Clostridium Difficile: A Growing Problem

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Purpose

The purpose of this course is to define *Clostridium difficile* and explain the different strains, risk factors, spread, symptoms, complications, diagnostic procedures, treatments, and methods to prevent spread of infection.

Goals

Upon completion of this course, one should be able to:

- Explain characteristics of *Clostridium difficile.*
- Identify at least one hypervirulent strain.
- Discuss at least 2 antibiotics associated with high risk of infection, 2 associated with moderate risk, and 2 associated with low risk.
- Discuss transmission.
- List at least 6 risk factors.
- Describe symptoms of mild and severe infection.
- List and describe 4 complications.
- Explain the most commonly used diagnostic procedures.
- Describe 5 elements of treatment.
- Explain the use and benefits of fecal transplantation.
- Describe 3 methods of preventing transmission of infection.

Introduction

Janice Carr, CDC, PHIL

Between 1993 and 2000, the number of hospitalized patients who developed an infection with *Clostridium difficile* increased 74%. Between 2000 and 2005, infections increased another 200%, and infection rates have continued to rise, spreading worldwide with outbreaks now in Japan, Canada, and Europe. It is now the most common hospital-acquired infection in the United States. According to the CDC, more than 3 million hospital-acquired infections occur each year. Current CDC estimates of *Clostridium*-related deaths in the United States annually include:

- Hospital-acquired, hospital onset: 9000.
- Hospital-acquired, post-discharge onset: 3000.
- Nursing home onset: 16,5000.

In addition, community-acquired *Clostridium difficile* infection has caused severe disease in some people. This pattern of hospital-acquired infections spreading into the community, while in the early stages, mirrors to some degree the spread of MR*SA* infections from the hospital to the community.

Clostridium difficile (often referred to as simple *C-diff)* is a Gram-positive spore-forming anaerobic bacterium that is commonly found in the soil, air, and animal feces, and sometimes in human feces. About 3% of the general population is a carrier of Clostridium, but the percentage of those infected is much higher in medical institutions where people often receive antibiotics and/or have compromised immune systems because of disease or treatment.

In a healthy system, the other bacterial flora keep *Clostridium* in check, but when the balance of bacteria changes, usually because of antibiotic use or immunosuppression, *C. difficile* begins to multiply rapidly, causing mild to severe diarrhea and sometimes pseudomembranous colitis, toxic megacolon, and death, often from intestinal perforation. *C. difficile* is responsible for up to 20% of antibiotic-associated diarrhea cases.

There are many different strains of *C. difficile,* but in 2003, a very virulent strain (B1/NAP1/027) was identified. O27 strains are particularly resistant to antibiotics and tend to cause worse disease. In 2006, a closely-related hypervirulent O27 strain (R20201) was isolated in England. While the new strains especially show resistance to fluoroquinolones, fluoroquinolones have not been used to treat *C. difficile;* however, those strains of *C. difficile* with some susceptibility to fluoroquinolones, which are widely used, may not spread through an institution as fast as resistant strains.

C. difficile has been historically associated with clindamycin and with other antibiotics—such as metronidazole, aminoglycosides, fluoroquinolones, aminoglycosides, and trimethoprim—to a lesser degree, but this picture may be changing as cephalosporins and some quinolones have been implicated in outbreaks.

Antibiotic-associated risk	
High risk	Clindamycin. Ampicillin. Amoxicillin. Cephalosporins.
Moderate risk	Penicillin. Erythromycin. Trimethoprim. Quinolones (such as ciprofloxacin).
Low risk	Tetracycline. Metronidazole. Vancomycin. Aminoglycosides (such as gentamicin).

Generally speaking, people who develop *C. difficile* have received more antibiotic treatment than controls, regardless of the type of antibiotic; so simply avoiding clindamycin does not significantly reduce risk.

How is the infection transmitted?

Clostridium difficile infection is transmitted by contact with fecal contamination, and *C. difficile* is a particularly hardy bacterium because the spores are highly resistant. *C. difficile* can spread from an active form of the disease, vegetative cells. However, vegetative cells need an anaerobic environment, so they survive outside the body for only up to 24 hours and are resistant to heat, drying, and routine chemical agents and disinfectants. The inactive form, *Clostridium* spores, on the other hand, can survive up to 5 months in the

environment and are highly resistant and hard to kill. Once ingested, the inactive form activates and begins to multiply.

If an infected person defecates, shedding vegetative cells and spores, and fails to thoroughly cleanse his hands, everything she touches in the environment, such as the tray table or light switch, may become contaminated. If a nurse comes into the room and touches the tray table and leaves the room without thoroughly washing his hands, then he can spread the spores to the next patient. If the next patient's hands are contaminated, and the person touches his mouth, he may ingest spores. If he touches food, the food may become contaminated. If the nurse touches his stethoscope, he can spread the infection to each patient he examines.

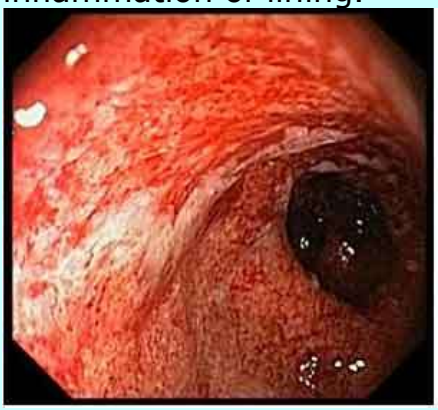
After just one or two days in a hospital, about 10% of patients become colonized with *Clostridium.* About 13% of hospitalized patients become colonized with *Clostridium* within 2 weeks and 50% with stays over 4 weeks, so the duration of contact with healthcare facilities is an important factor. Some people with a good immune response will show no symptoms or only mild diarrhea, but they may become carriers. Those most at risk for developing signs of infection include those taking antibiotics as well as the elderly and the immunocompromised, but there are a number of risk factors.

Risk factors
• Age: >65 have 10 times the risk of younger people. • Treatment with antibiotics. • Immunosuppression (chemotherapy, HIV). • Treatment in an intensive care unit. • Immunosuppressive treatment. • Severe and/or multiple underlying diseases. • Nasogastric tube. • Antacid/protein pump inhibitor use. • Sharing a room with an infected patient. • Hospitalization in a skilled nursing facility/nursing home. • Pre-existing colon disease (cancer, inflammatory bowel disease). • Prior *C. difficile* infection.

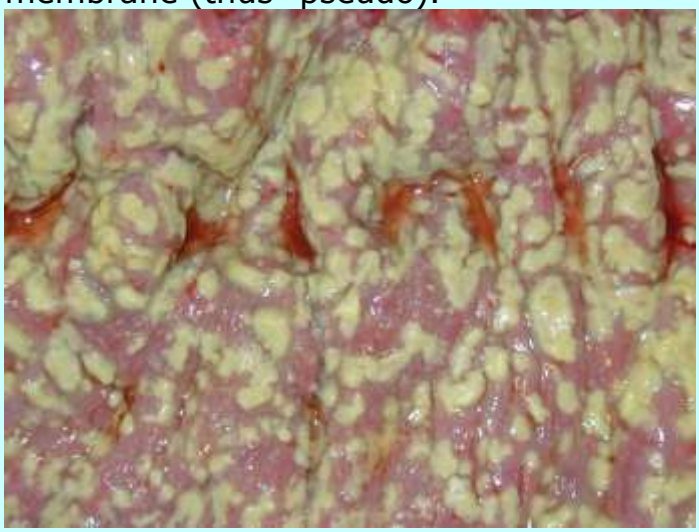
Researchers have cultured *C. difficile* from toilets, windows, bedrails, sinks, light switches, and hands of healthcare workers. Because *C. difficile* is spread in the same manner as *Staphylococcus aureus* and MR*SA*, some patients are co-infected.

What are the symptoms of *Clostridium difficile*-associated infection?

One of the problems with diagnosing and rapidly treating *Clostridium* is that while symptoms may occur rapidly in some people, in others symptoms are often delayed, sometimes for weeks. After the spores are ingested, *Clostridium* colonizes the colon and begins to produce toxins A and B that attack the lining of the intestines.

Mild	• Mild abdominal cramping and discomfort. • Watery diarrhea, usually 3-10 times daily and persisting for at least 2 days. • Low-grade fever. **Note:** While loose stools are common when taking antibiotics, if they persist for more than 3 days, occur more than 3 times daily, become watery or bloody, or a fever develops, these changes may indicate infection with *C. difficile.*
Severe	• Severe abdominal cramping and pain. • Nausea. • Watery and sometimes bloody diarrhea, >10 times daily. • Fever (102° to 103°F) • Dehydration. • Hypotension. • Decreased appetite. • Loss of weight. **Note:** A severe infection must be treated aggressively as the patient is at risk for developing life-threatening complications.
Complications	• **Colitis** results from toxins produced by the bacteria damaging the colon and causing severe inflammation of lining.  • **Pseudomembranous colitis** may occur if the toxins kill off the inner lining, resulting in

eroding ulcerated areas and surface covered with blood and purulent discharge. The appearance is that of a membrane covering the intestinal lining although it is not a true membrane (thus "pseudo).



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- **Toxic megacolon** may occur as gas and stool build up in the colon, causing the colon to become grossly distending and risking rupture.

- **Intestinal perforation** may result from ulcerations or rupture of megacolon with resultant peritonitis.
- **Kidney failure** may result from severe rapid dehydration.

	• **Death** may result from an initially mild infection if it is not recognized and treated promptly.

How is *Clostridium difficile* diagnosed?

When patients present with symptoms, testing should not be delayed because early diagnosis is critical to treatment.

Diagnostic procedures for *C. difficile*	
Stool tests	• Enzyme immunoassay (EIA). • Polymerase chain reaction. • Tissue culture assay. **Note:** Testing can usually identify toxins related to *C. difficile.* EIA usually produces rapid results but may also give a false positive so positive results should be verified with additional testing.
Flexible sigmoidoscopy	This can provide rapid confirmation of infection, as inflammation and/or pseudomembrane may be evident.
CT	CT may be used, especially to help diagnose complications. The CT will show thickening of the colon lining, indicating colitis, but cannot differentiate *C. difficile* infection from other causes.
CBC	As infection increases, the white blood count elevates, sometimes to 20,000 to 40,000, and white blood cells may also be evident in stool specimens. Dehydration and blood loss may affect hemoglobin and hematocrit.

What treatments are available for *Clostridium difficile* infection*?*

The first step to treating *C. difficile* is to stop the antibiotic that is causing the symptoms if at all possible. In some cases, this may require changing to a different antibiotic, such as metronidazole or vancomycin, which prevent *Clostridium* from growing, allowing the natural flora to regrow. One problem with *C. difficile* infection is that after treatment, infection recurs in about 25% to 33% of patients, so ongoing monitoring is important.

Treatments for *C. difficile* infection	
Antibiotic therapy	• Metronidazole (Flagyl®) is used to treat mild to moderate disease.

	• Vancomycin is reserved for severe disease or for those who don't respond to metronidazole. **Note:** For most infections, metronidazole is the drug of choice even though vancomycin may be more effective because use of vancomycin increases the overall danger of developing vancomycin-resistant bacteria. For recurrent infection, vancomycin may be given long-term and tapered or intermittently.
Probiotics	**Note:** According to the National Center for Complementary and Alternative Medicine, probiotics are beneficial live organisms, usually bacteria, similar to those found in the human intestines. • Saccharomyces boulardii (a yeast) may also be given with antibiotics to encourage restoration of a healthy balance of intestinal flora for both initial and recurrent infections.
Surgical intervention	• Repair of intestinal perforation. • Partial or complete colectomy. **Note:** Surgical intervention is used if other options are unsuccessful and the condition is life threatening.
Fecal transplantation	**Note:** This treatment is effective but is often reserved for those whole fail other treatments or have a recurrent infection, probably because of the "ick" factor, even among medical personnel. However, fecal transplantation is effective—and relatively inexpensive—and should probably be considered more frequently. Studies show it cures up to 90% of recurrent infections with a normal bowel movement often within 24 hours. A synthetic stool product is under development. A 4-day course of vancomycin is usually given prior to the transplantation to reduce the overall amount of *Clostridium.* The evening before and morning of the procedure, the person is given 20 mg of omeprazole to reduce stomach acid. A donor stool specimen (from an uninfected person) should be obtained within 24 hours of administration. Donors should be screened for hepatitis A, B, and C viruses, HIV,

	cytomegalovirus, Epstein-Barr virus, human T-lymphotropic virus, and syphilis and stools for ova and parasites and enteric bacterial pathogens. If possible a spouse or close family member is used as the donor because people in the same household tend to share similar intestinal flora. **Administration** includes: • Nasogastric: 25 to 30 g of donor stool is blended with saline or milk, filtered to remove particles, and then 25 mL of slurry is administered through a syringe into a nasogastric tube with the tip positioned in the duodenum. This method is most effective and least messy, but some people find this option repulsive. • Rectal: Up to 200 g of donor stool is needed for rectal administration, usually through colonoscopy or retention enema.
Supportive treatments	IV fluids and electrolytes may be necessary to treat dehydration resulting from diarrhea.

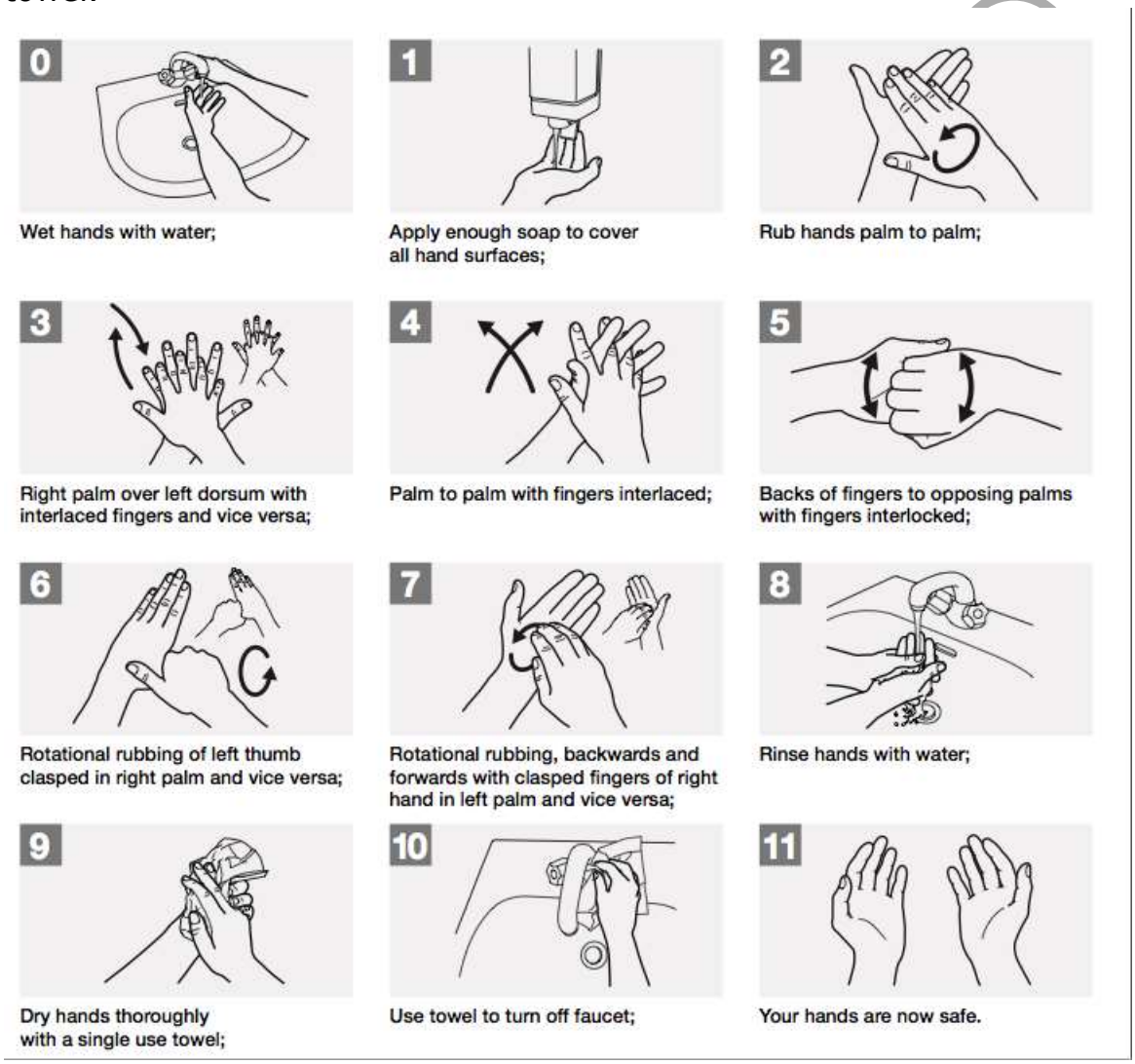
What preventive methods are needed?

Clostridium is spread by contact and—make no mistake—by healthcare providers who go from patient to patient and room to room spreading spores. While many hospitals provide alcohol-based sanitizers at point of care, the reality is that alcohol does not effectively kill *Clostridium* spores (especially since it's often used ineffectively), so healthcare providers should wash their hands the old-fashioned way with soap and water and thorough cleansing—not the quick dip under the water that often parades as washing. Handwashing should be done before and after contact with a patient. Visitors should be advised to wash their hands before and after visiting as well.

CDC and WHO guidelines for handwashing advise at least 40 to 60 seconds from start to finish. Many current guidelines suggest that washing with soap and water is only needed if the hands are soiled, and hand rubbing (with alcohol sanitizer) can be used otherwise; but the recent increase in *Clostridium* infections has engendered review of these guidelines.

The use of alcohol sanitizers has increased compliance with hand cleaning because use is fast and easy. While alcohol sanitizers serve a

useful purpose in preventing spread of other organisms, the CDC now recommends using either hand washing or alcohol sanitizing for routine infection control but switching to handwashing when *Clostridium* outbreaks occur. In fact, studies have shown that over 35% of spores remains on the hands after use of an alcohol sanitizer while thoroughly washing with soap and water removes up to 100% of spores. Handwashing for healthcare-related purposes should include use of chlorhexidine soap and water and drying with a disposable towel.



CDC

Preventive measures	
Reduce overuse of antibiotics	Routine prescription of antibiotics to treat primarily viral infections (such as bronchitis) should stop. Broad-spectrum antibiotics should be avoided unless absolutely necessary, and antibiotics should

	be prescribed for the shortest duration possible. When possible, antibiotic use should be based on culture and sensitivity.
Environmental cleaning 	Cleaning products and disinfectants should contain chlorine bleach as spores are resistant to many cleaning products.
Contact precautions 	Ideally, patients with diagnosed or suspected *C. difficile* should be in private rooms or co-horted with someone with the same infection. Standard contact precautions include the use of gown and disposable gloves for patient contact, including routine care and contact with potentially-contaminated areas or items in the environment. Visitors should also wear gowns and gloves. Personal protective equipment (PPE) should be donned prior to entering the room and discarded inside the room before exiting in order to contain pathogenic agents. If infected patients must be maintained in multi-patient rooms, then there must be >3 feet of spatial separation between beds as well as a curtain to reduce the danger of inadvertent sharing of items or contact between patients.

Summary

C. difficile is now the most common hospital-acquired infection in the United States. *C. difficile* is associated with antibiotic use and is most dangerous to the elderly and those who are immunocompromised. The bacteria spread through contact from fecal contamination by active vegetative cells (which cannot live more than a few hours in the environment) and inactive spores (which can survive up to 5 months in the environment). Mild symptoms include abdominal discomfort and diarrhea, but as the bacteria invade the lining of the colon, inflammation occurs leading to increased fever, cramping, and severe watery, bloody diarrhea. Complications can include colitis, pseudomembranous colitis, toxic megacolon, and intestinal perforation. Diagnosis is per stool tests, flexible sigmoidoscopy, CT, and CBC. Treatment includes stopping the causative agent and

treatment with the appropriate antibiotic (such as metronidazole or vancomycin), probiotics, surgical intervention, fecal transplantation, and supportive care. Prevention includes hand hygiene, environmental cleansing, and contact precautions.

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