Note: *Clostridioides difficile* was formerly named *Clostridium difficile*.

1. Case Definitions

   The following definitions are congruent with the 2018 Canadian Nosocomial Infection Surveillance Project (CNISP) definitions for CDI. These definitions will be used for reporting of healthcare-associated infections as part of the patient safety indicators identified for public reporting.

a) Surveillance case definition for primary episode of CDI:

   A “primary” episode of CDI is defined as either the first episode of CDI ever experienced by the patient or a new episode of CDI which occurs greater than eight weeks after the diagnosis of a previous episode in the same patient.

   A patient is identified as having CDI if:
   - the patient has diarrhea* or fever, abdominal pain and/or ileus **AND** a laboratory confirmation of a positive toxin assay or positive polymerase chain reaction (PCR) for *C. difficile* (without reasonable evidence of another cause of diarrhea)
   **OR**
   - the patient has a diagnosis of pseudomembranes on sigmoidoscopy or colonoscopy (or after colectomy) or histological/pathological diagnosis of CDI
   **OR**
   - the patient is diagnosed with toxic megacolon (in adult patients only)

*Diarrhea is defined as one of the following:
   - Six or more watery/unformed stools in a 36-hour period
   - Three or more watery/unformed stools in a 24-hour period and this is new or unusual for the patient (in adult patients only)

Exclusion:
- Any patients less than one year of age.
- Any pediatric patients (aged one year to less than 18 years) with alternate cause of diarrhea found (i.e. rotavirus, norovirus, enema or medication etc.) are excluded even if *C. difficile* diagnostic test result is positive.

CDI Case Classification and Definitions

Once a patient has been identified with CDI, the infection will be classified further based on the following criteria adapted from SHEA/IDSA practice recommendations ‘Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals’: 2014 Update at http://www.jstor.org/stable/10.1086/676023?origin=JSTOR-pdf and the best clinical judgment of the healthcare and/or infection prevention and control practitioner (ICP).

Outpatient Location: Includes, but is not limited to all outpatient clinics (oncology {including chemotherapy or radiation}, dialysis, day surgery, day hospital, transfusion clinic, interventional radiology).

Healthcare Exposure: The patient had two or more visits at any of the following locations (oncology {including chemotherapy or radiation}, dialysis, day surgery, day hospital, transfusion clinic, nursing station, interventional radiology or emergency department) OR had a single visit to the emergency department for greater than or equal to 24 hours.

Other Healthcare Facility: Includes other acute care, psychiatric, rehabilitation or long term care facility.
**Healthcare-associated (acquired in your facility) CDI case definition:**

- Related to the current hospitalization
  - The patient’s CDI symptoms occur in your healthcare facility 72 or more hours after admission.
- Related to a previous hospitalization
  - **Inpatient**: The patient’s CDI symptoms occur less than 72 hours after admission AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks.
  - **Outpatient**: The patient presents with CDI symptoms at your ER or outpatient location AND the patient had been previously hospitalized at your healthcare facility and discharged within the previous four weeks.
- Related to a previous healthcare exposure at your facility
  - **Inpatient**: The patient’s CDI symptoms occur less than 72 hours after the current admission AND the patient had a previous healthcare exposure at your facility within the previous four weeks.
  - **Outpatient**: The patient presents with CDI symptoms at your ER or outpatient location AND the patient had a previous healthcare exposure at your facility within the previous four weeks.

**Healthcare-associated (acquired in any other healthcare facility) CDI case definition:**

- Related to a previous hospitalization at any other healthcare facility
  - **Inpatient**: The patient’s CDI symptoms occur less than 72 hours after the current admission AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transfered within the previous four weeks.
  - **Outpatient**: The patient presents with CDI symptoms at your ER or outpatient location AND the patient is known to have been previously hospitalized at any other healthcare facility and discharged/transfered within the previous four weeks.

**Healthcare-associated CDI but unable to determine which facility (“Multiple Healthcare Exposures case”):** The patient with CDI **DOES** meet both definitions of healthcare-associated (acquired in your facility) and healthcare-associated (acquired in any other healthcare facility), but unable to determine to which facility the case is primarily attributable to. 

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**Community-associated CDI case definition:**
- **Inpatient:** The patient’s CDI symptoms occur less than 72 hours after admission, with no history of hospitalization or any other healthcare exposure within the previous 12 weeks.
- **Outpatient:** The patient presents with CDI at your ER or outpatient location with no history of hospitalization or any other healthcare exposure within the previous 12 weeks.

**Indeterminate CDI case definition:** The patient with CDI does NOT meet any of the definitions listed above for healthcare-associated or community-associated CDI. The symptom onset was more than four weeks but less than 12 weeks after the patient was discharged from any healthcare facility or after the patient had any other healthcare exposure.

**b) Surveillance case definition for recurrent CDI:**

**Recurrent CDI case definition:**
- A recurrent case of CDI is defined as an episode of CDI that occurs in a patient less than or equal to eight weeks following the diagnostic test date of the primary episode of CDI, provided the patient was treated successfully for the primary episode and symptoms of CDI resolved completely.

**Note:**
- Some hospitals may define a CDI case (successfully treated and symptoms resolved) that occurs less than or equal to eight weeks after a previous case as a “relapse”; however, for CNISP CDI surveillance, this is defined as a “recurrent” CDI case.

- A new episode of CDI that occurs after eight weeks following the diagnostic test date of the primary episode of CDI is considered a new infection

2. **Reporting and Other Requirements**

2.1 **Laboratory:**
- All positive diagnostic test results from the laboratory (e.g. toxin assay) are reportable to the Public Health Surveillance Unit by secure fax (204-948-3044).

2.2 **Healthcare Facility Infection Prevention and Control:**
- Outbreak Reporting: Refer to Section 8.3 for outbreak definition. CNPHI (Canadian Network for Public Health Intelligence) users should login to CNPHI and enter data into the Enteric Outbreak Summary. Non-users of CNPHI should report all outbreaks using the Enteric Outbreak Summary Report form and return it to the Public Health Surveillance Unit by secure fax (204-948-3044). Non-CNPHI users may request the form by email: outbreak@gov.mb.ca.

2.3 **Regional Public Health or First Nations Inuit Health Branch:**
- Cases of CDI will be referred to the region of case residence for any follow-up required as determined by the specific region. **NOTE: Completion and submission of a Manitoba Health Seniors and Active Living (MHSAL) case investigation form for the cases is not required by the Public Health Surveillance Unit.**
3. Clinical Presentation/Natural History

The clinical manifestations of infection with toxin-producing *C. difficile* range from asymptomatic colonization to severe, potentially life-threatening pseudomembranous colitis (1). The most common clinical presentation of CDI is diarrhea that develops in association with recent antimicrobial use (1, 2). The diarrhea is typically watery with a characteristic foul odor (1). Passage of mucous or occult blood in the stool may occur, but grossly visible blood in the stool is rare (1, 2). Accompanying clinical features may include fever, abdominal cramps, leukocytosis, and hypoalbuminemia (1, 2). Infrequently, patients with CDI develop toxic megacolon as a complication of infection, and present with abdominal pain and distension with minimal or no diarrhea (2). Other complications of CDI include dehydration, electrolyte disturbances, hypotension, acute kidney injury, and death (2). Current North American guidelines stratify treatment of CDI based on disease severity (2). Patients with CDI and a white blood cell count of >15,000 cells/µL and/or a serum creatinine level >1.5 times their premorbid baseline (> 133 µmol/L) are considered to have severe disease. Severe, complicated CDI is defined as CDI occurring in association with hypotension or shock, ileus, or toxic megacolon (2).

4. Etiology

*Clostridioides difficile* (*C. difficile*) is an opportunistic, gram positive, spore-forming anaerobic bacillus that is part of the normal intestinal flora (3). Pathogenicity is usually associated with the production of two toxins, A (enterotoxin) and B (cytotoxin). It was initially believed that toxin A was the most important toxin in *C. difficile* infection, but studies have shown that toxin B may be the more potent of the two toxins (4). The genes for A and B toxins, TcdA and TcdB respectively, are found in the pathogenicity locus (PaLoc) on the chromosome of some strains of *C. difficile*. There is another toxin called binary toxin produced by some strains, but its role in CDI is currently unknown. Nontoxigenic strains of *C. difficile* are not associated with CDI. When the normal intestinal flora is disrupted in patients by use of antimicrobials or other means, colonization resistance is lost and organisms such as *C. difficile* may overgrow and cause disease. The actively replicating (vegetative) organism produces toxin and causes CDI. The spore form does not produce toxin or cause disease unless it converts to the vegetative form.

5. Epidemiology

5.1 Reservoir and Source:

The reservoir for disease causing organisms is mainly humans; however, *C. difficile* can be found in water, soil, meats and vegetables. It is common in healthcare environments, where the spores are difficult to eradicate. In patients with disrupted microbial gut flora, ingested spores, which are resistant to stomach acid, can germinate and proliferate in the colon, producing one of the two major toxins: TcdA and TcdB (5). Hospitals, nursing homes and childcare facilities are major reservoirs for *C. difficile* (6). The source of *C. difficile* may be either endogenous (colonized patients’ own flora) or exogenous, such as contaminated hospital environment and equipment (commodes, bedrails, and bedpans). Approximately 3-8% of healthy adults have intestinal carriage of toxigenic *C. difficile*. In one large study, the NAP1 strain of *C. difficile* was predominant among patients with infection, while asymptomatic patients were more likely to be colonized with other strains (4). The prevalence of asymptomatic colonization with *C. difficile* is 7%-26% among inpatients in acute care facilities.
and 5%-7% among elderly residents in long term care facilities (1). Colonization with C. difficile and high levels of serum antibody against C. difficile toxin A appear to provide protection against CDI. Colonization with a non-NAP1 strain of C. difficile may result in the development of antibodies against toxin B that then confer protection against acquisition of the NAP1 strain (4). Intestinal colonization can be as high as 50% in healthy infants but is usually less than 5% in children older than five years of age (6).

5.2 Transmission:

The primary mode of transmission for C. difficile within healthcare facilities is by person-to-person spread by the fecal-oral route. The hands of healthcare workers transiently contaminated with C. difficile spores, as well as environmental contamination promote transmission in healthcare settings. Contamination of the environment around a CDI patient is thought to be an important source of cross-transmission to other patients. C. difficile spores resist dessication for months and can persist on hard surfaces for as long as five months (7). C. difficile spores resist routine disinfection processes (8). Onset of these infections may also be identified in Long Term Care Facilities and outpatient settings (9).

5.3 Occurrence:

**Worldwide:** In the early 2000s, widespread outbreaks of severe CDI with high mortality and increased use of colectomy to treat patients were reported from hospitals throughout the United States (US) and then in Canada. These outbreaks were caused by a group of C. difficile strains designated NAP1/B1/027 that also rapidly spread to the United Kingdom and other European Union countries. There were two distinct lineages of NAP1/B1/027, designated FQR1 and FQR2. FQR1 originated in the US and was widely disseminated in the US with spread to Asia and Switzerland. FQR2 was found in Montreal and multiple US sites and spread to the United Kingdom and Europe. Recent reports suggest that the current hospital incidence in the US is in the range of five to 10 CDI cases/10,000 days of care (5). In the United States, C. difficile was responsible for almost half a million infections and was associated with approximately 29,000 deaths in 2011 (10). Data analysis from 2008 indicates that CDI may have resulted in $4.8 billion in excess costs in US acute-care facilities (11). There is evidence to suggest increasing incidence of CDI in the community, even in healthy people previously at low risk. The sources of and risk factors for community-associated CDI (i.e. occurring in patients with no inpatient stay in the previous 12 weeks) are not well defined. An analysis of community-associated CDI cases identified during 2009-2011 CDC Emerging Infections Program Surveillance found the majority of cases (82%) had some kind of healthcare exposure in the 12 weeks prior to CDI diagnosis (1).

**Canada:** Healthcare-associated CDI incidence rose to as high as 22.5 CDI cases/1,000 discharges in the Montreal NAP1/B1/027 outbreak in 2003, with 30-day attributable mortality of 6.9% (5). The Public Health Agency of Canada through the Canadian Nosocomial Infection Surveillance Project (CNISP) collects national data on C. difficile. The most recent report is from January 1, 2012 to December 31, 2016 (updated December 2017). The national rate for C. difficile in 2009 was 4.65/1,000 patient admissions or 5.81/10,000 patient days compared to 3.13/1,000 patient admissions or 4.05/10,000 patient days in 2016. The attributable mortality rate 30 days after date of first positive CDI test in 2009 was 2.3% compared to 3% in 2016 (12).

**Manitoba:** CDI became reportable in 2005. A population-based CDI administrative dataset from MHSAL Epidemiology and Surveillance Unit was used to identify laboratory confirmed CDI cases
among individuals older than 17 years between July 2005 and March 2015. There were 5843 individuals who developed 8471 episodes of CDI during this period. The age-standardized (to 2006 Canadian population) rate of CDI decreased from 112/100,000 to 78/100,000 by the end of the period. Hospital-acquired CDIs decreased with no significant change in community-associated CDI. There was no decrease in CDI rates among those less than 60 years of age but there was a significant reduction in the older age groups (60-79 years and greater than 80 years). An increasing proportion of CDIs were community-associated. CDI in older individuals, men and recurrent episodes were more likely to be healthcare-associated. There was no significant decrease in rates of recurrent CDIs. The median age of CDI decreased over time for healthcare-associated and community-associated infections. The likelihood of developing any recurrence was 15%, a single recurrence was 9.3% and more than one recurrence was 5.7%. Individuals greater than 80 years of age had a five-fold increased risk of multiple recurrences. Subjects with recurrences were more likely to be older, female, have multiple co-morbidities and were more likely to present with a healthcare-associated CDI than a community-associated CDI. Lower income, co-existing diabetes, or pre-CDI exposure to antibiotics did not significantly increase the risk of recurrence. The above observations reported are based on administrative data rather than infection prevention and control reporting.

5.4 Incubation Period:
The incubation period is unknown. Colitis usually develops five to 10 days after initiation of antimicrobial therapy but can occur on the first day and up to 10 weeks after therapy cessation (6).

5.5 Risk Factors:
The risk is dominated by antimicrobial exposure, including duration, number and class of antimicrobial agents. Risk is highest during the first month after cessation of antimicrobial therapy and decreases between one and three months after therapy. Stomach acid-inhibiting agents such as proton-pump inhibitors, H₂ blockers, and histamine type 1 antagonists also increase the risk for CDI. It is likely that the combination of an antimicrobial agent and a proton-pump inhibitor increases the risk for CDI. Patient factors which are associated with increased CDI risk include advanced age, immunosuppression, use of chemotherapy, prior abdominal surgery, prior hospitalization and severity of underlying illness. Previous hospitalization suggests previous exposure to *C. difficile* and possibly the subsequent development of immunity.

Chemotherapy, proton-pump inhibitors and H₂ blockers may disrupt the bowel flora and allow for *C. difficile* colonization. Antibodies against toxin A are not significantly associated with healthcare-associated *C. difficile* colonization. Recent data confirm the role of humoral immunity, primarily directed against toxin B, at least for protecting against recurrent disease. The time to healthcare-associated *C. difficile* infection can be twice the time to healthcare-associated *C. difficile* colonization. This might be due to both toxigenic and nontoxigenic strains colonizing patients. Many of the toxigenic strains do not cause *C. difficile* infection because the patient has an appropriate anamnestic antibody response. For every additional year of age after 18, the risk of healthcare-associated *C. difficile* infection increases by approximately 2% (4).

Fluoroquinolone exposure and age older than 65 years were risks for CDI caused by NAP1/B1/027 (5). The prolonged use of nasogastric tubes is a risk factor in children (2). Patients with healthcare-associated *C. difficile* infection are more likely to have the NAP1 strain than are patients with healthcare-associated *C. difficile* colonization only (4).
5.6 Period of Communicability:

The period of communicability is not well defined. Asymptomatic patients may be colonized and patients who have been successfully treated may still have organisms and spores in their stool. Refer to Section 8.1 Management of Cases for infection prevention and control recommendations.

6. Laboratory Diagnosis

Unpreserved stool specimens should be sent to a clinical/medical laboratory when CDI is suspected. Diagnosis of CDI can be made by detecting Toxin A and/or B using a commercial Enzyme Immuno Assay (EIA), by detecting Toxin B with the Cytopathic Effect (CPE) assay, or by detecting the genes that encode Toxin A and/or B using a molecular assay. Although culture is rarely performed, a diagnosis of CDI can also be made by successful recovery of *C. difficile*, followed by a demonstration that the isolate is toxigenic. **The unpreserved specimen should be sent as soon as possible after suspected clinical diagnosis.** In most cases, toxin testing of a single stool specimen effectively establishes the diagnosis. A maximum of two stool samples per diarrhea episode (collected on separate days) will be tested but repeat testing (within 7 days) during the same episode of diarrhea is generally not recommended. If clinically CDI is highly suspected but the diagnostic tests are negative, consultation with a microbiologist may be warranted to determine if culture for *C. difficile* should be performed.

Note: A liquid or loose stool sample which takes the shape of the container more than 1/3 full (25 mL) without preservatives must be submitted to ensure a reliable laboratory result. Do not test stool from asymptomatic patients. Do not send specimens for “test of cure”. **FORMED STOOL OR STOOL LIQUEFIED ARTIFICIALLY IS NOT AN APPROPRIATE SPECIMEN AND WILL NOT BE TESTED FOR C. DIFFICILE BY MOST LABORATORIES.** If transport is more than two hours, the sample must be refrigerated.

7. Key Investigations for Public Health Response

Refer to Section 2.3 above. Regions may wish to liaise with infection prevention and control and/or follow their own regional practices.

8. Control

8.1 Management of Cases:

**Treatment:**
- Discontinue all current antimicrobial therapy when possible.
- Do not use antidiarrheal agents until CDI has been excluded.
- Refer to table below for treatment recommendations.

**Infection Prevention and Control:**
It is recommended that patients with CDI be maintained on Contact Precautions until:
- CDI is ruled out, and/or diarrhea is determined as not infectious; or
- If CDI is confirmed, until asymptomatic for at least 48 hours.

Discontinuation of Contact Precautions should be made in conjunction with the infection control practitioner/professional or delegate (8).
1. For non-severe presentations, guidelines suggest vancomycin is preferred for adults, based on a 10% outcome difference in recent clinical trials. However, the recommendation is not informed by a pharmacoeconomic evaluation or the impact of oral vancomycin in facilitating vancomycin resistant enterococci emergence and persistence.

2. Patients who present with fulminant *C. difficile* infection (hypotension or shock, ileus, megacolon) should be hospitalized and managed with input from appropriate specialists. Surgical consultation should be considered for patients with megacolon and ileus.

Note: Fidaxomicin 200 mg po twice daily for 10 days is also approved therapy for *C. difficile* infection in adults. There are restrictions on the availability of fidaxomicin in Manitoba and prescriptions should be provided in consultation with relevant specialists.
8.2 Management of Contacts and Exposed Individuals:

Contact investigation is not required.

8.3 Management of Facility Outbreaks:

**Outbreak Definition:** When there is evidence of continued transmission of *C. difficile* within a facility or when the incidence rate is higher than the facility’s baseline rate. When outbreaks are identified, heightened infection prevention and control measures should be implemented and investigation and epidemiological testing should be carried out in consultation with those responsible for Infection Prevention and Control and the Regional Health Authority (RHA) Medical Officer of Health according to RHA processes. Refer also to the Outbreak Management sections of the Public Health Agency of Canada documents Clostridium difficile Infection: Infection Prevention and Control Guidance for Management in Acute Care Settings (2013) at: https://www.canada.ca/en/public-health/services/infectious-diseases/nosocomial-occupational-infections/clostridium-difficile-infection-prevention-control-guidance-management-acute-care-settings.html and Clostridium difficile Infection: Infection Prevention and Control Guidance for Management in Long-term Care Facilities (2013) at: https://www.canada.ca/en/public-health/services/infectious-diseases/nosocomial-occupational-infections/clostridium-difficile-infection-prevention-control-guidance-management-long-term-care-facilities.html.

8.4 Preventive Measures:

- Public health education regarding personal hygiene, especially hand hygiene.
- Promotion of responsible use of antimicrobial agents in institutions and the community.
- Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk.
- Implement an antibiotic stewardship program. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present.
- Consider restricting use of fluoroquinolones, clindamycin and cephalosporins (except for surgical prophylaxis).
- Prevention in the healthcare environment is focused on preventing patient exposure to spores of *C. difficile* as well as good patient management if they become ill.
  - Patients suspected of having CDI should be placed on preemptive Contact Precautions pending the *C. difficile* test results, if test results cannot be obtained on the same day.
  - Daily cleaning with a sporicidal agent should be considered in conjunction with other measures (e.g., Contact Precautions, hand hygiene with soap and water) to prevent CDI during outbreaks or in hyperendemic (sustained high rates) setting, or if there is evidence of repeated cases of CDI in the same room.
  - In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand rub.
  - In CDI outbreaks or hyperendemic (sustained high rates) settings, perform hand hygiene
preferentially with soap and water instead of alcohol-based hand rub before and after caring for a patient with CDI given the increased efficacy of spore removal with soap and water. Hand hygiene should be performed at the point-of-care and at a designated hand washing sink. If a designated staff hand washing sink is not available at the point-of-care, ABHR (with an alcohol concentration between 60% and 90%) should be used and hand hygiene with soap and water should be performed as soon as a staff hand washing sink is available. Hand washing with soap and water is preferred if there is direct contact with feces or an area where fecal contamination is likely (e.g. the perineal area).

- There is insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials.
- Although there is an epidemiologic association between proton pump inhibitor (PPI) use and CDI and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI.
- Children with CDI should be excluded from childcare settings for the duration of diarrhea and infection prevention and control measures should be enforced (6).

References


