, leading to colitis,
pseudomembrane formation (5) and watery diarrhea.
Factors Underlying the Upsurge of *C. difficile* Disease

- Increasing virulence of strains
- Increasing resistance of strains to antibiotics
- Increasingly older, compromised population, more antibiotic exposure
- ?? Alcohol-based Handrubs
**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 common antibiotics overused in 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 progress to fulminant disease and death
- Increased rate of spore germination to active disease increases likelihood of relapse
- 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 presentation

• 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
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!
Question

Are we over–diagnosing and over-treating *C. difficle* infection?
C. Diff Lab Diagnosis- remember it is the toxin that causes the symptoms

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

• **C. diff PCR**- positive test tells you *C. difficile* carrying the toxin B gene is present 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. diff actively producing 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 has many potential negative consequences for both the patient and the hospital
Negative consequences of over-treating CDI

- Contact precautions adversely affect 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
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 negative.
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!
Bristol Stool Scale

Children’s version of the Bristol Stool Chart
Antibiotic stewardship role

- *treat the symptom, not the test result*
- “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 insists you do before sending the patient back

Up to 60% of patients remain positive after successful C. diff treatment (no longer Bristol type 7)

The Micro lab should refuse to test any stool except Bristol 7
Test time!
IV. Increased virulence of NAP-1 strain is a result of which of the following?

- Lower rates of germination
- Higher resistance to anti-fungal agents
- Gene mutation leading to reduced toxin production
- Ability to produce large amounts of toxin A and B that overwhelm treatment attempts
C. Diff case

- 28 year old male presented with abd pain and diarrhea (>10 Bristol type 7 stools daily) after a course of Augmentin for pneumonia. Diagnosed with CDI by PCR test positive for the Toxin B gene. Treated with 10 day course of metronidazole with resolution of his symptoms. Returned to baseline 2 to 3 Bristol type 4 stools per day. Starting six weeks later, again had abd discomfort for the next 3 weeks relieved by bowel movements with increased stool frequency (4 to 5 type 4 stools per day). PE showed a soft abdomen, WBC was 7.8, and repeat stool test for C. difficile toxin PCR was again positive. **What would you do next?**

- Diagnose recurrent C. diff infection (CDI) and prescribe another course of metronidazole
- Diagnose severe CDI and prescribe oral vancomycin
- Diagnose refractory CDI and consider fecal stool transplant
- Diagnose postinfectious altered bowel habits with C. diff colonization and recommend a high-fiber diet
Bottom Line

• C. diff testing should be restricted to patients suspected of having CDI who have multiple watery stools

• Asymptomatic C. diff colonization is a common reason for a false + stool PCR test

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

• Postinfectious functional abd symptoms occur in 25% of CDI patients and should be differentiated from recurrent CDI with a careful hx
To paraphrase Bill Clinton, when it comes to C. diff and UTI therapy...It’s the patient, stupid.