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Recommendations for the Development of New Hospital Guidelines due to the Effects of
Antibiotics on *Clostridium difficile* Colitis

Megan Kohsel

Abstract

Clostridium difficile colitis is an infection that causes inflammation of the colon and diarrhea. This can even lead to death in some cases. The incidence of this infection and its overall effects have been on the rise throughout the last twenty years as antibiotics have been prescribed more frequently. Therefore, it is necessary that the rate of *C. difficile* infection is lowered by improved guidelines for hospitals, so that fewer people are infected and also that fewer antibiotics are prescribed to avoid the infection with *C. difficile*.

What is *Clostridium difficile* colitis?

C. difficile is a gram positive, anaerobic, spore forming bacterium that has the ability to produce exotoxins that cause colitis in humans (Salyers et al., 1994). It is estimated that approximately 5% of the population naturally have *C. difficile* present as part of their intestinal microbiota (Wilson et al., 2011). When *C. difficile* becomes pathogenic due to many different factors, including suppression of natural microbiota due to antibiotics, *C. difficile* can cause colitis. The growth of the bacteria is due to the fact that the niches that the normal microbiota fill are no longer inhabited and *C. difficile* is able to exploit this uninhabited niche and the spores can germinate. This in turn can cause *C. difficile* colitis.

***C. difficile* virulence factors**

The first step in the pathogenicity of *C. difficile* colitis is the attachment of the bacterium to the mucus and cells that line the colon (Wilson et al., 2011). The toxins that *C. difficile* produces are able to damage the colonic mucosa, and the symptoms include the production of yellowish layer on the surface of the colon made up of fibrin, mucin, and dead host cells (Wilson et al., 2011). This damage causes an inflammatory response in the body and neutrophils are

recruited (Wilson et al., 2011). Once the yellowish layers of several different areas converge together, it is called a pseudomembrane (Wilson et al., 2011).

C. difficile that causes this pseudomembrane has the ability to produce two large AB-type protein toxins, toxin A (TcdA) and toxin B (TcdB) (Wilson et al., 2011). These toxins work by modifying the G proteins of host's cell membranes that control many cellular activities, one of these is actin polymerization (Wilson et al., 2011). TcdA works by causing the mucosal cells to become so filled with fluid that they are no longer able to control water movement (Wilson et al., 2011). TcdB collapses the actin cytoskeleton of tissue culture cells (Wilson et al., 2011). Also, TcdA works more slowly than TcdB which may account for why strains of *C. difficile* colitis that only produce TcdB are still able to cause damage (Wilson et al., 2011).

TcdA Mechanism

TcdA stimulates intestinal mucosal cells which produce cytokines and inflammatory proteins (Wilson et al., 2011). This attracts neutrophils (polymorphonuclear cells [PMNs]) creating a large inflammatory response (Wilson et al., 2011). Response of this magnitude results in mucosal cell destruction (Wilson et al., 2011). The neutrophils move between the cells to reach the area of infection, which can cause the tight junctions to become damaged (Wilson et al., 2011). This damage causes water flow between the cells to be uncontrolled (Wilson et al., 2011) This results in water to leak into the lumen of the intestine and for a pathway for TcdB to enter (Wilson et al., 2011).

TcdA targets two G proteins (Wilson et al., 2011). G proteins are important because they are responsible for many regulatory functions in mammals (Wilson et al., 2011). One of the functions that they are responsible for is the control of the polymerization and depolymerization

of actin (Wilson et al., 2011). With polymerization and depolymerization inhibited the actin cytoskeleton is not able to change as it naturally does (Wilson et al., 2011). This results in problems with neutrophil movement (Wilson et al., 2011).

TcdB Mechanism

TcdB gains access through the damage that TcdA causes (Wilson et al., 2011). Once inside the mucosal membrane of the intestines, TcdB damages the tissue on the underside of the mucosal membrane and intestinal wall (Wilson et al., 2011). Damage can become so extensive that LPS or bacteria from the colon are able to enter into the bloodstream and this can result in septic shock (Wilson et al., 2011).

How *C. difficile* may be transmitted

C. difficile is able to survive for extended periods of time through its spores. Therefore, it is important, especially in a hospital setting for doctors, nurses, patients, and visitors to use caution when working with a patient who has *C. difficile* colitis. Living bacteria or their spores can be transmitted by environmental surface contamination, staff or infected patients (Surawicz et al., 2013). Endospores are able to survive on surfaces for up to five months (Gerding et al., 2015). This means that if surfaces are not disinfected correctly, *C. difficile* spores are able to be transmitted up to five months after they were originally deposited on the surface (Surawicz et al., 2013).

Symptoms

There are several different stages of the disease that a patient may be experiencing (Shen et al., 2008). Symptoms of a mild to moderate infection include watery diarrhea three or more

times a day for two or more days and mild abdominal cramping and tenderness (Surawicz et al., 2013). Symptoms of a more severe stage of the disease that a patient could notice on their own without tests may include: watery diarrhea occurring anywhere from ten to fifteen times a day, severe abdominal cramping and pain, fever, blood or pus in the stool, nausea, dehydration, loss of appetite, weight loss, and/or swollen abdomen (Surawicz et al., 2013). The most severe stage is defined as the patient being required to stay in an intensive care unit (ICU). An endoscopic examination that shows the presence of pseudomembranes or the existence of two of more of the following symptoms: patients is over 60 years old, experiencing a fever of over 38.3°C, their albumin level is less than 2.5mg/dL, or their white blood cell count within 48 hours of admission is greater than 15,000/ μ L are indicators of severe stage (Shen et al., 2008).

Antibiotic Risk Factors

96% of people who have symptoms of *C. difficile* colitis were found to have received antibiotic within the last 14 days before their first symptoms appeared (Cohen et al., 2010). Furthermore, all patients with *C. difficile* colitis symptoms had received antibiotics within the last 3 months (Cohen et al., 2013). Many outbreaks of *C. difficile* colitis are associated with the use of fluoroquinolones (Cohen et al., 2013). While fluoroquinolones, which target DNA gyrase, have been associated with a higher risk for the development of *C. difficile* colitis (Cohen et al., 2013). This may be due fluoroquinolones being broad spectrum antibiotics. However, almost all antibiotics have been associated with *C. difficile* colitis (Cohen et al., 2013). Fluoroquinolones are broad spectrum antibiotics which causes them to be associated with a higher risk for the development of *C. difficile* colitis.

Also, it was discovered that the increased use of these antibiotic was associated with the emergence of a new hypervirulent strain of *C. difficile*, strain BI/NAP1/027 (Shen et al., 2008). Strain BI/NAP1/027 has been found in 67%-82% of illnesses in Quebec which led researchers to believe that it may be transmitted with a higher effectiveness than other strains (Cohen et al., 2013). This strain has an additional toxin, the binary toxin, which may account for its higher transmission rates (Cohen et al., 2013). This strain has been shown to cause a more severe disease in patients than those effected with other strains (Cohen et al., 2013).

Diagnostic Testing

Testing a patient quickly and accurately for *C. difficile* colitis is in the best interest of both the patient and the doctor. There are several different methods for testing but the best specimen for all testing methods is a watery, loose, or unformed stool that is promptly delivered to the laboratory (Cohen et al., 2013). Due to cost and efficiency, antibody-based testing is the preferred method of identifying the toxins (Cohen et al., 2013). These tests are also the easiest for the laboratory to perform (Cohen et al., 2013).

Cell Cytotoxicity Assay

This assay is looking for the effects of *C. difficile* toxins on human cells that are grown in culture (Cohen et al., 2013). Many laboratories use human foreskin fibroblast cells (Cohen et al., 2013). These cells are the most sensitive cell line for detecting the toxin (Cohen et al., 2013). This assay has a detection rate ranging from 67% to 100% (Cohen et al., 2013).

Enzyme Immunoassay (EIA)

EIA tests are designed to detect toxin A only or to detect both toxins A and B (Cohen et al., 2013). However, it is preferred that both toxin A and B are tested for as 1%-2% of the strains present in the United States do not produce toxin A (Cohen et al., 2013). Ninety percent of the laboratories routinely use this test as it is easy to perform and cost effective (Cohen et al., 2013). It also has been shown to have a sensitivity of 63%-94% with a specificity of 75%-100% (Cohen et al., 2013).

Culture

Testing in this method is highly preferred in many laboratories and is essential to the study of *C. difficile* (Cohen et al., 2013). When grown in a solid medium, the colonies are flat, yellow, ground glass-appearing with a surrounding yellow halo (Cohen et al., 2013). They stain as gram-positive bacteria. The agar that the bacterium is grown on must be selected carefully and the plates must be incubated in an anaerobic environment (Cohen et al., 2013). Many laboratories use this diagnosis for a patient carrying *C. difficile* colitis.

Glutamate dehydrogenase (GDH)

GDH is an enzyme that is produced by *C. difficile* (Surawicz et al., 2013). This enzyme is produced in higher amounts compared to toxins A and B (Surawicz et al., 2013). *C. difficile* produces a NAD-specific GDH that through an irreversible reaction converts L-glutamate into alpha-ketoglutarate (Girinathan et al., 2013). This test is not highly sensitive even though it is a rapid test that laboratories can perform (Cohen et al., 2013). Therefore, this is a test that should be used in conjunction with another test (Cohen et al., 2013). If this test produces a negative result, the patient is determined to not be infected (Cohen et al., 2013). However, if a positive result is obtained, further confirmatory tests are performed (Cohen et al., 2013). This allows for

an initial screening of patients to quickly rule out those who are not infected. GDH is routinely coupled with a cell cytotoxin assay when a positive result is yielded (Cohen et al., 2013). This is a cost saving mechanism that has saved between \$5,700 and \$18,100 per month (Cohen et al., 2013).

Polymerase Chain Reaction (PCR)

This test is now considered the “gold standard” test for *C. difficile*. PCR works by amplification of a DNA sequence. This allows the researcher to be able to easily identify a specific part of the DNA through tagging it with another sequence. This other sequence is normally some sort of sequence that under UV light is fluorescent allowing it to be easily detected. In the case of *C. difficile* the person running the test is able to selectively tag for TcdA and TcdB sequences (Belanger et al., 2003). This test is a diagnostic test that is simple and takes approximately an hour to complete (Belanger et al., 2003).

Current Treatment Options

Antibiotics

In order to successfully treat *C. difficile* colitis, it is important to have an early diagnosis. The cause that leads to this illness is usually an antibiotic treatment and this must be discontinued as quickly as possible (Cohen et al., 2013). Once the original treatment is stopped an antibiotic treatment including metronidazole or vancomycin are used to treat the *C. difficile* colitis (Salysers et al., 1994). Metronidazole is the drug of choice for someone experiencing their first case of *C. difficile* colitis (Cohen et al., 2013). Patients are given 500 mg orally 3 times per day for 10-14 days (Cohen et al., 2013). Vancomycin is dosed as 125 mg orally 4 times per day for 10-14 days (Cohen et al., 2013). The use of vancomycin is normally reserved for a patient

with a severe case of the disease (Cohen et al., 2013). While orally is the administration of choice, the antibiotics can be administered in one of three different ways: oral, rectal, or intravenously (IV) (Shen et al., 2008).

Fidaxomicin, commonly known as Dificid, is another antibiotic that was approved for use to treat *C. difficile* colitis in May of 2011 by the FDA (Cruz, 2012). However, it should only be used in cases that are caused by *C. difficile* in order to avoid the possible development of an antibiotic-resistance bacterium (Cruz, 2012). This drug works through the inhibition of RNA polymerases (Cruz, 2012). This results in the bacterium not being able to carry out RNA transcription. Dificid acts directly in the GI tract on *C. difficile* (Cruz, 2012). It has been given for 10 days at a dosage of 200 mg twice daily (Cruz, 2012).

Colectomy

There are cases when the disease is so severe that an alternate approach is taken. A colectomy is suggested for these patients (Cohen et al., 2013). However, this patient must have their serum lactate level and peripheral blood white blood cell count monitored to ensure they will be able to survive the surgery (Cohen et al., 2013). The postoperative mortality rate is 75% or higher when the lactate level of a patient is greater or equal to 5mmol/L (Cohen et al., 2013).

Fecal microbiota transplantation (FMT)

FMT is the process of delivering stool from a healthy donor into a patient (Bowman et al., 2015). The donor can be a spouse, close relative, or any healthy unrelated donor (Bowman et al., 2015). However, it has been shown that the first choice should be to receive the stool from someone who is genetically related to the patient (Bowman et al., 2015). The routes of administration are enema, colonoscopy, or by the upper gastrointestinal (GI) tract via ingestion

(Bowman et al., 2015). This method of treatment is preferred due to the decrease in probability that a relapse of *C. difficile* colitis will occur due to changes in the normal microbiota due to the continued use of antibiotics (Bowman et al., 2015). The goal of this treatment is to help the body reestablish its normal microbiota (Bowman et al., 2015). FMT restores the dominance of the microbiota to *Bacteroidetes* and *Firmicutes* which are the bacteria phyla that dominate a healthy gut (Bowman et al., 2015). It has been shown that this treatment option has an efficiency of 83%-90% (Bowman et al., 2015). Also, it has been shown to be a great option for people with compromised immune systems (Bowman et al., 2015). It allows them to receive relief from *C. difficile* colitis without taking more antibiotics or drugs.

To administer the stool, it is mixed with a nonbacteriostatic saline solution and then strained or blended to remove unwanted particulate (Bowman et al., 2015). If the solution is administered during a colonoscopy the solution is drawn up into a syringe and infused into the colon (Bowman et al., 2015). The larger the amount administered appears to provide a more effective treatment (Bowman et al., 2015). Greater than five-hundred mL of stool showed a 97% resolution in patients while 200mL only showed an 80% improvement of patients (Bowman et al., 2015).

After the treatment, the symptoms can subside and the patient can return to normal within several days (Shen et al., 2008). However, approximately 10% - 20% of individuals will experience a relapse of the illness (Salyers et al., 1994).

Why *C. difficile* Is a Concern

Not only is *C. difficile* a concern in regards to increasing antibiotic resistance and the health of patients, or even their deaths, but it is compounded with the problem that it is costing

approximately \$3.2 billion annually (Surawicz et al., 2013). This is astounding as we are currently in a period in our healthcare system where we are trying to reform it and make the services more readily available to someone with any income level. This one area could be saving patients billions of dollars each and every year. Also, if we are not able to gain control over this disease, it is going to continue to increase the costs that patients are going to have to face.

Solutions

There are several approaches we can take to reduce the risk of *C. difficile* disease.

Education

The first step to creating a mind set to reduce the amount of antibiotics prescribed to patients (Karras et al., 2003). Doctors sometimes prescribe antibiotics to patients simply because they want to fulfill the perceived expectations of the patient (Karras et al., 2003). However, it has been shown that about only 33% of the patients had any expectation that the physician was going to prescribe them an antibiotic (Karras et al., 2003). This mentality of physician prescribing antibiotics simply because of their perception of patient's expectations needs to be curbed through education in order to be the first step towards helping to eliminate the risk of *C. difficile*. Also, in their education, doctors need to be informed about the risks that prescribing certain antibiotics such as cephalosporins, clindamycin, and fluoroquinolones have in increasing the risk for *C. difficile*.

Not only is education necessary for physicians but education of the effects of antibiotics needs to be passed down to the patients as well. When physicians are getting ready to prescribe the antibiotics that are known to be associated with causing *C. difficile* colitis, they need to explain the risks to their patients. Patients have the right to know that the antibiotic they are

being prescribed could lead to a hospital stay for them and in extreme cases could lead to death. Patients deserve a brief education on the risks before they decide if taking the antibiotic is the right choice for them. In some cases, a patient may have another treatment option or may be able to wait a while longer and let their body continue to try and fight the infection off.

Prevention of transmission

Transmission is imperative so that the bacterium is not spread around the hospital to other patients. One of the best ways to help reduce the spread of it is to increase the standard of handwashing that physicians, nurses, and any other person coming into contact with an infected patient are required to do.

Anyone coming into contact with the patient should use either hand-sanitizer or hand washing before entering the patient's room, and they must also wear gloves and a gown. This will create a barrier between the physician and the patient that can be disposed of upon leaving the room. The rate of transmission has decreased from 7.7 cases per 1,000 discharges to 1.5 cases per 1,000 discharges in the United States since then institution of gloves (Cohen et al., 2010).

Also, whoever comes into contact with the patient will be required a rigorous handwashing when exiting the patients room. It has been found that antibacterial soap is not any more effective at reducing diarrhea causing bacteria from hand than normal soup (Burton et al., 2011). Not being required to use antibacterial soap is good in the application of *C. difficile* due this eliminating a possible pathway for increase antibiotic resistance. Therefore, when the person exits the patient's room, they must use a sink with non-antibacterial hand soap and wash their hands for at least twenty seconds ensuring all parts of their hand including under their fingernails

are properly cleaned. This practice of handwashing before interacting with the next patient will result in the removal of the greatest amount of possible transmission between patient rooms.

Hospital Layout

Patients that are suspected or confirmed for infection with *C. difficile* should be placed in a single room. This decreases the chances of the patient spreading the bacterium to their roommate. In cases where single rooms are not available, if more than one patient has *C. difficile* they should be placed in a room together. Quarantining patients to the smallest area possible will result in an increased control of the spread of the bacterium.

Hospital Cleaning Staff Responsibilities

C. difficile is an endospore forming bacterium. It is able to survive on surfaces for weeks to months after it was deposited there. Therefore, not only is it important that people who are interacting directly with the patient be conscious of their actions, but those that come into contact with the room after the patient has left and before the room is cleaned for the next patient. For example, the staff that cleans the room must take extra precautions. The solution being used to clean the room should be sporicidal which means that it will kill spores (Gerding et al., 2008). Many hospitals make the mistake of not using a different cleaning agent when dealing with rooms, in which patients who had *C. difficile* colitis were staying. This can be a great problem due to the fact that some common cleaning agents that hospital cleaning staff use to clean the rooms can actually encourage sporulation of endospores (Gerding et al., 2015). For example, it has been found that quaternary ammonium-base detergents will, in fact, encourage the germination of endospores (Gerding et al., 2015). Therefore, it is necessary for hospitals to use chlorine-based disinfectants or high-concentration vaporized peroxide solutions (Gerding et al.,

2015). It has also been found that a 1:10 dilution of concentrated sodium hyperchlorite (bleach) is a great sporocidal solution (Gerding et al., 2015). This is a good option for hospitals as it is not a difficult solution to make and it can be made relatively inexpensively.

However, cleaning staff must not get complacent in their cleaning routines when dealing with rooms that have been exposed to *C. difficile*. The staff must thoroughly clean all bed railings, call buttons, television remotes, or any other surface that a patient could have touched (Gerding et al., 2015). During an outbreak in the hospital of *C. difficile* there should also be meeting with management and cleaning staff in order to help the cleaning staff to better understand the importance of cleaning the room (Gerding et al., 2015). This will help to greatly reduce the continued spread of the bacterium.

FMT in a Pill

FMT is a good treatment for patients. However, it can be time consuming and difficult to find donors that are good matches for the patient and to administer the FMT. Research should be conducted in order to determine which bacteria in the FMT are causing the patient to recover from *C. difficile*. The parts of the FMT that are found to be the solution that gets rid of the over population of the *C. difficile* should be put into a pill. This pill will be easy to administer and convenient for the patient and doctor. This will eliminate the need to put the patient under anesthesia to perform a colonoscopy. It will reduce costs incurred by the patient and the time that doctors must spending trying to combat the bacterium. Also, with a pill, there will be no instruments that will need to be disinfected for the spores. Transmission of spores to another patient will greatly be reduced.

Continued Care Practices

Not only should all of these practices be applied in the hospital setting, but when a patient gets discharged, these cleanliness practices should be continued in order to eradicate the bacterium at the house (Gerding et al., 2015). This will keep the bacteria from spreading again from the patient's house to a visitor or healthcare provider that has been to their house.

At home, the patient's restroom should be cleaned with a 1:10 dilution of concentrated sodium hyperchlorite (bleach). Also, any other areas of the house that they come into contact with should be cleaned. Visitors should use a restroom other than the one the patient is using if available. Also, visitors should wear gloves and a gown when interacting with the patient. This will form a barrier between the patient and the visitors. This practice also decreases the probability of the visitor transmitting the bacterium to places outside of the home.

It is also suggested that only those needing to have direct contact with the patients be admitted into their home. With technology today, there are many options to video conference with the patient. This limits the exposure that others have to the bacterium. Until the *C. difficile* colitis is resolved this should be the preferred method of interaction with the patient.

Once the patient's symptoms have subsided, all hard surfaces in the home should be cleaned with the 1:10 dilution of concentrated sodium hyperchlorite (bleach) in order to kill spores that are present in the home. Once the home has been cleaned, visitors will be allowed to visit the patient.

Further Development of Care

In order to reduce the risk of incidence of *C. difficile* colitis, it is necessary to research it to gain a better understanding. Therefore, it should be necessary that culturing for *C. difficile* be performed on toxin-positive stool (Cohen et al., 2013). This will allow research to be done to

gain more information about how the bacteria are changing and insight into how to combat them. This will also lead to the ability to better diagnosis a patient. It has been found that approximately only 30% of hospitalized patients who have antibiotic-associated diarrhea will have *C. difficile* colitis (Cohen et al., 2013). Being able to better understand the bacterium will help to further develop testing to better identify those who are infected.

Conclusion

C. difficile colitis is a disease that can be controlled. There simply has to be education in place in order to help physicians and patients better understand the risks of the antibiotics that they are prescribing and taking. Also, there must be education and practices put into place about how to maintain a clean environment so that the bacteria do not have a chance to spread from person to person and increase the risk of more people acquiring the bacteria. As a community, we can keep these bacteria from taking the lives of those that with a few simple practices could have been saved.

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