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Newsletter

Clostridioides difficile
(Formerly known as "Clostridium difficile")

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Introduction
Clostridioides difficile is a Gram-positive, spore forming obligate anaerobe, and the causative organism of antibiotic-associated diarrhoea and colitis. Colonisation of the intestinal tract occurs via the faecal-oral route and is facilitated by disruption of normal intestinal flora due to antimicrobial therapy. The organism is capable of elaborating exotoxins that bind to receptors on intestinal epithelial cells, leading to inflammation and diarrhoea. Genetic analysis has led to the recent name change for this organism from *Clostridium difficile* to *Clostridioides difficile*. The understanding of *C. difficile* epidemiology, pathogenesis and treatment is changing rapidly. These topics will be addressed in this newsletter.

Pathogenesis
The steps in the pathogenesis of *C. difficile* associated diarrhoea (CDAD) or CDI (*Clostridioides difficile* infection) include:
- Disruption of normal gut flora
- Colonisation with toxigenic *C. difficile*
- Elaboration of the toxins that mediate the local inflammation and mucosal damage

C. difficile is non-invasive. Pathogenic strains elaborate two potent exotoxins that mediate diarrhoea (Toxin A or "*enterotoxin*"), and colitis (Toxin B, or "*cytotoxin*"). Both toxins bind to surface receptors prior to internalisation. Once within the cytoplasm they disrupt the normal cytoskeleton and induce apoptosis. Not all strains of *C. difficile* are pathogenic, not all strains carry the toxin genes and not all strains that carry the toxin genes cause disease.

Epidemiology
C. difficile causes 20 – 30% of all antibiotic-associated diarrhoea cases and is associated with more than 90% of cases of pseudomembranous colitis. Many factors can contribute to *C. difficile* infection, but it is most strongly associated with recent/current antibiotic use. Almost all antibiotics, including agents used to treat *C. difficile*, have been associated with CDI, but some antibiotics may pose a higher risk than others. It is important to note that one can develop CDI even if no antibiotics have been used. CDI can also be associated with chemotherapeutic agents and other drugs such as methotrexate, as well as prolonged use of proton-pump inhibitors (PPIs), as these agents also alter the gut flora. Other important risk factors include advanced age, hospitalisation, severe illness, enteral feeding, gastrointestinal surgery, obesity, haematopoietic stem cell transplantation, and inflammatory bowel disease.

While CDI is an important nosocomial disease, it is regularly encountered as a community-acquired infection. *C. difficile* (both toxigenic and non-toxigenic strains) can colonise the gastrointestinal tract of healthy asymptomatic individuals. There is limited data on community-acquired CDI in South Africa. However, a recent study in Cape Town found that up to 32% of *C. difficile*-associated diarrhoea may occur in this setting. There is also a dearth of information on molecular epidemiology of *C. difficile* in South Africa. The NAP1/BI/027 strain is well known in America and Europe as it is hyper-virulent and associated with outbreaks. This strain has not been confirmed in SA to date.

Clinical manifestations
Diarrhoea with colitis
This is the commonest presentation of CDI comprising $\geqslant$ 3 loose stools per day, abdominal cramping, nausea, low-grade fever < 38.5 °C and leucocytosis up to 15 x 10^9cells/L. Endoscopy reveals a spectrum of changes from local erythema to areas of colitis. Occasionally, CDI presents acutely as ileus, with little or no diarrhoea. This is due to pooling of secretions in a dilated, atonic colon. Such patients are usually severely ill, with colonic (and possibly small bowel) dilatation, often with colonic thickening, fever, and leucocytosis. In some cases, this presentation seems benign initially but progresses rapidly to more severe disease.

Fulminant colitis

The hallmarks of fulminant colitis are diarrhoea, lower quadrant or diffuse abdominal pain, abdominal distention, fever, hypovolaemia, lactic acidosis, hypoalbuminaemia, elevated creatinine, and marked leucocytosis (often up to 40 x 10^9cells/L). Complications of fulminant colitis include hypotension, sepsis, renal failure, toxic megacolon, and bowel perforation with peritonitis. Severe hypotension may occur in the setting of severe CDI and/or in the setting of bowel perforation with peritonitis. In addition, CDI may develop during antibiotic treatment for septic shock caused by a separate bacterial infection. The diagnosis of toxic megacolon is established based on severe systemic toxicity together with radiographic evidence of colonic dilatation (> 7 cm in its greatest diameter). Bowel perforation presents with abdominal rigidity, involuntary guarding, diminished bowel sounds, rebound tenderness, and severe localised tenderness in the left or right lower quadrants. Abdominal radiographs may demonstrate free air in the abdomen. Patients with fulminant colitis warrant radiographic imaging and prompt surgical evaluation.

Recurrent disease

Recurrent *C. difficile* infection is defined by complete resolution of CDI symptoms while on appropriate therapy, followed by subsequent reappearance of symptoms after treatment has been discontinued. Up to 25% of patients experience recurrent *C. difficile* within 30 days of treatment. Less commonly, recurrent CDI can occur as late as three months after discontinuation of treatment. Once patients have experienced one recurrence, they are at significantly increased risk for further recurrences.

Recurrent disease may be mild or severe. Risk factors for recurrence include age > 65 years, severe underlying medical disorders, need for ongoing therapy with concomitant antibiotics during treatment for CDI, and lack of an antibody-mediated immune response to toxin B.

Recurrent symptoms are most commonly due to relapse of the initial infecting strain; less frequently, re-infection with a new strain may occur. Persistent diarrhoea without resolution during initial therapy should prompt an evaluation for other causes and should not be considered recurrent disease. In the absence of an alternative diagnosis, such patients should be considered to have refractory CDI.

Diagnosis

There are several algorithms and methods for diagnosis. Laboratories may therefore differ in their approach to testing. While the tissue culture based toxin neutralisation test remains the gold standard, it has largely been replaced in South Africa by one of the following two protocols:

- Two-step procedure using a screening test followed by a specific test. The screening test detects the enzyme glutamate dehydrogenase (GDH), a protein produced by all strains of *C. difficile.* It is very sensitive, but not specific, as it cannot distinguish between the presence of toxin-producing and toxin-negative strains of the organism. All positive GDH tests need to be confirmed by a specific test for toxin production. Detection of toxin is specific for CDI, but testing for toxin alone has poor sensitivity. Toxin degradation occurs at room temperate within 2 hours.
- Detection of toxin genes by real-time PCR. A number of rapid molecular methods are available to detect the genes of *C. difficile* that encode toxin production. The test is performed directly on stool samples and has a sensitivity of around 100% and specificity of 94%.

Both methods can occasionally give discordant or equivocal results that are difficult to interpret and may require retesting.

A third diagnostic protocol includes anaerobic culture on a selective medium followed by PCR to detect the toxin genes or enzyme immunoassay to detect toxin production. This process is time-consuming and laborious. Although it may take 48 – 72 hours to culture *C. difficile,* this method has excellent sensitivity.

Management

Infection control

Contact precautions must be instituted. In hospital, this includes donning gowns and gloves before entering the room of the patient. Alcohol-based hand sanitisers are less effective in controlling the spread of *C. difficile,* as the spores are resistant to alcohol rubs. Handwashing with soap and water is preferred. Infection control precautions should ideally be continued until the patient has been discharged. If insufficient facilities are available for isolation of individuals throughout their hospital stay, some authorities allow cessation of isolation 48 hours after the diarrhoea has settled, as the risk of spread is diminished by this time. Contact precautions, however, must be maintained. New data suggests that even asymptomatic carriers can be a reservoir of infection.

Antibiotic treatment

The inciting antibiotic should ideally be stopped. If this is not possible, then the narrowest spectrum antibiotic that is least likely to be associated with CDI should be chosen. Asymptomatic patients do NOT require treatment. Similarly test-for-cure after symptoms have resolved is also not recommended as toxin genes can persist in the stool for weeks after clinical resolution.

Table 1 shows adult treatment recommendations for different clinical situations.

Table 1. Antibiotic treatment of *C. difficile* in adults[#]

Initial episode:
- Mild/moderate disease: Metronidazole 400 mg 8 hourly po OR vancomycin 125 mg 6 hourly po for 10 – 14 days
- Severe disease, pregnant or breastfeeding: Vancomycin 125 mg* 6 hourly po for 10 – 14 days (all patients with severe disease should be referred for a surgical opinion)
- Severe, complicated disease or critically ill: Vancomycin 125 mg 6 hourly po AND metronidazole 500 mg 8 hourly ivi for 10 – 14 days

First relapse:
- Mild/moderate disease: Conservative management if symptoms are mild, otherwise treat as for initial episode.
- Severe, complicated disease/critically ill: Treat as for initial episode.
- Alternative: Fidaxomicin 200 mg BD po for 10 days

Second relapse:
- Tapering and pulsed vancomycin with or without probiotics. If used, probiotics may be commenced during the final tapering phase and continued for 2 weeks thereafter. The vancomycin tapering regimen is as follows:
  - 125 mg 6 hourly po for 7 to 14 days
  - 125 mg BD po for 7 days
  - 125 mg daily po for 7 days
  - 125 mg every other day po for 7 days
  - 125 mg every 3 days po for 14 days
- Alternative: Fidaxomicin 200 mg BD po for 10 days

Subsequent relapses:
- Fidaxomicin 200 mg BD po for 10 days (if not used previously)
- Faecal microbiota transplant

Contact the microbiologist for details on paediatric dosing.
* Increased doses of 500 mg vancomycin are not recommended as it has no added benefit.

NOTE: Vancomycin dose is made up from the powder contained in vials for injection. In South Africa vancomycin is available in single dose vials of 500 mg and 1 gram strength.

Adjunctive and newer techniques
- Surgery: Surgical intervention may be required for severely ill patients with toxic megacolon or other complications, including rapidly progressive disease. A surgical consult is advised in all patients with severe disease.
- Faecal microbiota transplantation (FMT): Administration via enema, colonoscopy (preferred route), nasogastric/jejunal route. The donor is usually a healthy family member. Stool is screened for common bacterial, viral and parasitic organisms, and the donor is confirmed to be negative for HIV and Hepatitis A, B and C. FMT is currently available only in selected gastroenterological units.
- Probiotics: The role of probiotics for prevention and treatment of CDI is an evolving area of study. Probiotics may be effective as an adjunct to antimicrobials in treatment of non-severe CDI in the setting of recurrent disease, but data is limited. Probiotics should only be used in patients where there are no significant comorbidities. There is limited data to support routine administration of probiotics to prevent CDI.
- Monoclonal antibodies: Unlike antibiotics, monoclonal antibodies neutralise toxin and do not cause collateral damage to normal gut flora. Several compounds have been developed of which one, Bezlotoxumab (“Zinplava”) an anti-toxin B, has been approved for human use. A single dose has been shown to significantly reduce the rate of CDI recurrence (17% vs 28% with placebo).
- Anion binding resins: Can be used as adjuncts to bind toxin and prevent it from acting on its receptor sites. Resins may, however, also bind intra-luminal drugs potentially affecting their activity against *C. difficile.*
- Vaccines: A number of vaccines are in development. Some are designed to block attachment and colonisation by *C. difficile,* whereas others are intended to stimulate host anti-toxin antibodies.

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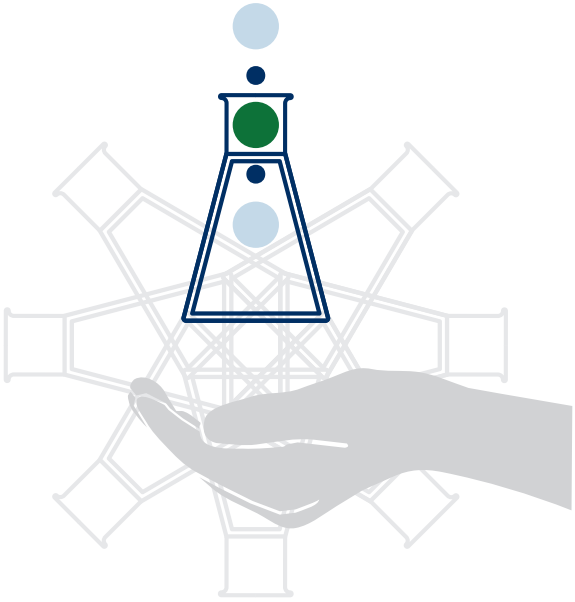

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