C. difficile Infection: From Canine Detection to Poop Enemas

Structure:
1. 
2. 

3. Objectives:
   • To review and understand *C. difficile*...
      • Changing Epidemiology
      • Diagnosis
      • Transmission/ Control
      • Treatment
      • Future Directions

4. Cost/Economic Burden of C. diff in Canada

The incidence of *Clostridium difficile* infection has increased by about 20 times over the past 10 years, and rates are about 20 per 100,000 population.

“The economic burden of hospital-acquired Clostridium difficile infection: a population-based matched cohort study”
- The main study outcomes were up-to-3-year costs, which were evaluated in 2014 Canadian dollars.
- Results — We identified 28,308 infected subjects (mean annual incidence, 27.9 per 100,000 population, 3.3 per 1,000 admissions), with a mean age of 71.5 years (range, 0-107 years), 54.0% female, and 8.0% elective admissions. For elective admission subjects, cumulative mean attributable 1-, 2-, and 3-year costs adjusted for survival (undiscounted) were $32,151 (95% CI, $28,192-$36,005), $34,843 ($29,298-$40,027), and $37,171 ($30,364-$43,415), respectively. For nonelective admission subjects, the corresponding costs were $21,909 ($21,221-$22,609), $26,074 ($25,180-$27,014), and $29,944 ($28,873-$31,086), respectively.

5. What is C. difficile?
- *Clostridium difficile* is a gram-positive anaerobic bacilli which forms spores
- Part of our normal gut flora but resistant to many antibiotics

6. Risk Factors for C. Difficile:
   When patients are treated with antibiotics, it disrupts the normal balance of flora, killing off those that usually keep the c. difficile in check and allowing it to overgrow or even produce new more virulent strains
Hospital-acquired c. difficile introduces a virulent strain to susceptible patients who are at higher risk as they may be on antibiotics, PPIs or be immunocompromised.

**Why would PPI’s increase risk?**
The scientific hypothesis is that the gastric acidity protects the gastrointestinal tract from ingested bacteria. The scientific hypothesis is that **if you impair the gastric acid by means of an acid-suppressive agent**, that you may diminish the protective effect of the gastric acidity and thereby raise risk for gastrointestinal infection.

There are many different strains of *C. difficile* and one strain, **North American Pulsed Field type 1, known as NAP1**, is likely to cause serious illness.

In severe cases, *C. difficile* infection can result in bowel perforation and, rarely, death.

7. **Most common antimicrobials associated with CA-CDI:**
   a. Clindamycin (OR 16.8)
   b. Fluoroquinolones (OR 5.5)
   c. Cephalosporins (OR 5)

   **27% did not have antibiotic exposure**
   **17% did not have any risk factors**

8. **C. Diff Life Cycle**

*C. difficile* is an obligate anaerobe, acquired by the ingestion of spores via the fecal-oral route. These spores can survive even in harsh environmental conditions.

**Because C. difficile** spores are also resistant to alcohol-based cleaners, spores are especially prevalent in hospital environments and have been detected months after initial exposure.

**CDI pathogenesis.**
Development of disease is dependent on different stages of the *C. difficile* life cycle.

Initial spore exposure from various sources does not necessarily result in disease, particularly in a healthy individual. A **healthy, diverse microbiota is capable of interfering with C. difficile** spore germination and vegetative growth.

However, **if the metabolic and microbial environment of the gut has been perturbed, spore germination, vegetative outgrowth, and toxin production will occur.** Epithelial damage, inflammation, and clinically overt disease will result from toxin production.
Sporulation of *C. difficile*, release of spores into the environment, and transmission to new hosts perpetuates the infectious cycle.

9. Once colonized, *C. difficile* can lead to toxin-mediated inflammation and disease. *C. difficile* produces 2 major toxins responsible for disease, the large clostridial toxins A and B (TcdA and TcdB). These toxins are largely responsible for the damage to the mucosal epithelium and induction of an inflammatory response.

Another toxin, the *C. difficile* binary toxin (CDT), has been observed to disrupt the actin cytoskeleton, and some studies suggest its presence may increase strain virulence; however, its presence does not always correlate with disease severity.

The dynamic life cycle of *C. difficile* is complex, and multiple host factors may be involved at each step.

10. Diagnosis — Suspect in any hospitalized patient who has had Abx in previous 3 months; leukocytosis, fever common; WBC > 40 uncommon in other infections;

Appropriate stool specimen: watery; Watch out for nurses who add water to stool specimen so that it will not be rejected by the lab!!

11. Lab Tests for C. Diff:
There are a number of tests that are available to detect the infection and to determine if the strain that is present produces toxin. Some tests are very sensitive but take some days to complete, while other tests are rapid (several hours) but are not considered to be very sensitive or specific.

- Perform an initial screen on stool samples using a test for a *C. difficile* antigen called glutamate dehydrogenase (GDH). This test detects an antigen that is produced in high amounts by *C. difficile*, both toxin and non-toxin producing strains. It is considered to be very sensitive, but it is not very specific for toxin-producing *C. difficile*. This test indicates if *C. difficile* is present but not if the bacteria are producing toxins.

- Follow up positive screening results with either of the following for confirmation and to detect the presence of toxins:
  - Cell cytotoxicity test is a tissue culture to detect the *C. difficile* toxin. It is a test that looks for the effects of the cytotoxin (cytotoxicity) on human cells grown in culture. It is a more sensitive method to detect toxin, but it requires 24 to 48 hours to get the test result.
  - Toxigenic stool culture, which requires growing the bacteria in a culture and a second step to detect the presence of the toxins, is a very sensitive test for *C. difficile*. It is still considered to be the gold standard. However, it can take 2 to 3
days for results. A culture will also not distinguish between \emph{C. difficile colonization} and overgrowth/infection. Further testing for the toxin must be performed. \textbf{PCR assays} are rapid and very sensitive methods to confirm the presence of \emph{C. difficile} toxin. However, they are expensive. Some laboratories screen samples with the GDH test and confirm only the positive samples with the molecular assay. Not all laboratories have the capability of performing molecular testing.

12. C. Diff dog – first was in Netherlands; Ours had initial success in detection > 93% during a time of high C. diff activity in hospital, however without frequent “real” c. diff to smell, he’s losing his edge. He’s also not living in the hospital, so not available quickly to attend to patients

13. Colonization vs Infection:
Asymptomatic \emph{C. difficile} colonization is the condition where \emph{C. difficile} is detected in the absence of symptoms of infection.

It has been proposed that asymptomatic \emph{C. difficile} colonized patients may be protected from progression to infection because they can mount a humoral immune response to clostridial toxins.

However, asymptomatic \emph{C. difficile} colonized patients potentially act as an infection reservoir and may present a risk to others.

Lab Tests: A validation study comparing reference tests for \emph{C. difficile} (toxin assay positive versus cytotoxigenic \emph{C. difficile} culture positive/toxin assay negative) showed that detection of toxins was associated with more severe CDI outcomes. However, it has also been reported that patients with positive toxin assays can remain symptomless.

\textbf{Therefore, the sole presence of \emph{C. difficile} toxins is insufficient for a diagnosis of the disease. Consequently, symptomatic CDI has been defined as:}

- The presence of diarrheal \textbf{symptoms (three or more unformed stools in 24 or fewer consecutive hours)} and either
  - a stool test result positive for \emph{C. difficile} toxins or
  - detection of toxigenic \emph{C. difficile}, or
  - colonoscopic findings demonstrating pseudomembranous colitis.

\textbf{Asymptomatic \emph{C. difficile} colonization presents challenging concepts in the overall picture of this disease and its management.} Individuals who are colonized by the
organism may acquire protection from progression to disease, however they also have the potential to contribute to transmission in healthcare settings.

Do not treat symptom-free carriers of C. difficile.

14. Treatment Guidelines:

Components of treatment should include:

- **cessation of antibiotic therapy** if possible; if this is not possible, consultation with an infectious diseases physician should be considered
- **rehydration** of the client/patient/resident
- **avoidance of antimotility agents**, such as loperamide

Antibiotic therapy for CDI:
- Recommended 1st line therapy for mild to moderate CDI:
  - metronidazole 500 mg orally every 8 hours for 10 to 14 days
- Recommended 1st line therapy for initial episode of severe CDI*:
  - vancomycin 125 - 250 mg orally every 6 hours for 10 to 14 days

Severe CDI is defined as either the presence of pseudomembranous colitis on endoscopy, or CDI infection requiring treatment in an intensive care unit, or the presence of at least two of: age >60 years, temperature >38.5°C, white blood cell count >15 x 10⁹ cells per litre (15,000 per mm³).

- If outpatient therapy with oral vancomycin is being considered, discuss with pharmacy to ensure that treatment will not be interrupted.

**Why does Vanco have to be PO?**

Oral vancomycin is not appreciably absorbed or metabolized, but is excreted in the stool unchanged, which is ideal for the treatment of *C difficile* infection. Intravenous vancomycin should not be used, however, since bactericidal concentrations are not achieved in the colon.

Surgery:

In some cases, patients unresponsive to medical management are treated by surgical colectomy.

15. Referactory C. Difficile or Relapses: About 20% to 30% of patients treated for an initial episode have a recurrence

40% to 60% of those patients have subsequent (second or later) recurrences.
Fecal microbiota therapy is increasingly used as a treatment for *C. difficile* infection in the belief that importing the colonic microbiome of a healthy person is a simple way to reconstitute the normal colonic flora (microorganisms that live in the gut).

Only two centres in Ontario perform fecal microbiota therapy for *C. difficile* infection (St. Joseph’s Healthcare Hamilton, and Toronto East General Hospital).

**Based on referral experience, an expert estimated that about 500 to 1,000 patients per year in Ontario would be eligible to receive fecal microbiota therapy for recurrent *C. difficile* infection** (C. Lee, written communication, October 27, 2015).

16. **Benefits of FBT:** Health Quality Ontario

The provincial advisor on the quality of health care in Ontario

**Ontario Health Technology Assessment Series** Fecal Microbiota Therapy for *Clostridium difficile* Infection: A

Health Technology Assessment

**KEY MESSAGES**

- FBT reduced diarrhea associated with CDI better than antibiotics.
- Treatment-related adverse events (such as short-term diarrhea or abdominal cramping) were more frequent in patients treated with fecal microbiota therapy than in patients treated with antibiotics.

- FBT is cost-effective compared to Abx in recurrent CDI.

- If Ontario uses fecal microbiota therapy to treat patients with recurrent *C. difficile* infection, the health care system could save money.

- This review did not find evidence about using fecal microbiota therapy in people infected with *C. difficile* for the first time or in people who have refractory infection.

- Universal donors vs family members; screening of donor and recipient;

19: **Strategies to Improve overall Immune Response**

- Improving immune response will improve treatment outcomes
- Focus on modifiable risks: diabetes, protein malnutrition, undiagnosed immune disorders including cancer, HIV

20. **Preventing Re-occurrence:**

- most important is to avoid antibiotics
- if people can be switched to H2 blockers instead of PPI, that’s best

21. **Future Strategies:**
1. Problem of C. difficile will not be solved by novel antibiotic therapies
2. Minimizing antimicrobial use:
3. Novel strategies to treat infections
4. Bacterial Interference
5. Synthetic fecal flora to rePOOPulate the gut

Probiotics and Innoculation with non-toxigenic C. diff strains:
For colonization with vegetative C. difficile cells to occur, there must be a disruption of the normal intestinal microbiota which usually provides colonization resistance against C. difficile. The inhibitive effect of the natural gut microbiota may occur through competition for space and nutrients or the production of compounds that inhibit C. difficile proliferation. The concept of colonization resistance is important to understand the mechanisms that result in the development of disease. Therefore, there is potential to introduce non-pathogenic organisms as probiotic agents or non-toxigenic C. difficile strains to compete with toxigenic C. difficile strains as novel prevention and treatment strategies. However, Brouwer and colleagues have challenged this concept as they found that transconjugation of the pathogenicity locus can occur from toxigenic to non-toxigenic C. difficile strains