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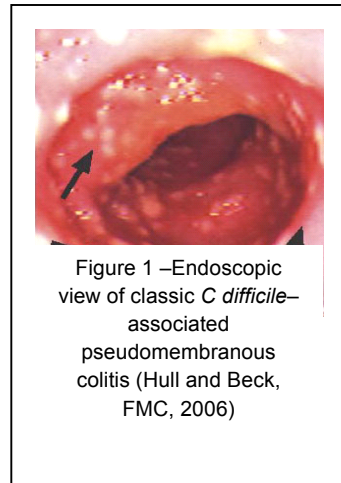
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Clostridium difficile Associated Disease (CDAD)

Rivka H. Borger

Abstract

Clostridium difficile bacteria (*C. difficile*) are a spore-forming species of bacteria that lies dormant in the colon, in the presence of normal intestinal flora. Due to overuse of certain antibiotics,



normal intestinal bacteria may be depleted, and combined with other possible risk factors, allow *C. difficile* bacterial spores to develop into active, infectious, and extremely resistant toxin-producing bacteria. The toxins cause severe damage and inflammation to the intestinal wall that can result in gastrointestinal discomfort and severe pseudomembranous enterocolitis that must be treated with a low-risk *C. difficile* targeting defense.

Introduction

Clostridium difficile bacteria (*C. difficile*) are a spore-forming species of bacteria that lie dormant in the human colon, in the presence of normal intestinal flora. It is a commensal bacterium in a minority of the population. Smaller numbers do not develop into significant disease. (Nation Master Encyclopedia, 2005) Most commonly due to overuse of certain antibiotics, normal intestinal bacteria may be depleted, and through nutrient competition, allow *C. difficile* bacterial spores to develop into active, infectious, and extremely resistant toxin-producing bacterial overgrowth. The toxins cause severe damage and inflammation to the intestinal wall resulting in a wide range of disease, but most commonly - severe enterocolitis. (Merck Manual of Diseases, 2006)

The following discourse will detail the morphology, mechanism of infection, causes, diagnoses, treatment, and prevention of *Clostridium difficile* Associated Disease.

Clostridium difficile Bacteria

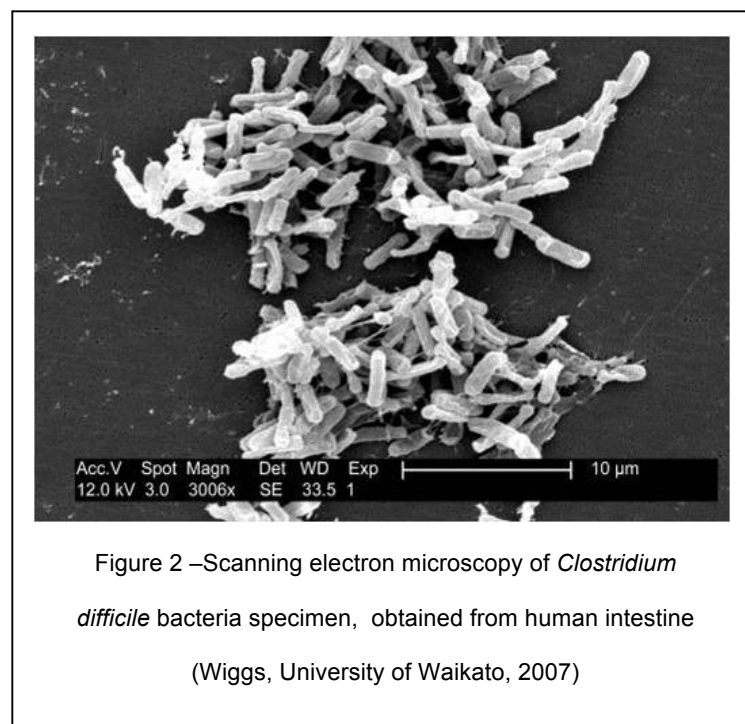
Clostridium difficile is a Gram-positive anaerobic rod-shaped bacterium (Kunkel, 2006). The species was named 'difficile' because it was initially hard to culture (Schroeder, MD, American Family Physician, 2005). It belongs to the *Clostridiaceae* Family and genus *Clostridium*, which form spores. They are motile bacteria that are numerous through nature, particularly soil. *Clostridium* show optimal growth at human body temperatures, but can exist under stress in the more tolerant spore form. (Nation Master Encyclopedia, 2005). The spores are resilient and resistant to high temperatures. Early studies demonstrated that *C. difficile* could be isolated from the gastrointestinal tracts of most neonates, identifying it as a commensal organism (Schroeder, 2005). It is found as part of the normal

intestinal flora, and passed out with the feces of those with *C. difficile* spores in their intestines. (EMIS and PIP, 2007)

Clostridium difficile produce at least two exotoxins: an enterotoxin (Toxin A) and a cytotoxin (Toxin B). They can kill cells by altering the apical membrane permeability of the mucosal cells of the intestinal wall, and are subsequently responsible for severe inflammation possibly leading to enterocolitis (Gerding et al, 1995). Another toxin, binary toxin, has been identified without a role in CDAD infection. (Nation Master Encyclopedia, 2005)

C. difficile can be passed through fecal matter and spores can lie almost anywhere in the environment.

Clostridium difficile is considered a member of infant intestinal flora as up to 50% of infants carry asymptomatic *C. difficile* in their intestinal tracts. It can grow to high numbers with elevated toxin production with no harmful effects to infants. (Bongaerts and Lyerly, 1996)



The normal intestinal flora under typical conditions keep the spores of *C. difficile* inactive by outnumbering them in strength. Upon depletion of normal flora, the dormant inactive spores develop into active, infectious, and resistant bacteria – replacing the lost bacteria due to imbalance (Merck Manual, 2006)

More recently, *C. difficile* infections are more rampant – severe, extremely resistant, and easily recurrable. (Kelly and LaMont, 2008). It is the most frequent etiologic basis for healthcare-associated diarrhea and a common cause of antibiotic-

associated diarrhea (AAD), accounting for 15-25% of all AAD episodes (Center for Disease Control and Prevention (CDC), 2004). There have been increasing rates of CDAD-associated mortality, and this can be due either to elevated risk population or identification of new highly virulent strains of the disease. (Center for Disease Control and Prevention (CDC), 2005).

Additionally, two studies have proven *C. difficile* to be the most frequent cause of nosocomial diarrhea. Multiple studies demonstrate the link between *C. difficile* and noscomial infection – many cases arise from contamination of hospital environment (Gerding, et al, 1995).

Clostridium difficile was first linked to disease in 1978 when it was identified as primary causative agent of pseudomembranous colitis. It can cause disease ranging from minor gastrointestinal

discomfort to severe enterocolitis, toxic megacolon, or death. (Sunenshine and McDonald, 2006)

Pathogenesis

Inflammation develops when environmental spores ingested infect the patient. Spores can survive the low pH of the gastrointestinal tract and survive well in the anaerobic environment of the large intestine, allowing for germination. Upon depletion of normal intestinal flora, *C. difficile* spores no longer have to compete with other microbes,

allowing them to thrive to full capacity, growing to large numbers – approximately 10^8 bacteria per gram of feces. In the absence of colonic flora depletion, colonization of *C. difficile* will be asymptomatic and harmless (Bongaerts and Lyster, 1997).

Antibiotic overuse is the most common form of intestinal flora depletion. The inactive spore form of *C. difficile*, once held in check by nutrient competition, becomes the dominant intestinal species. It is transformed to its infectious form, producing toxins that inflame and damage the intestinal mucosa.

Inflammation results in hyperleukocytosis, influxing towards the colon. Colitis is variable in degree, from mild to extremely severe. In pseudomembranous colitis, a more severe form, toxins destroy the tissue of the intestinal epithelia until the tissue falls off, mixes with leukocytes in pus discharge; giving the appearance of a white membranous patch on the inner intestinal lining. Some patients infected with *C. difficile* do not develop colitis, but are carriers of the disease, able to transmit it to other high-risk individuals.

Clostridium difficile bacteria's capacity to form spores allows the organism to persist in various areas of the environment. Additionally, the spores can be spread through fecal contamination, infecting at-risk individuals. (EMIS and PIP, 2007) Transfer can occur via the hands of healthcare workers as well. (Center for Disease Control, 2008). Infection used to be limited to elderly hospitalized individuals but has grown rampant more recently. (DeNoon, 2006).



Figure 3 –

Scanning electron microscopy of *Clostridium difficile* bacteria spreading on a surface

After colonic colonization, *C. difficile* bacteria carry out metabolic activities similar to other anaerobic organisms. The bacteria use some monosaccharides (i.e. glucose, fructose, mannitol, mannose, and xylitol), but not disaccharides (i.e. lactose or sucrose), oligosaccharides, or polysaccharides (i.e. starch). *C. difficile* uses substances not found free in nature, such as N-acetyl-glucosamine and N-acetyl-neuraminic acid, by using extracellular hydrolytic enzymes to degrade substrates for nutrition. It can then obtain carbohydrates, amino acids, and related nutrients allowing the bacteria to thrive in the intestine. With the depletion of normal flora, there are more nutrients available for the bacteria to thrive on. Additionally, when a large amount of resident intestinal bacteria are destroyed, it allows *Clostridium difficile* exposure to previously hidden sites of the intestine. They can be then used for microcolony formation or receptor sites for toxins in toxigenic strains. As the organism grows, it becomes harder for normal flora to replace it since the bacteria produces inhibitory metabolic products, such as p-cresol, ammonia, and isocaproic acid – all inhibiting growth of normal flora, and disturbing intestinal epithelial cell membrane function. (Bongaerts and Lyster, 1997)

Pathogenic strains of *Clostridium difficile* cause enterocolitis primarily through the production of toxin A (enterotoxin) and toxin B (cytotoxin). Both toxins are capable of stimulating proinflammatory cytokine production implicated in pseudomembranous colitis infection. Toxins act by altering regulation of cytoskeletal protein, leading to cell rounding and cell death. (Hull and Beck, College of Family Physicians of Canada, 2004) The toxins cause leukocyte chemotaxis and the upregulations of inflammatory mediators such as cytokines, producing colonic inflammation. Clinical evidence would be a significantly elevated white blood cell count, correlating to presence of infection. Focal ulcerations occur with increasing severity of colitis, and necrotic tissue form a membrane-like material. Thus, it is

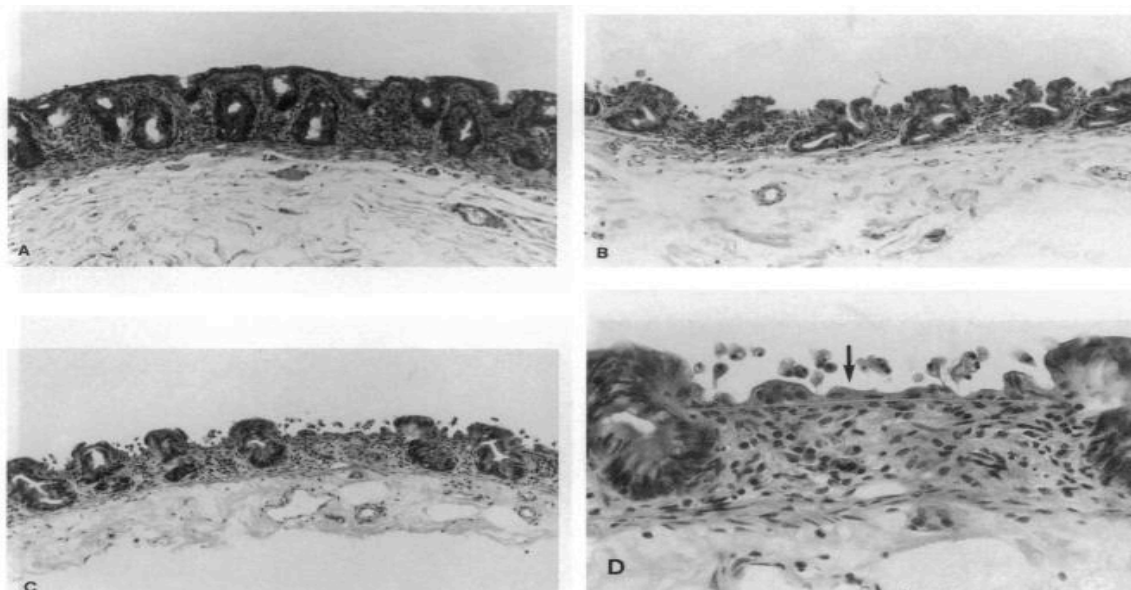


Figure 4 – The Potent Effects on Toxin B vs. Toxin A on Intestinal Epithelium

- (A) Control, treated with buffer alone – no toxins. (B) treated with 32 nM of toxin A for 5 hours. (C) and (D) treated with 3 nM of toxin B for 5 hours.
 (B) Exposure to toxin A shows disruptions of superficial epithelium with crypt epithelium intact. (C) treatment with toxin B shows disruption of superficial epithelium as well. (D) shows higher magnification of colonic damage wrought by toxin B.

(Riegler, et al, Journal of Clinical Investigation, 1995)

called pseudomembranous colitis (Schroeder, 2005).

Animal models show toxin A induction of epithelial desquamation, increased mucosal permeability leading to increased fluid secretion in the intestine. Toxin B has less enterotoxic effects in animals with less correlation as a cause of disease in humans, but recent *in vitro* data based on human intestinal epithelial cell testing suggests that toxin B is ten times more likely to induce colonic damage than does toxin A. In this experiment, human intestinal mucosa was exposed to varying amounts of both *Clostridium difficile* toxins A and B for five hours and subsequent damage was observed. Significant damage was observed afterward, both electrophysiologically and morphologically. Both toxins caused disruption to cellular F-actin and patchy damage and exfoliation was noted on superficial intestinal epithelium. The difference lay in the potency of individual toxins. While both toxin A and toxin B caused severe intestinal damage, toxin B disrupted the colon in a minute concentrated amount, while toxin A's measurement was significantly greater. This suggests the high potency of toxin B in *Clostridium difficile* Associated Diseases. (Riegler et al, 1995)

In a 1999 study hypothesizing how *C. difficile* – induced alterations in intestinal barrier facilitate microbial entry to the intestinal mucosa (thus facilitating microbial pathogenic shift within the intestine), mature enterocytes were deliberately treated with varying concentrations of toxins A and B followed by an hour incubation with an enteric microorganism such as *Escherichia coli*. Effects of toxins A and B were assessed on all aspects of enterocyte function ability. Testing of the effects of toxin A and B on mature enterocytes *in vitro* resulted in damage and alterations in enterocyte actin, increased bacterial adherence and paracellular transmigration, thus correlating that Toxins A and B may facilitate bacterial adherence and penetration of the intestinal epithelium. (Feltis, et al, 1999)

If the infecting strain is toxigenic, the patient is at risk for disease. There are other factors that possibly affect its potency such as fimbriae (enabling bacterial adherence) and glycocalyx (antiphagocytic capsule), both of which are produced in greater numbers in toxigenic strains of *C. difficile*. Some highly virulent strains produce elevated protease levels, linked among other clostridial pathogens to increased virulence. Other extracellular hydrolytic enzymes may play a similar role (Bongaerts and Lyerly, 1997).

C. difficile bacteria can also have specific antibiotic-resistant genes, targeting specific antimicrobial agents through unique bacterial physiology and biochemistry. An example of this would be the *ermB* gene, encoding a 23S ribosomal methylase that causes resistance to macrolide-lincosamide-streptogramin (MLS) antibiotics. This marker was noted in several cases of *C. difficile* after use of Clindamycin, a lincosamide derivative. (Hull and Beck, 2004).

Another strain of *Clostridium difficile* bacteria has been identified relatively recently, named North American pulsed-field gel electrophoresis type 1 (NAP 1), causing several outbreaks in North America and Europe. It is resistant to both gatifloxacin and moxifloxacin antibiotics (both of the fluoroquinolone antibiotic group), unlike other strains previously designated. NAP 1 produces 16 times greater toxin A and 23 times greater toxin B than other strains do, possibly related to a deletion in a negative regulatory gene. It also produces a third toxin, binary toxin, whose purpose has not been deemed significant yet. (Sunenshine and McDonald, 2006). This new strain has become the more dominant strain, due to the high rate of mutation. It is highly virulent and has raised *C. difficile*-related death rates by 35% yearly (DeNoon and Chang, 2008). Additionally, resistance to fluoroquinolone antibiotics gives the NAP-1 strain with the ability to spread more rapidly among healthcare environments where those antimicrobial agents are most frequently used. (Center for Disease Control and Prevention (CDC) 2005)

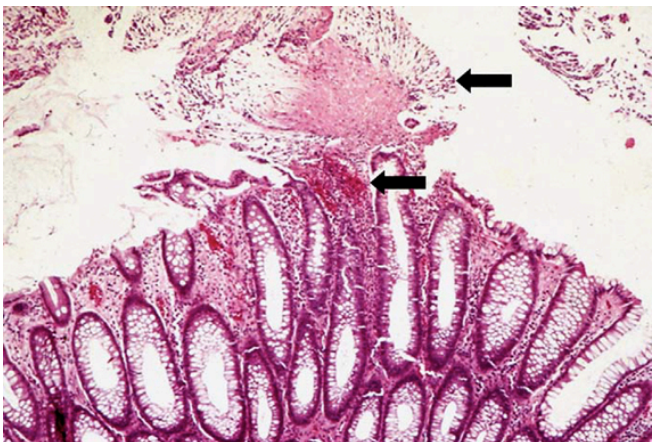


Figure 5– marked exudates protruding through mucosal ulcerations

(Cleveland Clinic, 2006)

Causes and Risk Factors

The primary cause of infection is due to antimicrobial therapy, more prevalent in certain antibiotic groups.

Antimicrobial agents that target anaerobic bacteria are potentially more lethal, possibly because they alter intestinal flora and microbial ecology. (Gerding et al, 1995)

Almost all antimicrobial agents except for aminoglycosides are associated with *Clostridium difficile* infection (Sunenshine and McDonald, Cleveland Clinic Journal of Medicine, 2006). Clindamycin has been identified as a

targeting agent, confirmed by *ermB* gene isolation, encoding methylase enzyme causing antibiotic resistance to lincosamides (Clindamycin belonging to that family). (Hull and Beck, College of Family Physicians of Canada, 2005). Other common high-risk antibiotics are broad spectrum penicillins, second and third generation cephalosporins, erythromycin, sulfonamides, chloramphenicol, tetracycline, and fluoroquinolones. Fluoroquinolones in particular were isolated in a cohort study as the predominant risk factor for CDAD in a specific epidemic in Quebec 2003-4 (Pepin et al, 2005). It is most commonly due to oral antibiotics but can also occur due to intravenous or intramuscular antibiotics. (Merck Manual, 2006). Other antimicrobial agents, including antiviral and antifungal drugs increase the risk as well (Mayo Clinic 2006). Risk more than doubles with greater than three days of antimicrobial therapy.

Reduced-risk antibiotics include vancomycin, metronidazole, and antipseudomonals. (Schroeder, 2005).

The critical point of infection is right after normal intestinal flora depletion before replenishing (Bongaerts and Lyerly, 1997).

Other drugs may increase susceptibility as well, such as drugs and conditions that decrease gastric acidity. Over the counter antacids and proton pump inhibitors such as aciphex, prevacid, and related drugs would put a patient at higher risk (Merck Manual, 2006). Proton pump inhibitor (PPI) utilization is associated with upper gastrointestinal tract colonization and altering of intestinal flora. Decreased gastric acidity is a known risk factor for infectious diarrheal illnesses. Since *Clostridium difficile* bacteria thrive on higher gastric pH levels, decreased gastric acidity may also pose a risk factor for CDAD. This is supported by CDAD cases reported from patients receiving *Helicobacter pylori* treatment – combining proton pump inhibitors with antibiotics. A study comparing rate of *C. difficile* infection in patients undergoing gastric acid suppressive therapy with those who did not, with PPI usage increasing the risk significantly. (Dial et al, CMAJ, 2004). Two case-controlled studies conducted over ten years showed the increase in rate of *Clostridium difficile* infection due to PPI usage and H₂ blockers. (Dial, et al, JAMA, 2005).

Additional risk factors included use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Being methicillin-resistant *Staphylococcus aureus* positive increases susceptibility in hospital patients. (Dial, et al, JAMA, 2005).

Exposure to *Clostridium difficile* can occur through a variety of methods. Transfer of pathogenic organisms is highly prevalent via the hands of health-care workers and is considered the most likely mechanism. (Centers for Disease Control and Prevention (CDC) 2007).

Other risk factors include underlying illness, weakened immune system, recent hospitalization, residency in long-term care facilities, recent surgery – primarily abdominal/gastrointestinal, chronic colon disease such as inflammatory bowel disease or colon cancer. Additionally, previous infection with *Clostridium difficile* increases patient susceptibility to reinfection. (Mayo Clinic, 2006). Highest risk patients are those with recent immunosuppressive therapy or recent surgical procedures, partly due to patients' inability to generate IgG antibody immune response against *Clostridium difficile* toxin A. IgG immune response ability does not protect against colonization but can decrease risk of morbidity, mortality, or recurrence with *C. difficile* infection (Schroeder, 2005).

Cancer chemotherapy and increased age and severity of underlying illness are other possible risk factors (Hull and Beck, 2005)

Clinical Manifestations of Enterocolitis

More commonly, patients experience colonization rather than disease. Such patients exhibit no clinical symptoms even though they would test positive for *C. difficile* organism and/or toxins. Other times, patients contract *Clostridium difficile*-Associated Disease (CDAD) and exhibit clinical symptoms (Centers for Disease Control and Prevention, 2005).

Common symptoms for *Clostridium difficile* infection are watery diarrhea (characterized by at least three bowel movements daily for more than two days but usually ten or more), abdominal cramping and tenderness, nausea, loss of appetite, and fever of up to 104 – 105 degrees F. (Centers for Disease Control and Prevention, 2004). It is also possible to have an abnormal heartbeat (Healthwise, 2006). Other symptoms include blood or pus in the stool, dehydration, and weight loss (Mayo Clinic, 2006). Watery diarrhea is the most common symptom of CDAD in children (Infectious Diseases and Immunization Committee, 2000). Rarely are symptoms manifested outside the gastrointestinal tract, but can include cellulitis, bacteremia, visceral abscess formation, and reactive arthritis. A common indicator would be leukocytosis with a white blood cell count greater than $30.0 \times 10^9/L$ (Hull and Beck, 2004).

Symptoms can appear immediately after or during antimicrobial therapy, but can often appear several weeks after completing all antibiotics. This was evidenced in a study of cancer outpatients diagnosed with CDAD where the median interval (range 2-60 days) from discharge to infection was 20.3 days – a 3 week delay (Sunenshine and McDonald, 2006).

Range of disease can vary in different individuals from asymptomatic colonization to severe fulminant pseudomembranous colitis.

Many cases are mild. Such patients develop mild to moderate watery diarrhea with abdominal cramping and nausea, similar to ordinary viral gastroenteritis. They may last a short duration to several weeks but usually improve without treatment (EMIS and PIP, 2007). Systemic symptoms are usually

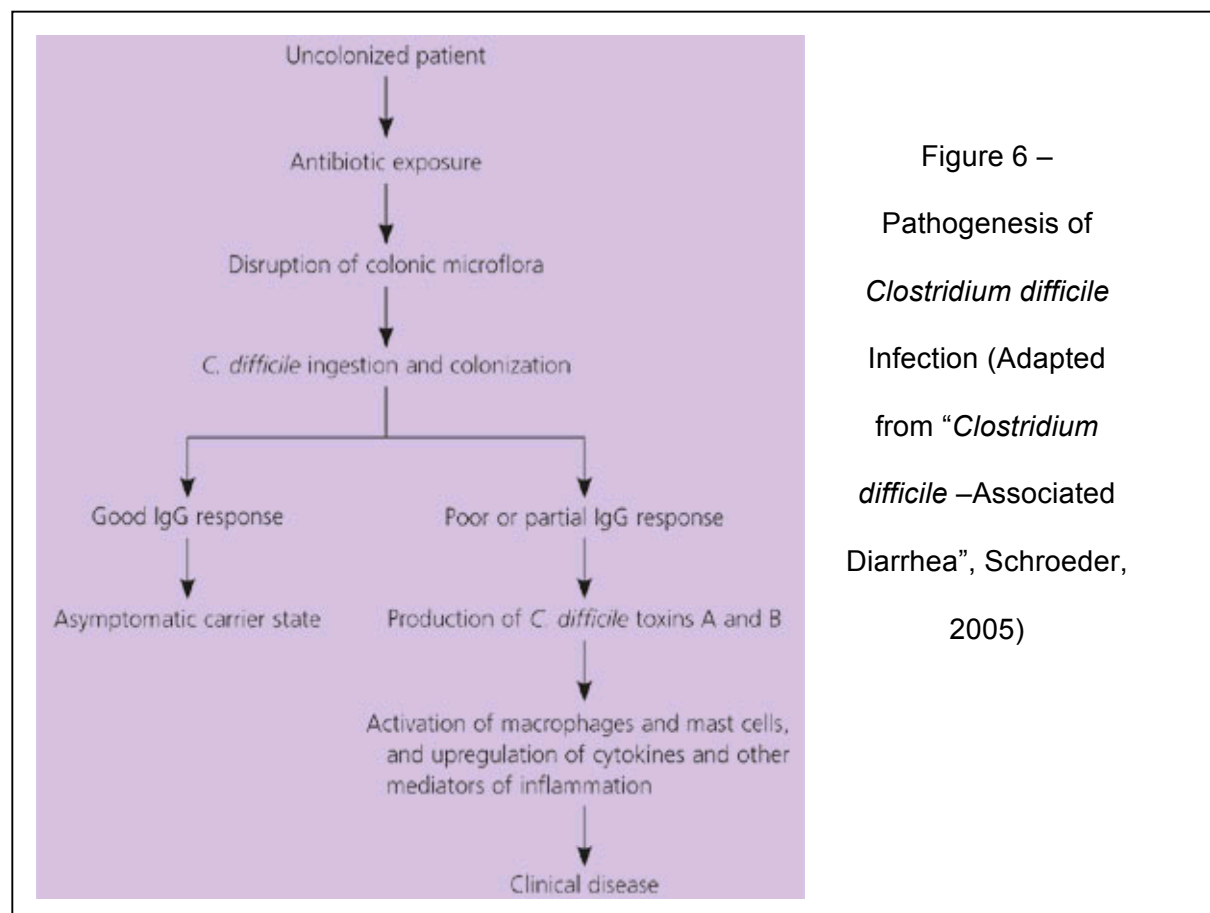


Figure 6 –
Pathogenesis of
Clostridium difficile
Infection (Adapted
from “*Clostridium
difficile* –Associated
Diarrhea”, Schroeder,
2005)

absent and disease would only be considered due to abdominal tenderness upon physical examination (Sunenshine and McDonald, 2006). They may also include low grade leukocytosis and tenesmus – a sudden urge to evacuate the rectum (Hull and Beck, 2004).

Moderate infectious symptoms include leukemoid reaction – a stress response to disease with an increased leukocyte count of approximately $50.0 \times 10^9/L$, fever, dehydration, nausea, vomiting, and abdominal tenderness. Hull and Beck, 2004).

The severest cases present with dehydration and electrolyte disturbance, severe bloody diarrhea, fever, and abdominal pain and cramping (EMIS and PIP, 2007). It may lead to sepsis and shock, acidosis (increased acidity of blood plasma), tachycardia, multisystem organ failure including kidney failure (due to rapid dehydration), hypoalbuminemia, paralytic ileus, ascites (fluid accumulation in the peritoneal cavity), acute abdomen – colonic perforation, toxic megacolon (toxic colitis with dilatation), and death. Endoscopic evaluation of the colon will show pseudomembranous white patches or lesions

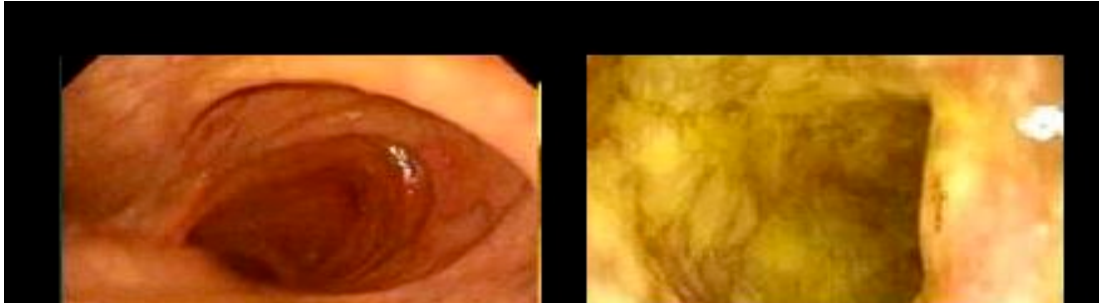


Figure 7 – (L) Image of normal cecum

(R) Image of pseudomembranes formed from *Clostridium difficile* overgrowth of cecum.

with erythema and edema. The lesions are yellow plaques 2-10 mm in diameter with interposed normal intestinal mucosa (Hull and Beck, 2004). Should a patient develop paralytic ileus or toxic megacolon, it may actually lead to a decrease in diarrheal episodes. (Sunenshine and McDonald, 2006). Toxic megacolon is rare but has been documented in several cases, leading to a mortality rate of 33% for those who develop it. A critical factor in survival would be early diagnosis of *Clostridium difficile*-associated pseudomembranous colitis (Cone and Wetzel, 1982).

Diagnosis

Detailed history is the first step to proper diagnosis. Patients are screened for recent antibiotic usage, abdominal pain, diarrhea, and related symptoms. Doctors may still test without presence of diarrhea since in rare instances *C. difficile* bacteria can cause abdominal pain and tenderness without diarrhea (MedicineNet, 2008). *C. difficile* is also suspected when diarrhea develops during or soon after hospitalization (EMIS and PIP, 2007).

Treating without diagnostic laboratory basis is not indicated, especially since only 30% of hospitalized patients with diarrhea have CDAD, even during epidemics. There are some exceptions for which empiric therapy would be necessary – including severely ill or rapidly deteriorating high-risk patients (Sunenshine and McDonald, 2006).

Patients with CDAD often have leukocytosis with strong elevation in severe enterocolitis. Physicians may screen leukocyte count as well as for white blood cell presence in the stool. Confirmation of those two tests proves positive for colitis and would need more testing to diagnose CDAD (MedicineNet, 2008). Stool leukocyte measurement may have limited diagnostic accuracy (Nation Master Encyclopedia, 2005). A sudden rise in the leukocyte count to between $30-50 \times 10^9/L$ cells combined with severe bandemia (immature white blood cells) is an indicator of fulminant colitis. Patients should be monitored for leukemoid reaction as shock can progress very quickly (Schroeder, 2005).

Stool assay for *Clostridium difficile* is a routine method. It is not always reliable as it sometimes produces false-negatives (Mayo Clinic, 2006). Additionally, although the most sensitive test possible, it

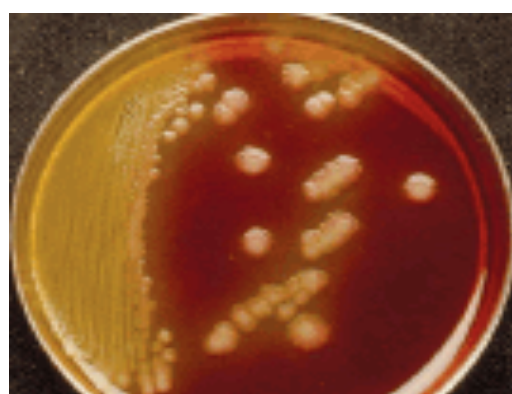


Figure 8 – anaerobic culture of *Clostridium difficile* bacteria on Cycloserin-Cefoxitin Fructose Agar (Anaerobe Systems, CA)

can also cause false-positives due to the available non-toxigenic strains. It must grow 48-96 hours anaerobically for proper results. (Centers for Disease Control and Prevention (CDC), 2005). It has an overall sensitivity of 95% but has a low specificity, necessitating toxicity testing (Canadian Paediatric Society, *Paediatrics & Child Health*, 2000). It is not specific for pathogenic toxin-producing strains of *Clostridium difficile* and is not as clinically helpful (Schroeder, *American Family Physician*, 2005). It is the least chosen method of testing in hospitals due to cost and length of procedure. It does however have an advantage of lending itself to molecular typing of strains, useful in a *C. difficile* outbreak (Sunenshine and McDonald, 2006).

Antigen detection for *C. difficile* are rapid tests completed in less than an hour, used to detect presence of *C. difficile* antigen by latex agglutination or immunochromatographic assays. It must be combined with toxin testing for diagnostic confirmation (Centers for Disease Control and Prevention (CDC), 2005).

Toxin testing includes both enzyme immunoassay and tissue culture cytotoxicity.

Enzyme immunoassay detects toxins A, B, or both together. It uses monoclonal antibodies to detect toxin (Hull and Beck, 2004). Assay is completed same-day but is less sensitive than tissue culture cytotoxicity assay (Centers for Disease Control and Prevention (CDC), 2005). Enzyme-linked Immunoabsorbant Assay (ELISA) has a sensitivity rate of 63-99% and a specificity of 93-100%. Experts recommend sending as many as 3 samples to rule out disease if patients receive negative result, but

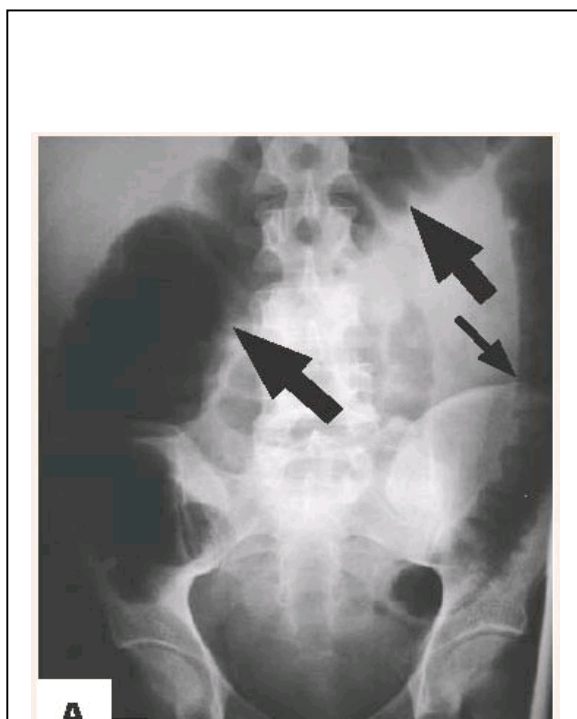
may not be necessary as much with ELISA (Nation Master Encyclopedia, 2005). The majority of combination enzyme immunoassays have a sensitivity of 85-95%. It should not be used as an indicator of response to therapy since results remain positive for extended duration in 25% of successfully treated patients (Schroeder, 2005).

Tissue culture cytotoxicity tests only for presence of toxin B. It is called the 'gold standard' toxin bioassay (Canadian Paediatric Society, *Paediatrics & Child Health*, 2000). It requires 24-48 hours for a final result and is very sensitive for *C. difficile* (Centers for Disease Control and Prevention (CDC), 2005). Organisms are cultured on selective medium and tested for toxin production and cytopathic effect in cell culture. It is the most sensitive and specific test although it is slow and labor-intensive (Nation Master Encyclopedia, 2005). Due to its high specificity and sensitivity, one should be cautious for false results (Canadian Paediatric Society, 2000).

C. difficile toxin is very unstable. Toxin degrades at room temperature and may not be detectable 2 hours after collection of stool. False-negative results are prevalent due to delayed testing or lack of refrigeration.

Stool lactoferrin levels can also be a diagnostic test but has limited diagnostic accuracy as well (Nation Master Encyclopedia, 2005). Other rapid testing such as Immunocard (Meridian Diagnostics) is highly specific but has poor sensitivity with up to 20% false negative results (Canadian Paediatric Society, 2000). Latex agglutination-based assays recognize enzyme glutamate dehydrogenase but do not have sensitivity (Hull and Beck, 2004). Polymerase chain reaction (PCR) detects toxigenic *C. difficile*. Amplification of a gene portion of either toxin A, toxin B, or a combination of the two genes is performed. PCR can be conducted on the specimen organisms for presence of toxins that match with the reading of the known toxins. One testing conducted (Kato et al) amplified only toxin A from *C. difficile*. Others had similar or less success. It is not as sensitive as other testing methods (Gerding et al, 1995).

Colon examination is used to confirm diagnosis of *Clostridium difficile*. Patients undergo sigmoidoscopy or colonoscopy to screen for presence of inflammation and pseudomembrane appearance, both suggesting CDAD (Mayo Clinic, 2006). It should, however, be reserved for when a patient's condition needs rapid diagnosis, to rule out other diagnoses, or when clinical suspicion is high despite negative results. Colonoscopy can detect more than a sigmoidoscopy since it examines the whole colon where *C. difficile* can encompass, rather than just the sigmoid colon (Hull and Beck, 2004).



Imaging tests such as CT scans provide detailed images of the colon. Scans can show thickening of the colon wall, common in

pseudomembranous colitis (Mayo Clinic, 2006). In conjunction with the clinical history, presence of ascites, colon wall thickening, or dilation can predict severity of enterocolitis (Schroeder, 2005).

Treatment

No treatment is necessary for colonization without symptomology. Should symptoms be present with diagnosis confirmed, there are different treatment options.

If at all possible, the disease-causing antibiotics should be stopped. This alone can allow normal intestinal flora to regenerate. Overgrowth of *C. difficile* would be reduced with less symptoms ensuing. For mild to moderate diarrhea and other symptoms, cessation of antimicrobial therapy may be the only necessary cause of treatment (EMIS and PIP, 2007). CDAD typically resolves in 23% of cases upon removal from the antimicrobial treatment (Centers for Disease Control and Prevention (CDC), 2005).

Fluids may be given to prevent dehydration and restore electrolyte balance in the blood (Healthwise, 2006).

For severe cases of diarrhea or diagnosed colitis, patients will be treated with an antibiotic that eradicates *C. difficile* organisms, usually Vancomycin (Vancocin) or Metranidazole (Flagyl), for ten days. In a study of 189 patients with CDAD, 97% responded to initial antibiotic therapy (Sunenshine and McDonald, *Cleveland Clinic Journal of Medicine*, 2006). Symptoms should subside within 2-3 days. The antibiotics can also prevent perforation of the colon if treated in time (EMIS and PIP, 2007). Drugs are usually effective with few side effects (Centers for Disease Control and Prevention (CDC), 2007). In severe cases, intravenous medications may need to be administered (Robert Michael Educational Institute, 2007). Both Vancomycin and Metranidazole are equally effective. Physicians may choose to prescribe Metranidazole first since it is far less expensive than Vancomycin. Vancomycin is reserved for patients who are allergic to Metronidazole, do not respond to it, or have side effects. Other physicians choose Vancomycin primarily for severe colitis since it can achieve higher antibiotic levels in the colon and can theoretically be more effective at eradicating bacteria there with more area specificity (MedicineNet, 2008). It can, however, contribute to the growth of antibiotic-resistant bacteria. Metranidazole can not be used for women who are pregnant or breastfeeding. Both antibiotics kill only the active infectious form of *C. difficile*, not the tougher spores. Since spores are resistant and remain in the body, infection can return, requiring further treatment (Mayo Clinic, 2006). For those unable to tolerate oral medication, IV Metronidazole is used since it is excreted in the intestine (Canadian Paediatric Society, 2000).

Other drug regimens compared in randomized therapeutic trials for CDAD with good results are Bacitracin, Teicoplanin, and Colestipol. Cure rates in Bacitracin are somewhat lower than Vancomycin, and it should be treated as a secondary agent in treatment. Colestipol is even lower than Bacitracin (Gerding et al, 1995).

Some physicians prescribe supplementary probiotics to restore normal intestinal flora. A natural yeast, *Saccharomyces boulardii*, and *Lactobacillus* species has proven effective in treating *C. difficile* infections together with antibiotic (Sunenshine and McDonald, 2006).

Antidiarrheal medications such as loperamide, diphenoxylate, and bismuth compounds are contraindicated and can worsen the course of pseudomembranous colitis. Slowing of fecal transit time can possibly extend toxin-associated damage. Cholestyramine, usually used to lower cholesterol, is more effective in slowing bowel motility without causing more damage (Nation Master Encyclopedia, 2005).

If the disease causes fulminant colitis, surgical resection of the colon may be needed, especially with colon perforation (EMIS and PIP, 2007). In cases causing severe pain, organ failure, or inflammation of abdominal wall lining, surgical removal may be the only option (Mayo Clinic, 2006). Surgery should be considered especially if initial treatment does not resolve the disease and symptoms progress rapidly. Still, treatment should not be considered failure before 6-7 days of therapy (Sunenshine and McDonald, 2006). At times, a patient may relapse with recurring episodes of CDAD. Multiple courses of antibiotics may be needed. Probiotic treatment may be helpful for this (Canadian Paediatric Society, 2000). Approximately 15-35% of patients have recurrent disease. This could be from reinfection or germination from residual spores. The most likely reason for relapse is that *C. difficile* had not been completely eradicated during treatment (MedicineNet, 2008). There is no evidence that recurring infections cause more severe disease (Hull and Beck, College of Family Physicians of Canada, 2004). Another possible reason leading to relapse is the body's inadequate production of antibodies against the bacterial toxins (MedicineNet, 2008). Fecal enemas, however, are difficult to perform and there is an increased risk of transmitting retroviruses or other infectious diseases (Schroeder, 2005).

Fecal bacteriotherapy, sometimes commonly called a "stool transplant", has its basis in probiotic therapy research. Normal intestinal bacterial flora obtained from the feces of a healthy individual is infused through the intestine of the patient in an effort to restore normal flora balance, decreasing the strength of the *C. difficile* organisms and lessen likelihood of recurrence. This treatment is usually used for people with recurring episodes of disease. It has a success rate of nearly 95% (Nation



Figure 10 – Laboratory preparation of stool for fecal bacteriotherapy

(The Medical Post, 2009)

Master Encyclopedia, 2005). Anaerobic bacteria and fecal rectal enemas are usually obtained from healthy relatives to promote better acceptance by the patient's body. They are instilled rectally and can restore colonic flora (Hull and Beck, 2004).

For patients with multiple relapses possibly due to antibody deficiency, passive immunizations with human gammaglobulin can be administered intravenously. This will grant them large amounts of antibodies to eradicate the disease. Additional work is in progress to promote active vaccination against *C. difficile* toxins, to increase patient levels of antibodies. (MedicineNet, 2008)

Prevention

Most importantly, avoid using antibiotics unless absolutely necessary. Antibiotics will not eradicate viral illnesses, yet they are still used for that purpose several times annually. Even some common bacterial ailments like bronchitis and ear infections can be treated without antibiotics (Mayo Clinic, 2006). In particular, restriction of Clindamycin has been shown to decrease incident of CDAD (Schroeder, 2005).

If antibiotics are necessary, have the physician prescribe from a narrow-spectrum range to be taken in the shortest amount of time possible for least likelihood of disrupting intestinal flora (Mayo Clinic, 2006).

Use probiotic supplements – yogurt with live cultures, acidophilus, and similar during the antibiotic course. However, only *Saccharomyces boulardii* is proven effective against *C. difficile* specifically (Mayo Clinic, 2006). *Lactobacilli* have been proven effective against antibiotic-associated diarrhea, but not necessarily that caused by *Clostridium difficile*.

Any patient with CDAD, even asymptotically colonized, can transmit the disease to others. Only those on antibiotics, hospitalized, or with other prevailing risk factors are most likely to get ill. To reduce transmission, wash hands carefully especially after restroom use and before eating. Regularly clean surfaces used routinely, such as kitchens and bathrooms (Centers for Disease Control and Prevention (CDC), 2007). Ideally, a mixture of bleach and water should be used – with a ratio of 1:10 bleach to water. Patients with diarrhea should try to avoid using the same toilet other family members use unless it can be washed out each time with the bleach and water mixture (Robert Michael 2007).

Hospitalized patients known or suspected to have the disease should be treated using the 1994 Hospital Infection Control Practices Advisory Committee (HICPAC) Guideline for Isolation Precautions in Hospitals recommended contact precautions (Sunenshine and McDonald, *Cleveland Clinic Journal of Medicine*, 2006). Place those patients in private rooms if possible, or with other patients with *C. difficile*-associated disease. Use gloves and gowns to prevent transmission and wash hands with alcohol-based hand rubs or soap and water. Soap and water alone is best for direct care of CDAD patients as it is more effective against spore-forming bacteria. Dedicate equipment to them wherever possible. (Division of Healthcare Quality Promotion (DHQP), 2005) Visitors should wash hands with soap and warm water

before entering and leaving a CDAD patient's room. (Mayo Clinic, 2006). One hospital reported a 60% decrease in CDAD after instituting more stringent precautions (Sunenshine and McDonald, 2006).

Summary

Clostridium difficile-Associated Disease (CDAD) may be a slightly rare disease but with devastating effects. Due to depletion of normal intestinal flora in conjunction with other risk factors including immunocompromised state or recent hospitalization, dormant resistant spores transform to virulent possibly toxigenic infectious form of bacteria that can multiply rapidly. Although broad in arrange of symptomology, the possibility of leading to severe pseudomembranous colitis with risk of colonic perforation, toxic megacolon, or death exists. Treatment is possible – with expensive drugs and other measures, but not without the possibility of relapse, even numerous reoccurrences. Prevention must be taken to avoid susceptibility to this virulent and damaging organism altogether, by maintaining proper precautions. Should someone already have the disease, proper care must be implemented to ensure no further transmission as spores can be spread through contact and fecal-oral methods. Research is still preliminary for other treatments, including vaccination against *C. difficile* toxins. With proper prevention and treatment, and increase in patient antibodies to target the organism, even in the absence of normal intestinal flora, *Clostridium difficile*-Associated Disease can be eradicated.

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