



# **The Standard:** **Diagnostic Timeline, Methods, and Costs** **for *C. difficile***

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**Clinical Testing Methods for *C. difficile***

<b>Test</b>	<b>General Description</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Cell Cytotoxicity Test</b>	<ul style="list-style-type: none"> <li>- A tissue culture designed to measure the effects of the <i>C. difficile</i> toxin on human cells.</li> <li>- 24-48 hours to get test results</li> </ul>	<ul style="list-style-type: none"> <li>- More sensitive method to detect the toxin</li> </ul>	<ul style="list-style-type: none"> <li>- Not widely available</li> <li>- More steps (more room for mechanical mistakes)</li> <li>- Often done along with an Enzyme Immunoassay (EIA) for accuracy</li> </ul>
<b>Enzyme Immunoassay (EIA)</b>	<ul style="list-style-type: none"> <li>- EIA is used to detect the presence of a particular substance</li> </ul>	<ul style="list-style-type: none"> <li>- Faster than other tests</li> </ul>	<ul style="list-style-type: none"> <li>- Is not sensitive enough to detect many infections</li> <li>- High rate of false normals</li> </ul>
<b>Toxigenic Stool Culture</b>	<ul style="list-style-type: none"> <li>- Two step process that includes growing the bacteria in a culture followed by detection of the toxins</li> <li>- 2-3 days for preliminary results</li> </ul>	<ul style="list-style-type: none"> <li>- Considered the gold standard (lengthy process ,but yields more accurate results)</li> </ul>	<ul style="list-style-type: none"> <li>- Second step required, culture does not differentiate between colonization and overgrowth/ infection</li> </ul>
<b>PCR Assays</b>	<ul style="list-style-type: none"> <li>- Molecular test that can rapidly detect the <i>C.difficile</i> toxin</li> </ul>	<ul style="list-style-type: none"> <li>- Fast and sensitive</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive, and not all labs are able to perform molecular testing</li> </ul>

Table 1: Tests Used to Detect the Presence of Pathogenic *C. difficile* (1,2)

## Clinical Testing Procedure

This section summarizes the clinical testing procedure of *C. difficile* in the Canadian province of Ontario, as outlined in a series of clinical practice documents by Public Health Ontario. While there are many groups outlining clinical “best practices”, we opted to summarize those most relevant to the context of our iGEM team, as we are based in Hamilton, Ontario.

*C. difficile* infections are prevalent across acute, intermediate, and chronic care health facilities. *C. difficile* testing is commonly completed across these health settings to validate suspected cases of *C. difficile* infection (3).

The following steps outline practices for laboratories and health facilities to adopt to improve the clinical testing *C. difficile* in complex health settings (3-4):

1. Stool sample collection to occur as soon as possible after the onset of diarrhea.
2. Rapid turnaround time for *C. difficile* testing and reporting is essential, and should be pre-arranged with the microbiology laboratory serving the healthcare setting.
  - a. Turnaround time should be **less than 24 hours, and the test should be available seven days a week.**
3. All positive *C. difficile* tests should be reported as soon as possible to Infection Prevention and Control (IPAC) at the facility where the test sample originated.
4. For suspect cases, a single negative toxin test by enzyme immunoassay does not rule out *C. difficile*, and will require a second specimen to be sent.
5. Testing by molecular methods such as PCR are more sensitive, thus allowing for greater accuracy in testing results with a single test. **Molecular testing** using PCR is the **gold standard** testing method.
6. Testing for *C. difficile* must be repeated if the clinical status deteriorates or to diagnose a relapse following a period of absence of symptoms.
7. Testing can detect *C. difficile* colonization OR disease. Results of laboratory testing must be correlated with the clinical condition of the patient, who should be meeting the “case definition” (the clinical criterion) for *C. difficile* infection.

*C. difficile* case definitions include (4):

- A. Laboratory confirmation of *C. difficile*, together with diarrhea
  - a. Diarrhea must be loose/watery stool AND unusual bowel movement AND no other recognized aetiology
- B. Visualization of pseudomembranes on sigmoidoscopy or colonoscopy
- C. Histological/pathological diagnosis of pseudomembranous colitis

D. Diagnosis of toxic megacolon

**Areas of Clinical Practice Improvement**

Public Health Ontario has outlined in an extensive review of the existing practice guidelines across Ontario health facilities, that there are five top areas for future practice improvement (5). These five areas are outlined below, along with the recommendations suggested to address each respective area of concept. While some of these recommendations are broad, and may not directly apply to the clinical pathway of *C. difficile* management, they allow us to understand the current gaps in health system management of *C. difficile*.

Area of concern	Recommendation	Number (%) of reports in which best practices were not met or needed improvement (N=22)
Environmental services	Process in place for cleaning of shared patient equipment	13 (59%)
	System for identification and storage of clean and dirty equipment	10 (45%)
	Adequate resources dedicated to environmental services to allow thorough and timely cleaning and disinfection; appropriate levels of supervisory staff	8 (36%)
	Written policies and procedures with clear accountabilities and cleaning protocols	7 (32%)
	Clarity around which product to use for routine/additional cleaning	4 (18%)
	Cleaning performed on a routine and consistent basis	3 (14%)
	Education program in place for new and experienced environmental services staff	3 (14%)
	Total reports with at least one identified deficiency	18 (82%)
Antibiotic stewardship	Resources dedicated to support antibiotic stewardship program	16 (73%)
	Antibiotic stewardship program in place	12 (55%)
	Total reports with at least one identified deficiency	16 (73%)
Program staffing and medical leadership	Adequate number of ICPs and resources to implement the IPAC program (proportional to the size, complexity, case mix and estimated risk of the populations served by the facility)	14 (64%)
	Infectious diseases/IPAC physician support for the program or access to an external infectious diseases/IPAC physician	9 (41%)
	ICP(s) certified in IPAC (i.e. have their CIC)	3 (14%)
	Total reports with at least one identified deficiency	16 (73%)
Identification and isolation of CDI cases	Patient transfer only when medically necessary	9 (41%)
	Appropriate initiation of Contact Precautions when there is a suspected or confirmed case of CDI	7 (32%)
	Single-room accommodation with dedicated toileting facilities or commode chair	6 (27%)
	Appropriate signage	4 (18%)
	Surveillance system to track the number of confirmed cases of CDI acquired in the facility	3 (14%)
	Adequate access to personal protective equipment	3 (14%)
	Dedicated patient care equipment	1 (5%)
	Total reports with at least one identified deficiency	16 (73%)
Hand hygiene	Audit results shared with staff	10 (45%)
	Point-of-care alcohol-based hand rub	8 (36%)
	Total reports with at least one identified deficiency	15 (68%)

Table 2: Top five areas of concern where best practices were not met or needed improvement (5)

**Costs Associated with *C. difficile***

**Within Treatment (Canada):**

“Infected patients had 1.3- to 5.3-fold higher mean costs versus uninfected subjects. The mean attributable cost (adjusted for survival) of an incident community-acquired CDI patient was \$8,881 (95%CI: \$7,951-\$9,904) in the first year, \$2,663 in the second year, and \$2,480 in the third year.”(6)

Mean attributable costs were generally higher among those diagnosed in 2010 (possibly due to a virulent strain), males, those aged ≥65 years, and those who died within 1-year after the index date. (6)

**Within Testing/Diagnosis:**

**Evaluation of Diagnostic Tests for *Clostridium difficile* Infection**

**TABLE 1.**  
Comparison of results obtained with *C. DIFF* Quik Chek Complete, VIDAS, Xpert *C. difficile* PCR, Gene Ohm PCR, stool CCNA, *C. difficile* culture, and CCNA performed on culture isolates

Interpretation	No. of specimens	Test result <sup>b</sup> by:							
		<i>C. DIFF</i> Quik Chek Complete for:		VIDAS	Xpert <i>C. difficile</i> PCR	Gene Ohm PCR	Stool CCNA	<i>C. difficile</i> culture	Culture CCNA
		GDH	CDT						
<i>C. difficile</i> infection	8	+	+	+	+	+	+	+	+
	3	+	+	- <sup>a</sup>	+	+	+	+	+
	4	+	- <sup>a</sup>	- <sup>a</sup>	+	+	+	+	+
Toxigenic <i>C. difficile</i> carriage	2	+	-	-	+	+	-	+	+
	1	+	-	-	+	- <sup>a</sup>	-	+	+
	1	+	-	-	+	+	-	- <sup>a</sup>	NA
Nontoxigenic carriage	1	+	-	-	-	-	-	+	-
False-positive GDH result	2	+	-	-	-	-	-	-	NA
Negative	128	-	-	-	-	-	-	-	NA
Total	150	22	11	8	19	18	15	19	18

<sup>a</sup>Interpreted as a false-negative result.

<sup>b</sup>+, positive result; -, negative result; NA, not applicable.

From the table, it is suggested that *C DIFF Quik Chek Complete* and *Xpert C. difficile PCR* are the most accurate diagnostic tests.

Table 3: Comparison of rapid diagnostic tests for *C. difficile* and their effectiveness (3)

**Costs associated with commercial and noncommercial testing types for *C. difficile*:**

<b>Name/Method</b>	<b>Developer</b>	<b>Estimated Cost</b>	<b>Details</b>
<i>C. DIFF</i> Quik Chek Complete	Supplier: <a href="#">Alere</a> Developer/Producer: TechLab	*\$11.50/test USD \$14.48/test CAD	<30 min for results, ~9 min hands-on/test
Xpert <i>C. difficile</i> PCR assay	<a href="#">Cepheid</a>	*\$33.38/test USD \$42.04/test CAD	45 min results, ~5 min hands-on/test
VIDAS <i>C. difficile</i> panel	<a href="#">bioMérieux</a>	Not found	50/75 min results
Gene Ohm PCR	BD Diagnostics	\$25.83 USD/test \$32.53 CAD/test	~2 hours results
Illumigene <i>C. difficile</i> assay	<a href="#">Meridian Bioscience Inc.</a>	** \$26.00 USD/test \$32.75 CAD/test	2-5 min hands-on/test
CCNA	N/A	** \$12.00 USD/test \$15.11 CAD/test	5 min hands-on/test
<i>C. difficile</i> anaerobic culture	N/A	** \$27.00 USD/test \$34.01 CAD/test	30 min hands-on/test

Table 4: Comparison of rapid diagnostic commercial and noncommercial tests for *C. difficile* as a function of their estimated costs and time requirements (7-12)

\* "The material costs per test for each of these assays are \$11.50 (reimbursement cost, \$34.36) for the C.Diff Quik Chek Complete assay (hands-on time, ~9 min per specimen)

and \$33.38 (reimbursement cost, \$50.27) for the Xpert *C. difficile* PCR assay (hands-on time ~5 min per specimen).” (11)

\*\* “The reagent cost for each assay and the amount of technical time required to perform it were as follows: \$46 and 4 min, respectively, for the Xpert *C. difficile* assay; \$26 and 5 min, respectively, for the Illumigene *C. difficile* assay; \$12 and 5 min, respectively, for CCNA; and \$27 and 30 min, respectively, for anaerobic culture” (12)

### **Antimicrobial Susceptibility Testing**

Clinicians use AST to determine if an antimicrobial will be effective on a given bacterial or fungal infection. Data is mainly collected via breakpoints and expert rules.

“A **breakpoint** is a chosen concentration (mg/L) of an antibiotic which defines whether a species of bacteria is susceptible or resistant to the antibiotic. If the MIC is less than or equal to the susceptibility breakpoint the bacteria is considered susceptible to the antibiotic.” (13)

**Expert rules** are a different kind of guideline used in AST, which are based directly from other researchers’ findings (ex. A researcher has substantial evidence that x bacteria is resistant to y antibiotic, so he submits it as a potential expert rule). (13)

There are many organizations which run their own AST, and thus publish differing results (because they use different breaking points). The HP team decided to look into EUCAST (the European Committee of Antimicrobial Susceptibility Testing).

#### **How to test for AST:**

<b>Method</b>	<b>Process</b>	<b>Details</b>
Broth dilution tests	Prepare dilutions of antibiotics in test tubes, add bacteria and incubate overnight, observe any bacterial growth. The minimum amt of antibiotic that prevents growth is called the minimal inhibitory concentration (MIC).	Criticized for being easy to make errors during the process, since it requires many human-prepared solutions. However, prepared microdilution panels for this test can be bought frozen/dried for \$10-\$22.



Antimicrobial gradient method	Thin plastic strips are placed on an agar plate, establish an antimicrobial concentration gradient while incubating overnight. Can also be used to determine MIC.	Each strip is \$2-\$3 each, so vigorous testing will be expensive if it's on more than one drug.
Disk diffusion test	Bacteria spread on the surface of agar plate, antibiotic disks placed ovetop, incubate overnight, measure radial zones of growth to the nearest millimeter.	Results are "qualitative", meaning that the zones are only compared to one-another and not to a quantifiable MIC. Cheapest method, \$2.50-\$5/test
Automated instrument systems	Four automated instruments currently approved by FDA; three produce rapid results, one is overnight.	Time-efficient and more sensitive to subtle changes. For more information on these instruments, check the link below!

Table 5: Overview of commonly used susceptibility testing methods (condensed) (13,14)

**EUCAST on AST:**

**TABLE 7. Exceptional phenotypes of anaerobes**

Rule no.	Organisms	Exceptional phenotypes
7.1	<i>Bacteroides</i> spp.	Resistant to metronidazole and carbapenems
7.2	<i>Clostridium difficile</i>	Resistant to metronidazole and vancomycin

Table 6: Expert rule for *C. difficile* (14)



*Clostridium difficile*

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-03-10

Disk diffusion criteria for antimicrobial susceptibility testing of *Clostridium difficile* have not yet been defined and an MIC method should be used. If a commercial MIC method is used, follow the manufacturer's instructions.

Fluoroquinolones	MIC breakpoint (mg/L)		Notes Numbered notes relate to general comments and/or MIC breakpoints.
	S ≤	R >	
Moxifloxacin	1	1	1. Not used clinically. May be tested for epidemiological purposes only (ECOFF 4 mg/L).

  

Glycopeptides	MIC breakpoint (mg/L)		Notes Numbered notes relate to general comments and/or MIC breakpoints.
	S ≤	R >	
Vancomycin	2 <sup>1</sup>	2 <sup>1</sup>	1. The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

  

Tetracyclines	MIC breakpoint (mg/L)		Notes Numbered notes relate to general comments and/or MIC breakpoints.
	S ≤	R >	
Tigecycline	1,2	1,2	1. For tigecycline broth microdilution MIC determination, the medium must be prepared fresh on the day of use. 2. Not used clinically. May be tested for epidemiological purposes only (ECOFF 0.25 mg/L).

  

Miscellaneous agents	MIC breakpoint (mg/L)		Notes Numbered notes relate to general comments and/or MIC breakpoints.
	S ≤	R >	
Daptomycin	1,2	1,2	1. Daptomycin MICs must be determined in the presence of Ca <sup>2+</sup> (50 mg/L in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturers' instructions for commercial systems. 2. Not used clinically. May be tested for epidemiological purposes only (ECOFF 4 mg/L). 3. Not used clinically. May be tested for epidemiological purposes only (ECOFF 2 mg/L). 4. Fidaxomicin breakpoints and ECOFF have not been set because the available data show major variation in MIC distribution between studies. 5. The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility. 6. Not used clinically. May be tested for epidemiological purposes only (ECOFF 0.004 mg/L).
Fusidic acid	3	3	
Fidaxomicin	1E <sup>4</sup>	1E <sup>4</sup>	
Metronidazole	2 <sup>5</sup>	2 <sup>5</sup>	
Rifampicin	8	8	

Table 7: Breakpoint tables for *C. difficile* (15)

For instructions on how to read breakpoint tables, see page 2 of Eucast's breakpoint guide (15).

**Additional Readings, Documentation, Clinical Guidelines:**

1. [Guidelines for diagnosis, treatment, and prevention of C. difficile infections](#) (16)
  - a. American College of Gastroenterology guidelines- not entirely relevant to the Canadian context but still helpful for content
2. [Current knowledge on the laboratory diagnosis of C. difficile infection](#) (17)
  - a. Good review article that critically examines the American College of Gastroenterology guidelines
3. [Infection Prevention and Control Canada, Guideline Repository](#) (18)
4. Public Health Ontario: [Infectious Disease Protocol- Appendix A, Disease-Specific Chapters](#) (19)
5. Public Health Ontario: [Infectious Disease Protocol- Appendix B, Provincial Case Definitions for C. difficile infection](#) (20)

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