

CONTAGIOUS COMMENTS

Department of Epidemiology

Clostridium difficile Returns with a Vengeance

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Unlike old soldiers, old infectious diseases don't die. They bide their time and return, often in a more dangerous guise. So it is with *Clostridium difficile*. This bacterium has long been known to cause antibiotic-associated diarrhea, mostly in hospitalized elderly. Recently an obscure strain has re-emerged and is causing outbreaks of high morbidity and mortality in populations not previously considered at high risk, including children. An estimated 3 million cases of symptomatic gastrointestinal disease in the US per year are now ascribed to *C. difficile*, making it the most common bacterial cause of diarrhea in the country.

The Organism

C. difficile is a gram-positive, spore-forming, anaerobic bacillus found in humans, animals, and the environment. There are many strains and their circulation is diverse and dynamic. Some strains produce toxins, toxin B (a cytotoxin and the major virulence factor) and toxin A (an enterotoxin). "Toxigenic" strains can cause a broad spectrum of human gastrointestinal *C. difficile*-associated infections (CDIs) ranging from asymptomatic colonization to life-threatening disease.

Asymptomatic Colonization

Asymptomatic colonization is the most common form of CDI. Colonization is detectable in only 2-3% of healthy, community-dwelling adults, but increases significantly (up to 25% in some studies) once patients enter the hospital or a long-term care facility. Asymptomatic CDIs may actually be somewhat protective by boosting antibody levels against the toxins, or if non-toxigenic strains are involved, by competing with toxin-producing strains for nutrients or access to mucosal surfaces. Individuals who are asymptotically colonized can occasionally spread CDIs to others.

What Is the Clinical Picture?

Symptomatic CDIs typically begin 2-3 days after a colonization of a susceptible host by a toxigenic strain. There are three forms of illness: (1) acute diarrhea that can be mild to severe; (2) fulminant diarrhea associated with pseudomembranous colitis which can lead to death; and (3) recurrent illness. Diarrhea is usually profuse and watery, although stools can contain mucus or occult blood. Fever, cramping, abdominal discomfort, and a peripheral leukocytosis are common. In severe colitis, a colonic ileus or "toxic

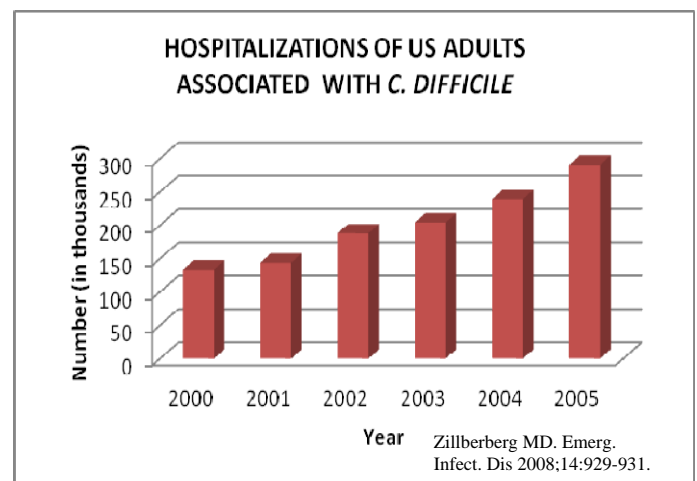
megacolon" can form. Complications include dehydration, electrolyte disturbances, hypoalbuminemia, intestinal perforation, renal failure, systemic inflammatory response syndrome, sepsis, and sometimes death. Relapses occur in up to 25% of cases, even after treatment with seemingly-effective antibiotics.

Who is at Risk?

Antibiotic use, even a single dose as for pre-surgical prophylaxis, is the most important risk factor for development of a symptomatic CDI. Other predisposing factors include advanced age, lengthy hospitalization, cancer chemotherapy, gastric surgery, tube feeding, and use of proton pump inhibitors. These factors probably perturb normal bowel flora, thus providing a "niche" for *C. difficile* to flourish.

The Changing Pattern of CDI in Adults

An alarming 20% annual increase in the rate of symptomatic CDIs in US adults began to occur early in this decade (Figure 1). The increase was accompanied by a quadrupling of CDI-associated mortality (up to 7% in some outbreaks), more rapid disease progression, and more frequent relapses. In addition, populations not previously considered at high risk of symptomatic disease were affected, including healthy peripartum women, children and young adults, and community-dwelling individuals without recent healthcare contact or exposure to antibiotics.



The “Hypervirulent” Strain

This new pattern of disease has now been linked to the emergence of a “hypervirulent” strain of C. difficile, which is highly-resistant to fluoroquinolones and was probably selected from a previously susceptible strain by overuse of antibiotics. Its official designation is “NAP1/B1/027” which stands for North American pulsed-field gel electrophoresis pattern 1, restriction endonuclease pattern B1, and PCR ribotype designation 027. Virulence and communicability are related to three new properties: 1) increased spore production which improve the bacteria’s ability to survive in the environment; 2) a deletion in the regulatory region of the toxin gene which increases toxin production by up to 20-fold; and 3) acquisition of a third “binary” toxin.

The NAP1/B1/027 strain has now been detected in over 40 states, including Colorado. Its appearance is probably an important factor in the increasing burden of CDI observed. The ageing population and increasing acuity of patients in healthcare facilities may be contributing factors as well. Unfortunately, methods of strain surveillance and evidence-based case definitions for CDIs are yet to be established, so it is difficult to compare infection rates and severity due to individual strains across different healthcare settings. Whether the hypervirulent strain will ultimately predominate or will be replaced by other strains is also unknown. Indeed, the rate of increase of CDIs in adults has leveled off recently.

C. difficile Infections in Children

Soon after birth, up to 70% of infants become asymptotically colonized, even with toxigenic strains of C. difficile. These infections can be transient or continuous and can involve multiple strains. Sources of acquisition are obscure. Rates of asymptomatic colonization decrease with age to less than 6% in the second year of life, and down to 2-3% as in healthy adults. Severe symptomatic CDIs, however, still occur in some infants, especially if there is underlying intestinal pathology such as necrotizing enterocolitis or Hirschsprung’s Disease.

As with adults, the number of symptomatic CDIs in US children over a year of age has been steadily increasing. One recent study estimated that as many as 8000 hospitalized children carried this diagnosis in 2006. The pattern of disease in pediatrics seems to be changing as well. Whereas most illnesses in children were once exclusively associated with hospitalization or antibiotic use, almost half of all cases are now community-acquired and lack a history of antibiotic use. Whether the severity and recurrence rates are increasing in children, as in adults, remain to be determined. The clinical consequence of the hypervirulent strain in children is similarly unknown.

Who and How to Test for C. difficile

There should be a high index of suspicion of C. difficile-associated disease in patients with diarrhea and prior antibiotic use, patients with current or recent healthcare system contact, or patients from the community presenting with diarrhea without antibiotic exposure if tests for other relevant

pathogens are also performed and are negative. Endoscopic findings of pseudomembranes or friable rectal mucosa also suggest C. difficile.

Laboratory testing for *C. difficile* toxins or toxin genes is necessary to establish the diagnosis. Only patients who are currently symptomatic should be tested, due to the high rate of asymptomatic colonization in healthcare facilities and in young children. Stools are the preferred specimen because rectal swabs do not contain enough fecal material for analysis. Most laboratories accept only unformed stools, although formed stools from patients with *C. difficile*-associated ileus or pseudomembranous colitis, who often pass only solid feces, can be sent. A single specimen is usually sufficient for analysis, provided that sensitive assays are ordered. Positive results in children younger than a year of age can be difficult to interpret due to asymptomatic colonization. We accept specimens from such children, but it can be difficult to interpret positive results in this age group.

Many methods are available for detection of *C. difficile*, none of which distinguishes between colonization and disease. Table 1 lists these assays in order of decreasing sensitivity. In past years, our laboratory offered a cytotoxin B assay, as well as a cost-sparing, 2-step algorithm consisting of a screening test for the *C. difficile* common antigen, followed by toxin tests on antigen-positive specimens. We discontinued both approaches for several reasons. Toxins are unstable and can degrade before specimens are tested. The algorithm also delayed positive result and can miss some cases because the hypervirulent strain “under-expresses” its common antigen.

We now perform a highly sensitive, real-time PCR (polymerase chain reaction) for the toxin B gene. This DNA amplification test is inherently more sensitive than a toxin immunoassay because DNA is more stable than toxin in stool. The assay is performed on automated instrument which also provides results within hours. The cost of PCR is somewhat higher than for immunoassays, but the clinical and financial consequences of falsely-negative or delayed results can be significant. If clinical suspicion for CDI remains high and the toxin B PCR is negative, toxigenic culture should be considered. Follow-up “tests of cure” are not recommended due to the prolonged shedding of bacteria and spores.

LABORATORY TESTS FOR *C. DIFFICILE*

Assay	Analytes	Sensitivity	Time to Result	Comments
Toxigenic culture	Viable toxigenic organisms	++++	4-5 days	Gold standard.
PCR	Toxin B gene	+++	Usually same day	Excellent. Used by our laboratory
Cytotoxin	Toxin B	+++	2-3 days	Excellent
Immunoassay	Common antigen	++	Usually same day	Must further identify toxin positives by another method
Immunoassay	Toxin A and B	++	Usually same day	Less sensitive than PCR or toxigenic culture

How Is Transmission Prevented?

Modes of transmission for C. difficile help understand how to prevent spread.

- *C. difficile* can survive for prolonged periods in the environment and on surfaces by producing spores, which can be shed for prolonged periods of time even after disease recovery. Spores are hardier than the vegetative form and protect the organism from undesirable environmental conditions.
- Patients and healthcare workers (HCWs) can easily acquire and/or transmit *C. difficile* from direct contact with stool, skin, clothing, or bedding of patients with diarrhea, and from the “fecal veneer” containing spores and bacteria that contaminate nearby items or surfaces.
- Transmission occurs via the fecal-oral route, basically meaning one literally “ingests” *C. difficile*. Spores can survive gastric acid in the stomach and proceed to the colon, where they germinate.

How long does C. difficile survive in the environment?

The vegetative state of the organism dies rather quickly when outside the GI tract, generally within 24 hours. However, spores can persist in the environment for many months. They are resistant to many routine cleaning and disinfection procedures.

What are some of the common sources of healthcare associated disease transmission?

- Infected humans
 - Symptomatic - major reservoir
 - Asymptomatic colonization – minor role
- Contaminated hands
 - HCW – facilitates transient hand carriage to patients during procedures and care
 - Patients and families – facilitate contamination of the environment
- Inanimate objects
 - Environmental surfaces
 - Contaminated commodes and bathrooms

Common patient care items that are shared or used between patients e.g. TV controls, electronic thermometers, scanners, toys

What prevention strategies reduce transmission in healthcare?

- Early recognition of suspected or diagnosed patients with symptomatic CDI. At this time, testing of asymptomatic patients is not recommended.
- Contact isolation precautions
 - Private room (preferable). Contact Epidemiology if cohorting is being considered.
 - Gloves and gown. Change gloves if visibly soiled or after touching/handling items contaminated with feces.
 - Hand hygiene upon removal of gown and gloves and exiting the patient room.
 - Patient dedicated equipment whenever possible to prevent cross contamination.
 - Reusable equipment must be cleaned and disinfected between patients with an EPA-approved product. Appropriate contact time (per manufacturer’s recommendations) of the disinfectant on the surface is important.
- Judicious use of antimicrobial agents, especially clindamycin or third generation cephalosporins, which can promote symptomatic disease in colonized patients.
- Patient education (hand hygiene and personal hygiene).
- Environmental cleaning with an EPA-approved germicide. At Children’s, we use a bleach (sodium hypochlorite) based solution called Dispatch® for any patient in contact precautions to assure that all patients with *C. difficile* will have this disinfectant used. The bleach solution kills the spores whereas other disinfectants only kill the vegetative organisms.

The solution must have contact with the surface for 3 minutes according to the product label to be effective.

*Can alcohol-based (waterless) hand hygiene products be used when caring for patients that have *C. difficile*?*

Yes. While common antimicrobial agents in hand hygiene products (e.g. alcohol, chlorhexidine, triclosan) are not effective in killing spores, CDI rates have not been found to increase as the use of alcohol-based hand hygiene products has increased. In addition, HCWs should be wearing gloves when caring for patients with *C. difficile*. This practice alone has been shown to significantly decrease transmission. In fact, the introduction of a virulent strain of *C. difficile* to a facility and not the increased use of alcohol-based hand hygiene products has been attributed to increased incidence of CDI.

We do know that a benefit of washing with soap and water is that the friction and water combination removes and dilutes the spores, but does not actually kill the spores. The important message however is that HCW should be wearing gloves and should not use alcohol-based hand hygiene products when their hands are visibly soiled. The CDC state that alcohol-based hand hygiene products can be used during routine care of patients with *C. difficile*. In the event that a facility is having ongoing transmission or an outbreak of *C. difficile* that cannot be controlled with usual infection prevention efforts, removing the alcohol-based products may be considered as an additional measure of prevention.

*When can contact precautions be discontinued for a patient with *C. difficile*?*

At Children's, we take into consideration the time since completion of treatment, resolution of symptoms, baseline and current stool pattern, degree of continence, as well as repeat *C. difficile* test results if warranted. We have developed an algorithm to assist in the decision making process which can be found at <http://planettch/policiesfitz/general/pdf/6095.pdf>

How is *C. difficile* Disease Treated?

Antimicrobials

Oral metronidazole (*Flagyl*[®]) is the drug of choice for most individuals with an initial episode of a mild-moderate, symptomatic CDI. Vancomycin administered orally (and per rectum if there is an ileus), with or without intravenous metronidazole, is used to treat more severe forms of the disease. Vancomycin is preferred when there is underlying intestinal tract disease or an inadequate response to metronidazole. Colostomy may be required for severely-ill patients. Drugs that decrease intestinal motility (e.g. loperamide) should not be given.

Recurrences of *C. difficile* disease occur in up to a quarter of cases. Recurrences can represent relapses of disease due to the original strain or re-infection of susceptible patients with other strains. Initial recurrences are usually treated with the same regimen as for the initial episode. Metronidazole is not recommended beyond the initial recurrence because long term chronic therapy has the potential for cumulative neurotoxicity.

A tapered and/or pulsed vancomycin regimen can be used for the second or later recurrences to encourage colonic flora recovery. Management of subsequent recurrences becomes more challenging. Other antimicrobials that have been used include rifaximin, nitazoxanide, tigecycline, bacitracin, teicoplanin, and fusidic acid. Several novel antimicrobial agents are under development.

Non-Antimicrobial Approaches

Many non-antimicrobial approaches have been evaluated or are being investigated to treat recurrences. These approaches are appealing because they avoid continued suppression of protective normal bacterial flora. One strategy is to reduce toxin load by use of intraluminal toxin binders (such as the anion-exchange resin tolevamar) or other toxin neutralizers such as antitoxins. Biotherapeutic approaches attempt to restore the protective colonic flora. Administration of probiotics for this purpose has been disappointing. Fecal transplants (transfer of stool from healthy individuals), have been highly effective in small studies so a large clinical trial of such transplants is now underway. Another strategy is immunotherapy, using vaccines or passively-administered antibodies. Vaccines may not be useful in the elderly patients, who often fail to mount protective antibody responses. Data using pooled human intravenous immunoglobulin is insufficient to recommend this approach. Infusion of monoclonal antibodies against toxins A and B is promising.

Conclusions

C. difficile-associated gastrointestinal disease has "emerged" over the past decade as a global public health problem in adults and now in children. Healthcare facilities can play an essential role in control efforts by implementing good antimicrobial stewardship programs and adhering to proven infection control practices. Considerable research is still needed to understand sources of infection and transmission, pathogenesis, the effect of the hypervirulent strain, especially in children, and effective means to treat and prevent recurrences. *C. difficile* is certainly aptly named because "*difficile*" is Latin for "difficult."

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