

## CLOSTRIDIUM DIFFICILE INFECTION

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### Microbiology

*Clostridium difficile* (*C. difficile* or CDiff) is a spore-forming, obligate and fastidious anaerobe, gram-positive bacillus.

Toxins: It is the cause of pseudomembranous colitis and CDiff antibiotic-associated diarrhea (CDAD). Disease is related to the action of toxin(s) produced by these vegetative organisms.

Two toxins, A and B, have been characterized. Some strains produce toxins with high toxicity, some produce a less toxic toxin and some do not produce toxins.

A hyper-virulent epidemic strain (BI/NAP1/027) has been described. This hypervirulent strain produces a 16-fold higher concentration of toxin A, 23-fold higher concentrations of toxin B and a binary toxin whose role is not yet defined, but is associated with more severe diarrhea.

Vegetative forms of CDiff die rapidly (less than 24 hours) outside the colon; however CDiff is capable of producing spores which are very resistant, persist for months and are very resistant to cleaning and disinfection products. Spores that are resistant to stomach acidity allow CDiff to pass through the stomach.

### Epidemiology

Illness is usually associated with antibiotic treatment, either during antimicrobial therapy, or a few weeks after discontinuation of therapy.

CDiff can be isolated from soil and frequently is present in the environment. Spores of CDiff are acquired from the environment, or by fecal-oral transmission from colonized persons.

Intestinal colonization: The rate of fecal colonization is:

- Often greater than or equal to 20% among adult patients hospitalized for more than one week. The risk of CDiff acquisition increases in proportion to length of hospital stay.
- 1% to 3% among community residents. Asymptomatic fecal carriage of CDiff in healthy neonates is very common, often exceeding 50% during the first six months of life.

Source of spores: Both asymptomatic patients and patients with CDAD had CDiff recovered from skin and environmental samples at a frequency of more than 50%; spores on the skin of asymptomatic patients were easily transferred to the investigators' hands. Incontinence did not increase contamination rates. Of note, CDiff was cultured from the skin samples of 19% of non-carriers (i.e., patients with negative stool culture results). These findings differ from those previously reported and suggest that contamination of

the patient and the environment occurs frequently, and occurred in a significant proportion of patients with CDAD and in patients categorized as asymptomatic (Clin Infect Dis. (2007) 45 (8): 999-1000. doi: 10.1086/521855). The highest contamination is observed around patients with CDAD, and to a much lesser extent around carriers.

Some studies have shown that environmental samples tested were not identical to the isolates found in the stool of the patient currently residing in the room. This suggests that the environmental CDiff isolates may have been from prior occupants of the room. These asymptomatic CDiff carriers could have been the prior inhabitants of the contaminated room. Current guidelines do not routinely recommend enhanced environmental sodium hypochlorite bleach cleaning; however, several investigators have reported CDiff rate reduction when this measure was implemented only with patients known to have CDiff infection.

Transmission in health care facilities occurs by direct spread from the hands of personnel (by transient carriage), fomites, or the contaminated environment. Contaminated commodes, telephones, and rectal thermometers have been implicated as potential sources in outbreaks. Activities that carry an increased risk of transmission are: oral care, oral suctioning, administration of feeding (enteral tube feeding, prolonged nasogastric tube insertion), or medication, intubation, use of electronic rectal thermometers, antacid treatment, repeated enemas, and gastrointestinal tract surgery.

The environment in hospitals and child care facilities are major reservoirs. Spores of CDiff are found on environmental surfaces (where the organism can persist for months), and on the hands of hospital personnel who fail to practice good hand hygiene. Hospital epidemics of CDAD have been attributed to a single CDiff strain and to multiple strains present simultaneously.

Another major risk factor for developing disease includes antimicrobial therapy.

Most individuals affected are older than 60 years of age; increasing age has been identified as a risk factor for CDiff acquisition and diarrhea.

Antibiotics as risk factors: The initial antibiotic that led to the recognition of CDAD was clindamycin. Penicillins, ampicillin, clindamycin, cephalosporins (third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime), and trimethoprim–sulfamethoxazole are the antimicrobial drugs most frequently associated with CDiff colitis, but colitis has been associated with almost every antimicrobial agent. Penicillin/β-lactamase-inhibitor combinations such as ticarcillin/clavulanate and piperacillin/tazobactam pose significantly less risk; however, all antibiotics, including vancomycin and metronidazole (the agents most commonly used to treat CDAD), have been found to carry a risk of subsequent CDAD. In general broad-spectrum antibiotics are more likely than narrow spectrum antibiotics to cause CDAD.

Rates observed in hospital with a problem ranged from one per 1,000 hospital admissions to 25 per 1,000 hospital admissions. In high incidence hospitals, patients become colonized at a rate of 8% per week. Patient who have become colonized with CDiff are at lower risk of CDAD. In some hospitals the proportion of colonized patient reaches 20%.

Changing epidemiology: The proportion of hospitalizations with CDAD listed as any diagnosis has increased steeply in the past 10 years. It also appears that the severity of cases is also increasing as evidenced by more treatment failures, colectomies and mortality.

#### Prevalence in HCF:

CDiff infection rates continue to escalate in many health care facilities (HCF). CDiff infection outbreaks have been documented, and rates as high as 39.9 cases per 1,000 hospital admissions have been reported. Although there are no benchmarks for CDiff infection rates, some experts believe that a rate of:

- less than or equal to five cases per 1,000 hospital admissions (or discharges) is likely to be acceptable;

- a rate greater than five cases per 1,000 hospital admissions (or discharges) is a concern,
- greater than 10 cases per 1,000 hospital admissions (or discharges) a major concern, and
- greater than 20 cases per 1,000 hospital admissions (or discharges) is alarming.

CDiff outbreaks are usually linked to a single strain, rarely by a wide array of strains.

A new strain of CDiff identified by pulsed field electrophoresis (PFGE) called North America PFGE type 1 (BI/NAP1/027 toxinotype III strain) generates 16-fold higher concentrations of toxins A and 23-fold higher concentrations of toxin B and an additional “binary” toxin which may cause more severe diarrhea. This strain is also highly resistant to fluoroquinolones.

The incubation period is unknown. One study suggested an incubation of seven days, others suggested a longer incubation. Community-onset diseases that occur within 30 days of discharge from a hospital may be considered nosocomial.

### **Pathogenesis**

In 1978, the role of CDiff as a cause for antibiotic-induced pseudomembranous colitis was recognized. Spores of toxigenic CDiff are ingested, survive gastric acidity, germinate in the small bowel, and colonize the lower intestinal tract, where they may elaborate two large toxins: toxin A, an enterotoxin, and toxin B, a cytotoxin. These toxins initiate processes resulting in the disruption of epithelial-cell barrier function, diarrhea, and pseudomembrane formation. The role of the binary toxin of the new strain has not yet been established.

The normal gastro-intestinal flora is an important mechanism against intestinal pathogens. Some of the normal flora

- May compete with CDiff for attachment to receptors in the colonic epithelial cells
- May deprive CDiff from nutrients in the lumen
- May produce inhibitory or lethal substances against CDiff.

Patients admitted to a HCF may come in contact with CDiff, but CDiff may not be able to establish itself as a colonizer as long as the normal flora persists. Antibiotics may disrupt these protective mechanisms and facilitate colonization of the gut.

After colonization and development of toxins, the toxins attach to cell receptors and induce cell death. After cell death, a shallow colonic ulcer becomes filled with white blood cells and other inflammatory cells, mucus and finally a pseudomembrane.

### **Clinical Description**

1- Colonization is defined as the presence of CDiff (positive culture or positive test for a toxin) in a person with no clinical symptoms (no diarrhea).

2- Non specific diarrhea: Most antibiotic-associated diarrhea does not have a specific cause, is usually mild and self-limited.

3- CDiff Associated Disease (CDAD) is an infectious diarrhea in which the organism has been acquired by patients who have taken antibiotics recently (within the past two months). Patients have diarrhea, nausea, vomiting, lower abdominal pain and tenderness, fever, anorexia, malaise. Stools are watery, voluminous, lacking gross blood or mucus.

Patients colonized with CDiff were initially thought to be at high risk for CDAD. However, four prospective studies have shown that colonized patients actually have a decreased risk of subsequent CDAD. At least three events are proposed as essential for the development of CDAD:

- 1.Exposure to antimicrobial agents is the first event and establishes susceptibility to CDiff infection.
- 2.Exposure to toxigenic CDiff. Given that the majority of patients do not develop CDAD after the first two events, a third event is clearly essential for its occurrence.
- 3.Candidate third events include exposure to a CDiff strain of particular virulence, exposure to antimicrobial agents especially likely to cause CDAD, and an inadequate host immune response.
- 4-Pseudomembranous colitis (PMC) generally is characterized by diarrhea, abdominal cramps, fever, systemic toxic effects, abdominal tenderness, and passage of stools containing blood and mucus. Infection also may result only in mild diarrhea or asymptomatic carriage, especially in newborn infants and in children younger than one year of age.

### Laboratory Tests



- **Only test patient who are suspected of having CDiff infection (CDAD), patients with diarrhea**
- **Do not screen asymptomatic patients**
- **Do not repeat a negative test**
- **Do not perform a test of cure**
- **Do not place asymptomatic patients in contact precautions**

Rationale for not testing of asymptomatic patients or cured patients: testing for CDiff should only be done on symptomatic patients (with diarrhea) for the following reasons:

- Testing of asymptomatic patients is not indicated for identification of carriers since treatment of carriers is futile.
- Specificity and sensitivity of the tests were designed for CDAD. Testing asymptomatic patients results in a poor positive predictive value. Most positive test results would be false positives.
- A positive test in an asymptomatic patient may result in additional antibiotic treatment which can increase the risk of the patient developing CDAD.
- Testing is not indicated for a test of cure (toxin may persist in the stools even after a successful treatment). Persistently positive test results at the end of treatment are not predictive of CDAD relapse.
- Only 10% of initially negative tests will return positive after a second round of testing. In this group of repeat testing, there are numerous false positive tests; thus the recommendation not to repeat a negative test.

Although CDiff toxin rarely is recovered from stool specimens from asymptomatic adults, it may be recovered from stool specimens from neonates and infants who have no gastrointestinal tract illness. This finding confounds the interpretation of positive toxin assays in patients younger than 12 to 24 months.

Given the high prevalence of asymptomatic persons and the expected effectiveness of standard precautions in patient without diarrhea, the impact of isolation on patient safety, the cost associated with a private room and additional barriers, contact precautions is **NOT** recommended for asymptomatic patients.

### Stool collection

Only watery or loose stools should be collected. They should be submitted in clean water-tight containers. Transport media is not necessary; it could even cause false positive results. Store at refrigerator temperature; avoid freezing.

## **Tests**

Most diagnostic tests detect the toxin:

Enzyme immuno-assay for toxins: Testing for toxin is performed by enzyme immunoassay (EIA) or cell cytotoxin assay, which has been the “gold standard” for toxin B. The EIAs are sensitive, cheap and easy to perform. Commercially available EIAs that detect both toxins A and B may be used, or an EIA for toxin A may be used in conjunction with cell culture cytotoxicity assay for toxin B. Latex agglutination tests should not be used.

Cell cytotoxicity assay: Stool extract is added to tissue cell culture with /without neutralizing antitoxin. Toxin is presumed to be present if a cytotoxic effect is produced in cultures with un-neutralized extract and prevented in cultures with neutralized extract. This test is the most specific for CDAD, but is not the most sensitive. It takes 48 to 72 hours for the result.

Stool culture: CDiff is easily recovered from stools using cycloserine-cefoxitin-fructose agar selective medium. Plates need to be in an anaerobic environment for four hours before inoculation to enhance yields on culture. This method is very sensitive but produce false positives due to non-toxigenic isolates and takes more than 72 hours to get a result.

Glutamate dehydrogenase (GDH) test: This test can be used as a screening test because it is inexpensive, fast and sensitive but it is not specific (it may be positive with bacteria other than CDiff). It detects GDH which is not specific to toxin producing CDiff. A negative test may be useful to rule out CDAD if the test is negative; however, a positive result is often a false positive test and should be confirmed by another test.

Molecular typing: Only for in-depth epidemiologic studies.

Sigmoidoscopy or colonoscopy visualization of pseudo-membranes is indicative of pseudo-membranous colitis (PMC) which is caused by CDiff in 90% of cases.

## **Surveillance**

CDiff is not a reportable condition. Facilities experiencing difficulties with CDiff may request help from an epidemiologist from the Infectious Disease Epidemiology Section to investigate and control outbreaks of CDiff.

In order to carry out CDiff infection surveillance, a case definition is necessary. Note that a case definition is for surveillance purpose only and not the same as a clinical diagnostic. A case definition is not appropriate for clinical decision making

**A case of CDAD** is defined as an individual patient with diarrhea in which:

- 1-The patient has a diarrheal stool sample positive for CDiff toxin A or B or a toxin-producing CDiff
- or
- 2-Pseudomembranous colitis found in endoscopy or surgery
- or
- 3-Pseudomembranous colitis at histologic examination

**A case of healthcare facility associated CDAD** is defined as above with onset of symptoms more than 48 hours after admission or less than four weeks after discharge

**A case of community associated CDAD** is defined as above with onset of symptoms in the community or less than 48 hours after admission, or more than 12 weeks after last discharge

A symptomatic patient with an additional positive toxin assay within two weeks or less after the last specimen tested positive is a **continuation of the same CDAD** and not a new case

A symptomatic patient with an additional positive toxin assay within two to eight weeks after the last specimen tested positive is a **recurrent CDAD**

A symptomatic patient with an additional positive test more than eight weeks after the last specimen tested positive is a **new case of CDAD**

## Treatment

- 1-All CDAD patients need fluid and electrolyte replacement,
- 2-Avoid anti-peristaltic agents and opiates
- 3-Discontinue antimicrobial therapy as soon as possible in patients in whom clinically significant diarrhea or colitis develops.

These simple measures will suffice for 20% of patients, particularly those with mild disease (mild diarrhea, no fever, no leukocytosis).

However, patients who do not respond to these mild measures, patients with severe symptoms, and patients who absolutely antibiotic therapy, do require **specific therapy against CDiff**.

Agents such as **metronidazole, vancomycin, amino-glycosides** are preferred. **Nitazoxanide, bacitracin, teicoplanin and fusidic acid** are also useful for treatment.

CDiff are susceptible to metronidazole and vancomycin, and both are effective. Treatment is administered for seven to 10 days. Drugs that decrease intestinal motility should not be given. Average time to resolution of diarrhea with treatment is three days, up to six to seven days.

1-First line: **oral metronidazole 500mg three times a day or 250mg four times a day for 10 days**; Metronidazole is cheaper than vancomycin and not prone to promote VRE. If oral therapy is not tolerated, IV therapy is indicated until oral ingestion becomes possible. Contra-indications are allergy, pregnancy or verified resistance

2-Second line: **Oral vancomycin 125mg every 6 hours**. IV vancomycin does not deliver sufficient concentration in the gut lumen to be of any use.

3-other drugs are:

- Nitazoxanide, an anti-protozoal used against cryptosporidium and giardia, at a dosage of 500 mg two times per day for seven days, or at a dosage of 500 mg two times per day for 10 days.
- Bacitracin 25,000 units four times daily for seven to 10 days
- Teicoplanin orally 100-400mg twice a day for 10 days
- Fusidic acid orally 500mg three times a day for 10 days

Recurrences are found in 10% to 20% of cases. Early recurrences within 30 days are usually due to the same strains. Later recurrences are usually caused by new strains.

Asymptomatic persistence of CDiff and its toxins in stools following treatment is common. It is NOT recommended to repeat stool testing or re-treatment. **Only symptomatic patients should be treated.**

**Hospital precaution and isolation:** Standard/Contact precautions

### **Control Measures:**

#### 1-Interrupt transmission from person-to-person

- Hand-washing is preferred as alcohol-based hand sanitizers are not be as effective against the spore- forming CDiff.
- Contact precautions including
  - Gloving whenever touching:
    - the patient
    - surfaces possibly contaminated including areas in contact with the patient
    - high touch surfaces as bedrails, light switches, and faucets
  - Gowning whenever getting in the room. There is no evidence that the use of gowns by itself is an efficacious control measure. Gowns are used in conjunction with contact precautions.
- Patient placement: Private room with a bathroom solely used by the patient is the ideal placement. If a private room is not available, cohorting with another CDAD may be done. If sharing a room, there should be at least a three foot separation between beds to avoid inadvertent sharing of items between patients. A curtain or a red tape on the floor may help clearly identifying areas of restricted access.
  - Proper handling of contaminated waste (including diapers) and fomites
- Patient transport: Transportation or movement outside the room should be limited. Patients need to be taught proper hand hygiene prior to getting out of their room. Contact precautions status need to be communicated to all HCP susceptible to come in contact with the patient.
  - Discontinuation of contact precautions after diarrhea stops.

Management of a colonized patient: Patient colonized with a toxigenic C.diff on admission may be at higher risk of developing CDI during hospitalization. Studies have yielded opposite observations, some showed that colonization led to lesser future incidence of Cdiff, others showed a slightly increased risk of CDI. The challenge in the management of these patients is not to avoid exposure to Cdiff, but **to reduce the risk of Cdiff toxin expression by restricting use of 1-antibiotics, 2-acid-sppressive agents and 3-narcotics.**

The following are NOT recommended:

- Routine stool culture for CDiff in asymptomatic patients or health care providers, even during outbreaks
- Culturing hands of health care providers for CDiff
- Treating a patient empirically for CDiff before completion of toxin results unless the patient is very sick with a compatible syndrome, or there is hospital-wide high prevalence of CDiff.

#### 2-Environmental control

The environment plays a major role in the transmission of CDiff. Any object or surface coming in contact with feces becomes a source of spores. Spores of CDiff may persist for months on hard surfaces. Spores may be found in CDAD patient rooms and to a lesser extent in colonized patient rooms. The heaviest contamination is found:

- On any surface in the bathroom (commode, sink, floor, tub, shower...),
- In the immediate surroundings of the patient: beds, bedrails, over the bed tables, chairs and any patient furniture, bed sheets
- High touch surfaces such as TV and light control buttons, call buttons, door handle, monitor cables

- Patient care equipment, instruments, devices are also contaminated through fecal shedding or the hands of the patient or of HCP. Most CDiff are found on rectal thermometers, blood pressure cuffs, tube feeding, glucose meters, infusion pumps, feeding pumps, flow-control devices on IV or tube feeding lines.

CDiff spores are fairly resistant to quaternary ammoniums and phenolic compounds which are not sporicidal. Their use may stress the vegetative forms and entice them to form spores at a faster rate, an effect termed ‘hypersporulation’. Only chlorine based (bleach) or vaporized hydrogen peroxide disinfectants are active on spores; however, these products must be used at recommended concentration with sufficient contact time.

A 10% solution of sodium hypochlorite (household bleach has about 6% ClONa) is adequate. It must be made fresh daily (one part bleach and nine parts tap water). The addition of one part vinegar (5% acetic acid) may improve the germicidal action.

A problem is that chlorine-based disinfectants may be corrosive and pit some equipment.

Thorough cleaning is necessary to maximize the disinfectant action of the germicide. Therefore it is useful to use a commercially available solution which contains a detergent, or use a detergent for thorough cleaning before applying the bleach solution. **A contact time of one minute should be sufficient.** Wetting the surface with the bleach solution and allowing it to dry should provide sufficient contact time.

- Thorough cleaning of bathrooms of CDAD patients. Wear glove and gown when cleaning bathrooms.
- Thorough cleaning of high touch areas in the patient room
- Assign equipment specifically to the patient to avoid cross-contamination
- Environmental cleaning with solutions containing hypochlorite decreases surface contamination with CDiff. Use of detergents is important for cleaning but must be followed by disinfectants containing chlorine which is the only sporicidal germicide, provided the dilution and contact time are correct.

### 3-Education of healthcare providers, patient and visitors

HCP need to understand the difference between CDAD and CDiff colonization, the great propensity of CDiff to contaminate and persist in the environment as spores, the effective methods for environmental disinfection, the importance of handwashing, the proper implementation of contact precautions, and the prudent use of antibiotics.

Participation of patients and visitors is crucial to minimize the contamination of the environment.

### 4-Prevent onset of CDAD

- Limit the use of antimicrobial agents: Restrict the use of clindamycin and of broad-spectrum antibiotics (particularly cephalosporins); encourage the proper use of antibiotics.
- Carriers of the organism appear to be resistant to acquisition of outbreak-associated strains. Individuals with asymptomatic colonization are no more likely to develop CDiff diarrhea than are those with negative stool cultures. Metronidazole is not effective in eradicating asymptomatic carriage with CDiff, and treatment with oral vancomycin results in only transient elimination of fecal carriage of the organism. Antibiotic treatment of asymptomatic patients excreting CDiff is not recommended.
- In child care settings, children with CDiff colitis should be in a separate protected area or excluded from child care for the duration of diarrhea.

## **Answers for Questions of Parents or Guardians of Infants Between the Ages of One Month and Six Months, Regarding Colonization and/or Infection with *Clostridium difficile***

There is a culture of *Clostridium difficile* in the stool of a one-month to six-month old baby. How significant is this?

*Approximately 1/4 to 1/3 of all infants between one and six-months of age are colonized by Clostridium difficile (C diff). It is important to remember that, although colonization, (the growth of the organism in the GI tract), is common, disease caused by C diff (mild to severe diarrhea) is not.*

Does this mean there is nothing to worry about?

*Pediatric C diff-related hospitalizations are increasing, but most are reported in children older than one-year of age and most are related to previous antibiotic use. That does not mean that discovery of C diff in an infant is meaningless. Perinatal infants, infants one month of age or younger, are usually not at risk for development of Clostridium difficile infection (CDI) related symptoms. The most susceptible children are between three and 18 years of age, but children one month to two-years of age lie somewhere between the previous two age groups when considering risk of disease.*

If my child has no symptoms of disease, no diarrhea, should I have the child screened for C diff?

*No. Routine testing of children younger than one year of age is not recommended. Why? Because asymptomatic colonization is fairly common in children younger than one-year of age.*

If my infant has diarrhea, and if cultures have shown growth of C diff, does this mean that C diff is the definite cause of the diarrhea?

*No. Several studies have shown that viruses, most notably noroviruses and rotaviruses (also caliciviruses and others) can exist in the child's intestines concurrently. Often cultures of C diff are incidental findings and play no role in pathogenesis; however, this is difficult to determine. Alternative etiologies should always be considered in patients younger than one-year of age. In adults and children older than one-year of age, presence of C diff toxins are used to confirm C diff as a causative agent; however, in children younger than one-year of age, detection of C diff toxins does not confirm causality. Many researchers suggest that children in the younger than one-year age group lack receptors for these toxins. Nevertheless, pediatricians usually follow an algorithm to determine whether C diff should be treated with appropriate drugs.*

Is the incidence of C diff infection increasing in the one-month to six-month of age group?

*The answer to this question is complicated. Some researchers suggest that increases in pathogenic strains in both hospital and community acquired varieties have led to a corresponding increase in hospitalizations in very early age groups. Nevertheless, co-infectious with various viruses, associations with certain risks (e.g. antibiotic use, use of medications that increase stomach pH [proton pump inhibitors]; repeated enemas; use of diapers; invasive procedures in hospital settings; underlying intestinal diseases; GI tract surgery; kidney problems; malignancies; and impaired immunity), and longer durations of exposure in healthcare facilities are thought to play a role in colonization. Formula-fed infants also tend to have higher rates of colonization than breast-fed infants. Many researchers have stated that no increase in disease from C diff in the very young has occurred.*

What is the real risk of severe disease from C diff in an infant between one-month and six-months of age?

*Although development of severe disease is not impossible, most incidents of severe disease related to C diff have been in children older than one-year of age. One study concluded that most children in the one to six-month age group experienced a fairly mild illness (lower morbidity and mortality than in older age groups).*

How will the presence of C diff in the intestinal tract affect my child in the future?

*Any effects on health in later life, if there are any, have yet to be determined. It should be noted that higher prevalence of C diff colonization in the very young, usually disappears by the time children reach three-years of age.*

Did I cause my child to be colonized or infected with C diff?

*Environmental contamination, rather than direct transmission from the mother, is thought to be the primary source.*