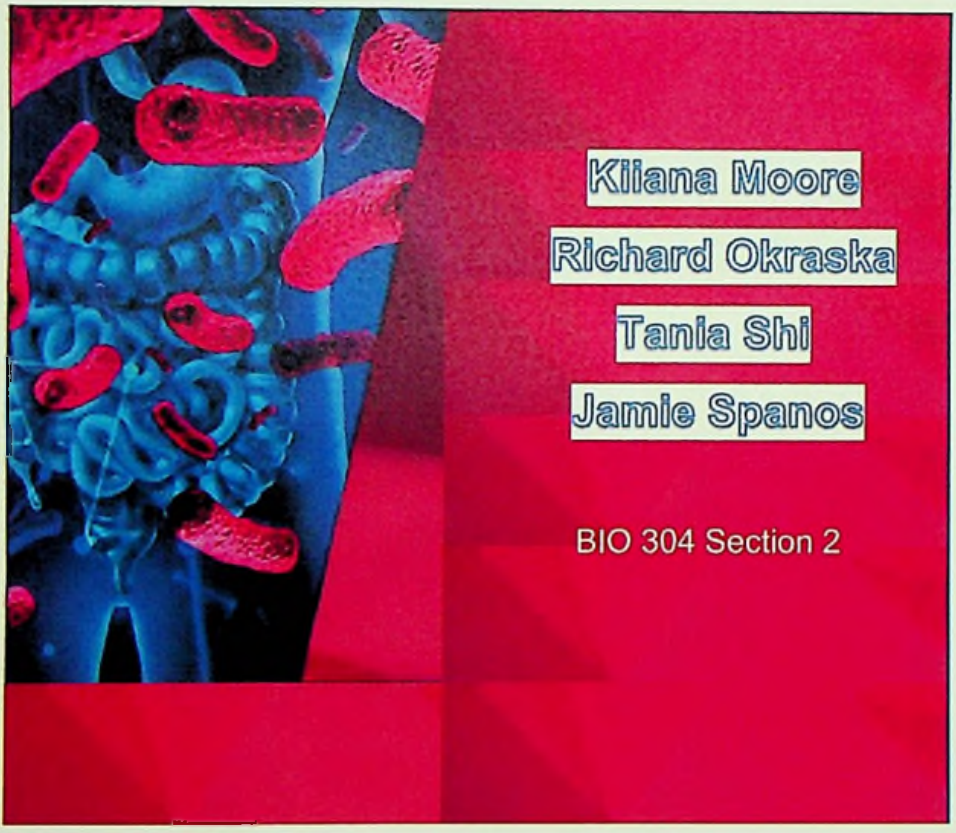
Clostridium difficile



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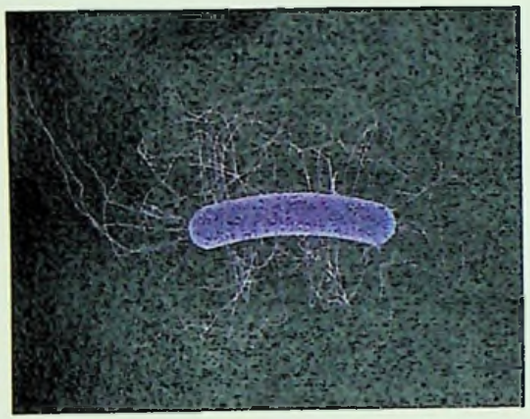
BIO 304 Section 2

What is *Clostridium difficile*?

- *C. difficile* is a bacterium that causes diarrhea and inflammation of the colon.
- According to the CDC, it is estimated to cause **almost half a million illnesses** in the United States each year.
- People on antibiotics are **7 to 10 times more likely to get *C. difficile*** while on the drugs and during the month after.
- **1 in 5 patients** who get *C. difficile*, will get it again
- **More than 80%** of *C. difficile* deaths occur in people 65 and older.
- *C. difficile* **costs up to $4.8 billion each year** in excess health care costs for acute care facilities alone.

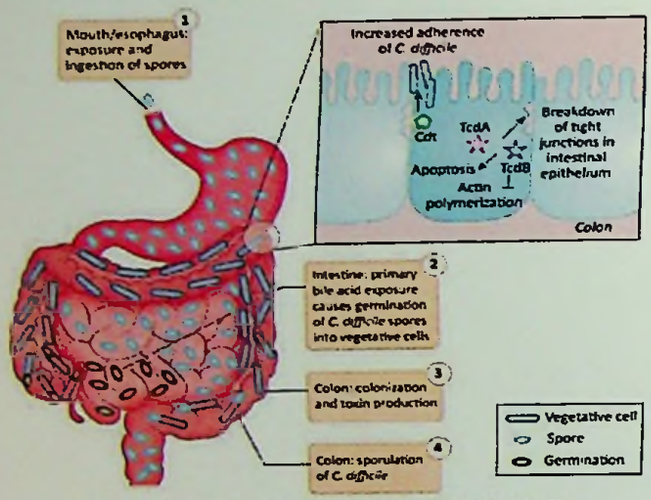
Structure of *C. difficile*



https://www.cdc.gov/media/images/releases/2015/p0225-clostridium-diff...jpg

- *C. difficile* is a spore-forming, anaerobic Gram-positive bacillus.
- The spores are coated with a peptidoglycan cortex and several layers of protein, which allow them to survive in harsh environments and in the presence of oxygen.
- The cell envelope of the vegetative cell contains a thick layer of peptidoglycan in the cell wall; S-layer, which has been implicated in bacterial adhesion to host tissues; and peritrichous flagella for enhanced motility in the mucus-rich environment of the gut.

Oral-Fecal Route



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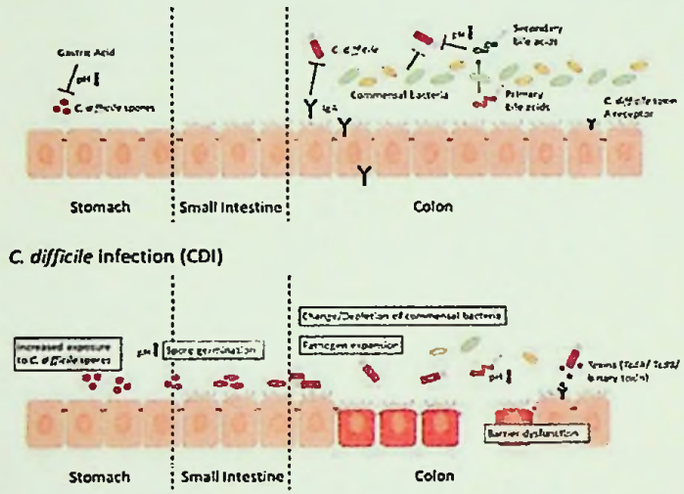
- *C. difficile* are transmitted via the oral–fecal route.
- The spores are able to survive the gastric acidity and germinate upon exposure to primary bile acids in the small intestine. Colonization occurs in the large intestine.
- *C. difficile* cells can then sporulate and exit the body via diarrheal shedding.
- Fomites that become contaminated with feces could serve as reservoirs for the *C. difficile* spores. The spores can be transferred to patients via the hands of healthcare personnel who have touched a contaminated surface or item.

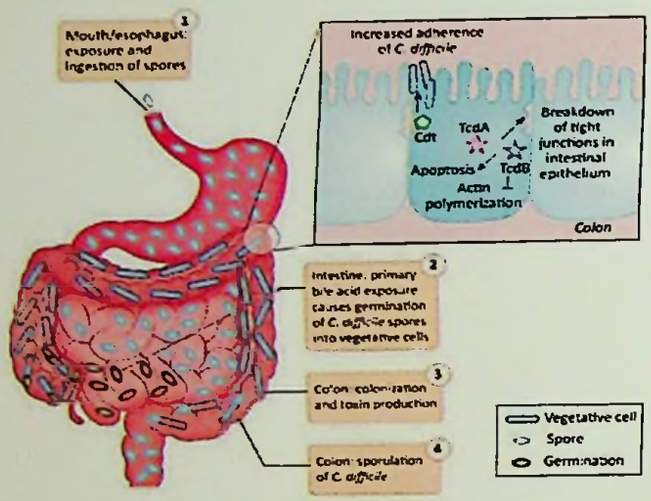
Requirements for Growth



https://www.frontiersin.org/articles/10.3389/fmicb.2018.00646/full

- C. *difficile* are obligate anaerobes and only germinate in the anaerobic environment of the intestines.
- Germination occurs in response to a combination of amino acids or calcium and primary bile acids in the intestines, which indicate favorable conditions for vegetative growth.
- Colonization occurs when the gut flora is disrupted because there is less competition for nutrients, and there is a decrease in production of secondary bile acids, which are essential to inhibit *C. difficile* growth.
- Decreased levels of immunoglobin A (IgA), which are antibodies that contribute to mucosal immunity, also allow proliferation of *C. difficile*.

Oral-Fecal Route



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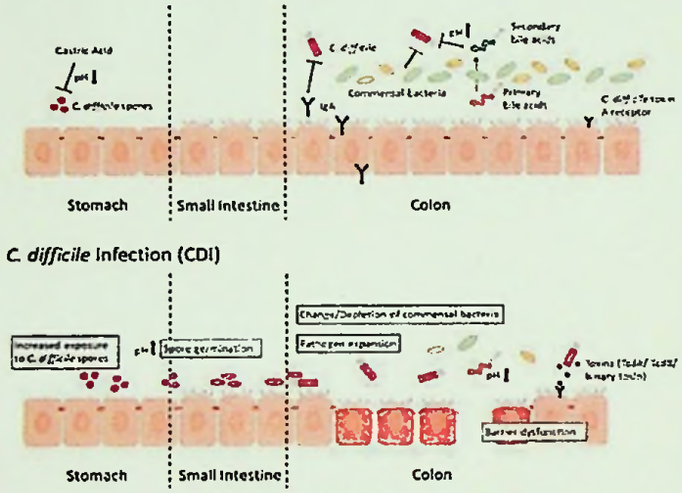

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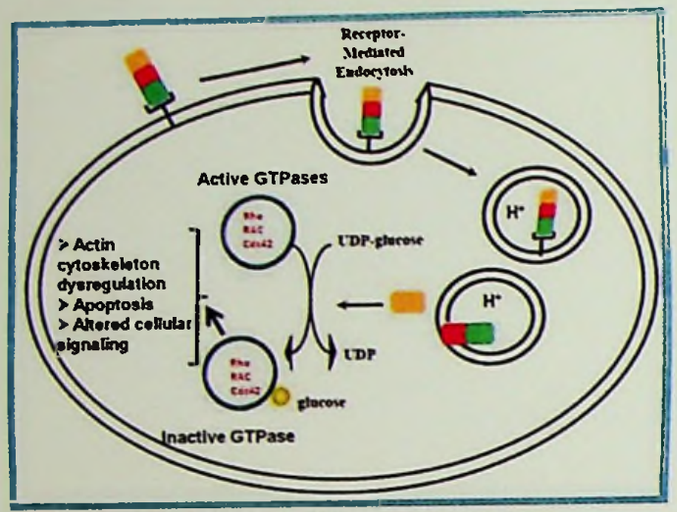
Pathogenesis



https://digitalcommons.library.tmc.edu/utgsbs_dissertations/250/

- *C. difficile* produces toxins TcdA and TcdB that causes the onset of disease symptoms.
- Toxins enter the cell through receptor-mediated endocytosis, and low pH within the endosomes result in the release of the glucosyltransferase domains of the toxins.
- Glucosyltransferase irreversibly inactivates Rho GTPases, leading to disruption of cytoskeleton and tight junctions, and ultimately cell death.
- The toxins also induce proinflammatory mediators and cytokines, causing cell apoptosis or necrosis in epithelial and immune cells.
- Individuals who lack membrane receptors required for the toxins may be asymptomatic.

Diagnosis

Laboratory Diagnosis

- Molecular tests: test for the gene encoding toxin B
- Antigen detection: detect the presence of *C. difficile* antigen.
- Toxin testing: tissue culture cytotoxicity assay detects toxin B only; enzyme immunoassay detects toxin A, toxin B, or both A and B.
- Stool culture for *C. difficile*

Colonoscopy or Sigmoidoscopy

- A colonoscopy enables a doctor to examine the entire colon and rectum, whereas a sigmoidoscopy allows him or her to view only the rectum and the lower part of the colon.
- These tests can indicate whether inflammation is present, indicating a *C. difficile* infection. They also allow a doctor to take tissue samples, to further test for infection.

CT Scan

- Uses X-rays and a computer to create three-dimensional, cross-sectional images of the body to view complication of *C. difficile* infection, such as a hole in the intestines.

Blood Test

- Can reveal high levels of white blood cells, a sign of infection.

SIGNS & SYMPTOMS OF C.DIFF

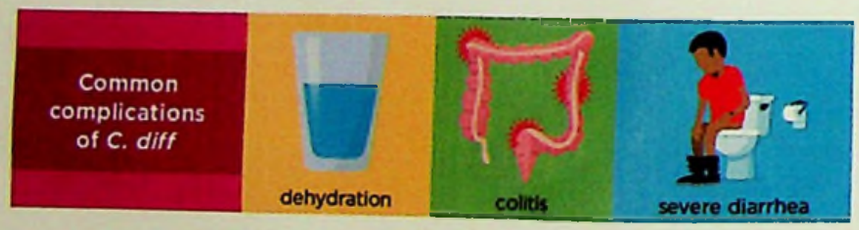
Mild to Moderate infection symptoms:

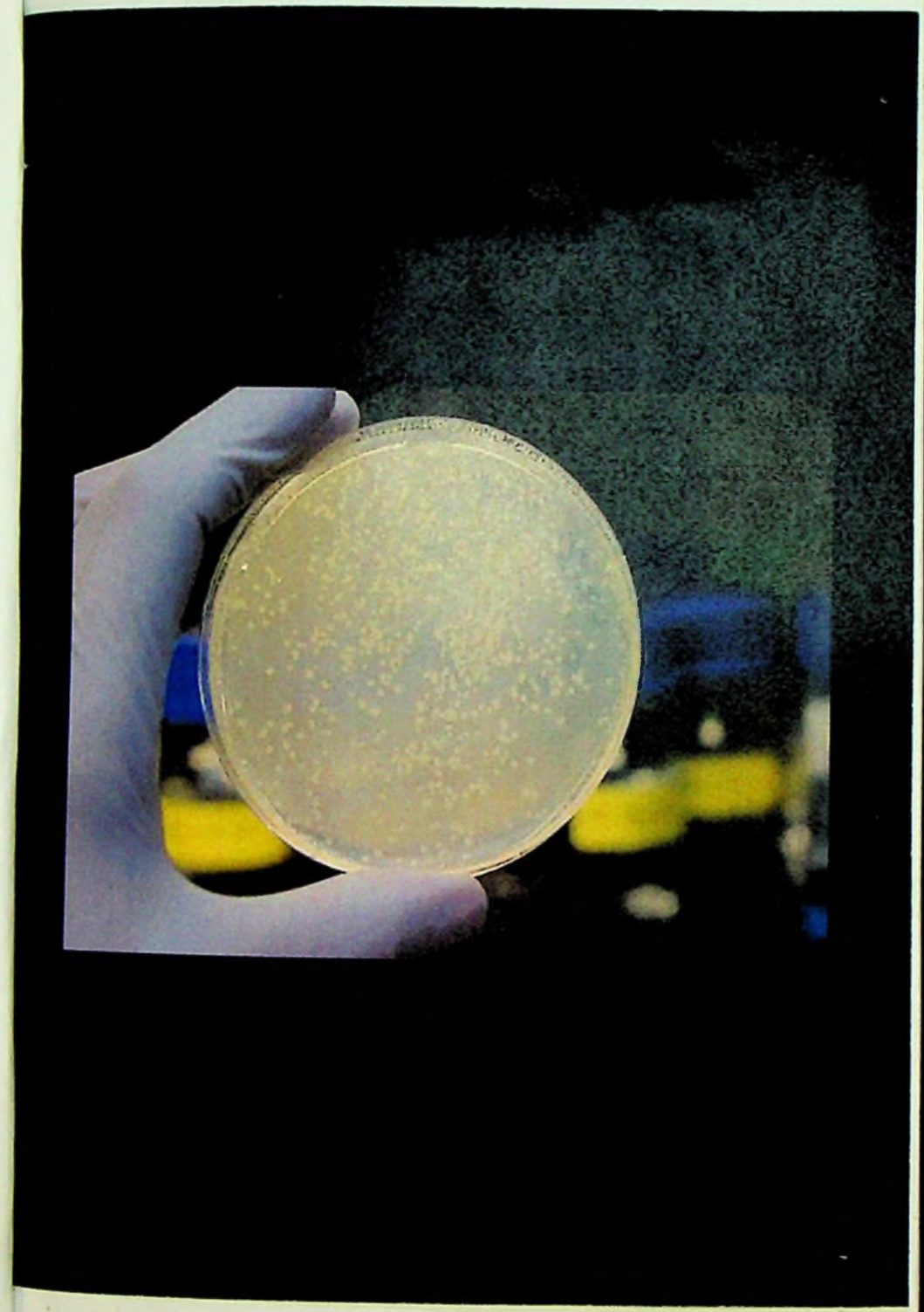
- Watery diarrhea (3+ times a day) for two or more days
- Mild abdominal cramping and tenderness

Severe Infection Symptoms:

May require hospitalization. Colon may become inflamed creating patches of raw tissue that can bleed or produce pus. Severe infection may also cause severe intestinal inflammation, enlargement of the colon and sepsis. Many people with these conditions are admitted to the ICU

- Dehydration
- Inflamed colon
- Watery Diarrhea (10-15x a day)
- Abdominal cramping and pain
- Rapid Heart Rate
- Fever
- Blood or pus in stool
- Nausea
- Loss of appetite
- Weight Loss
- Swollen abdomen
- Kidney Failure
- Increased White blood cell count



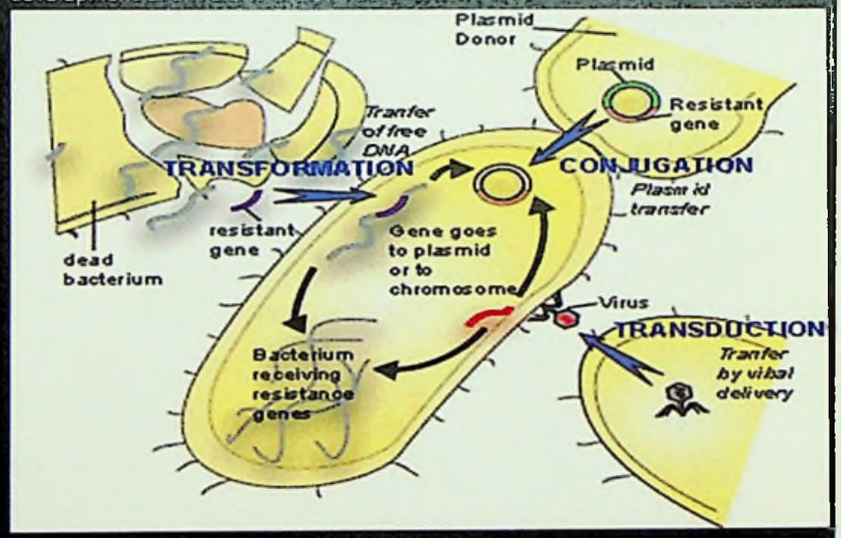


DRUG RESISTANCE!

Clostridium difficile (*C. difficile*) is known to be resistant to multiple antibiotics, such as aminoglycosides, lincomycin, tetracyclines, erythromycin, clindamycin, penicillins, cephalosporins, and fluoroquinolones, which are commonly used in the treatment of bacterial infections in clinical settings.

RESISTANCE MECHANISMS

- Intra- or interspecies transfers of mobile genetic elements via conjugation, transduction, and/or transformation or the natural occurrence of gene mutations facilitate C. difficile in obtaining antibiotic resistance genes.
- Selective pressure in vivo leads to alterations in the antibiotic targets and/or in the metabolic pathways in C. difficile, which on one hand, directly causes antibiotic resistance, while on the other hand, may stimulate biofilm formation.
- Biofilm formation via different mechanisms further promotes the development of antibiotic resistance in C. difficile.



TREATMENT

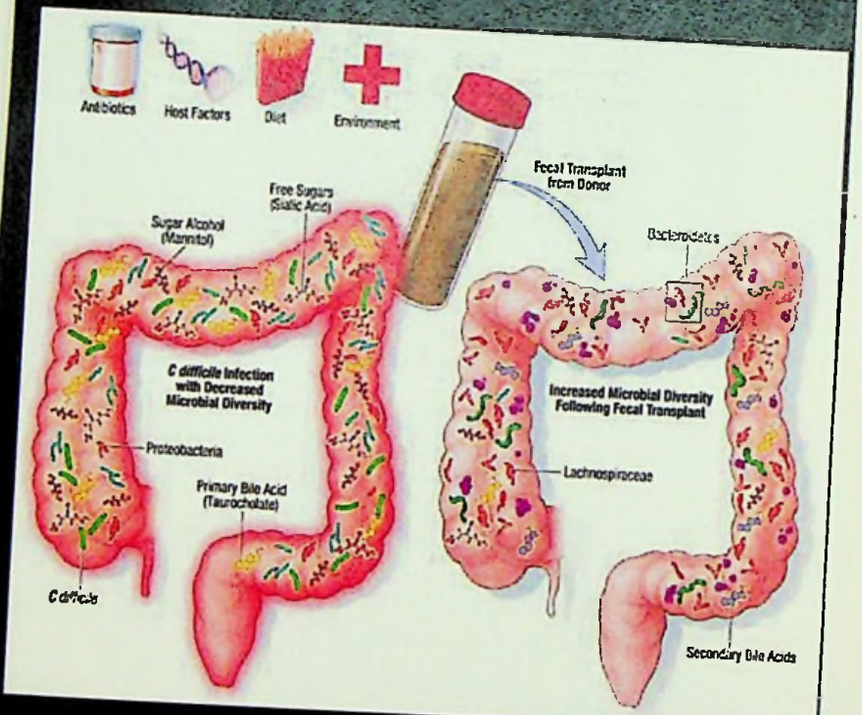
The first step in treating C. difficile is to stop taking the antibiotic that triggered the infection, when possible. Depending on the severity of your infection, treatment may include:

- Antibiotics. Ironically, the standard treatment for C. difficile is another antibiotic. These antibiotics keep C. difficile from growing, which in turn treats diarrhea and other complications. Your doctor may prescribe vancomycin or fidaxomicin.
- Surgery. For people who have severe pain, organ failure, toxic megacolon or inflammation of the lining of the abdominal wall, surgery to remove the diseased portion of the colon may be the only option.

Treatment for secondary infections:

- Antibiotics: Antibiotic therapy for recurrence may involve one or more courses of medication. In general, guidelines recommend not repeating the same therapy used for an initial infection for a recurrent infection. The effectiveness of antibiotic therapy declines with each subsequent recurrence.
- Fecal microbiota transplant (FMT): Also known as a stool transplant, FMT is emerging as an alternative strategy for treating recurrent C. difficile infections. Though FMT is considered experimental and is not yet approved by the FDA, clinical studies are currently underway. FMT restores healthy intestinal bacteria by placing another person's (donor's) stool in your colon through a colonoscope or nasogastric tube. Donors are screened for

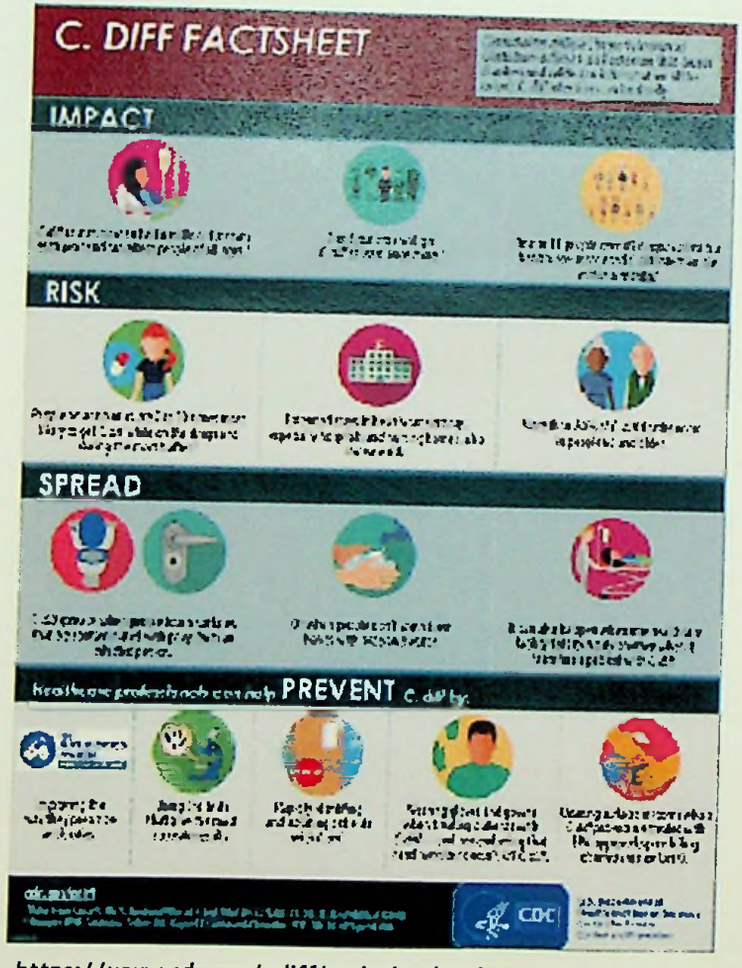
medical conditions, their blood is tested for infections, and stools are carefully screened for parasites, viruses and other infectious bacteria before being used for FMT. Research has shown that FMT done one or more times has a success rate higher than 85% for treating C. difficile infections.



Environmental Disinfection and Hand Hygiene

- Patients who are housed in rooms that were previously occupied by patients with C. difficile are at risk for acquiring the same drug-resistant organism.
- Spore-forming organisms such as C. difficile are capable of persisting on surfaces for as long as 5 months.
- Surfaces and devices that are contaminated with feces can be a reservoir for C. difficile spores.
- The heaviest contamination is on floors and bedrails.
- Windowsills, commodes, toilets, bedsheets, call buttons, scales, blood pressure cuffs, electronic thermometers, flow-control devices for intravenous catheters, and feeding tube equipment are surfaces that can also become contaminated.
- Environmental contamination is an important thing to be aware of because it is shown that health care workers are an important vector for transmission to patients.

- Only chlorine-based disinfectants and high-concentration, vaporized hydrogen peroxide are sporadical.
- Washing hands helps reduce the likelihood of recurrent disease as a result of the reinfection of the patient, even if they are an outpatient.
- Use of gloves and gowns can reduce the rate of C-Difficile.



https://www.cdc.gov/cdiff/reducing.html

Engage the Facility Antibiotic Stewardship Program

- implement the 7 Core Elements of Hospital Antibiotic Stewardship.
- Assess the appropriateness of prescribing antibiotics that pose the highest risk for C-Difficile, especially fluoroquinolone and 3rd and 4th generation cephalosporins.
- Develop facility-specific treatment recommendations for common infections that include first and second-line antibiotics.
- Evaluate antibiotic treatment of conditions that commonly lead to high-risk antibiotic use, such as asymptomatic bacteriuria, urinary tract infections, and pneumonia to minimize the use of high-risk antibiotics.
- Ensure that patients receive the shortest effective duration of antibiotic therapy. Include inpatient antibiotic duration when determining post-discharge antibiotic duration.

https://southrx.com/2018/07/06/sps-pharmacists-help-create-facility-antibiotic-stewardship-programs/

CLINICAL TRIALS

Pfizer Vaccination Trial:

- Investigational study done on those 50 years or older who are at risk for developing C.Diff
- Study will decide whether vaccine prevents disease and whether it is "safe and well tolerated"
- Every subject receives either 3 doses of vaccine or placebo
- Subjects are to be followed up with three years post vaccination/ placebo

Finch Therapeutics:

- Investigational study done on those who have recurrence of C.Diff infection
- Studying safety and effectiveness of CP101 (oral administration) drug to prevent recurrence of C.Diff
- Designed to deliver bacteria to intestine which may help overtake surplus of C. Diff bacteria that cause the infection
- Not yet approved by Food and Drug Administration to treat C.Diff (investigational)
- May aid in restoring diverse community of bacteria in a healthy human gut

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