Consensus Statement on the Testing for *Clostridium difficile* in Montana
Endorsed by the Montana Infectious Disease (ID) Network
December 2017

The Montana Infectious Disease (ID) Network is a strategic statewide collaborative and its membership includes the ID physicians currently practicing in Montana. The ID Network's vision is to serve as an advising regional, clinical, and readiness partner in the area of infectious and communicable disease.

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This consensus statement was originally reviewed and endorsed by the Montana Healthcare Associated Infection Prevention Initiative Roundtable on June 4, 2013 and final revisions were endorsed in December 2017.

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Introduction:

The diagnosis of *Clostridium difficile* infection (CDI) continues to trend upward in the context of increased antibiotic utilization and diagnostic test sensitivity. Because the vast majority of CDI diagnoses and surveillance rely heavily on laboratory identification, testing methodologies that are professionally endorsed and standardized can improve both the clinical interpretation of test results and the accuracy of local epidemiology related to CDI.

The Montana ID Network, a collaborative group of infectious disease physicians from across the state, has endorsed the following guideline with the intention of helping healthcare providers as they consider testing patients for CDI.

CDI is defined as the acute onset of diarrhea with documented toxigenic C. difficile or its toxin with no other documented cause for diarrhea.

Who/When to test:

- Patients who have clinical diarrhea (>3 unformed stools in a 24-hour period that take the shape of the container) for at least 1 to 2 days.
- Patients with the 2 biggest risk factors:
    - Exposure to antibiotics – especially broad-spectrum antibiotics.
    - Exposure to the organism – usually through admission to a health care facility setting, including hospitals, long-term acute care hospitals, critical access hospitals, long-term care facilities, nursing homes, rehabilitation facilities and dialysis settings.
- Patients with additional risk factors that increase the risk
    - Older age
    - Gastrointestinal surgery
    - Nasogastric tube feeding
    - Reduced gastric acid – medications including proton pump inhibitors
    - Concurrent disease including inflammatory bowel disease

Who <u>not</u> to test:

- Patients who may have other reasonable explanation for diarrhea (e.g. taking medication such as stool softeners, laxatives, Reglan, lactulose or bowel prep)
- Patients with formed stool
- Patients without clinical diarrhea (>3 unformed stools in a 24-hour period that take the shape of the container) unless toxic mega colon is suspected
- Patients that have tested positive in the past 30 days
- Do not retest to determine that treatment was effective treatment (test of cure)

How to test: Refer to testing algorithms attached as addendums.

- Glutamate dehydrogenase (GDH) or Lactoferrin screening tests for *C. difficile* can be used in two- or three-step screening algorithms with subsequent toxin A and B EIA testing.
    - Using GDH or Lactoferrin as a screening tool is effective because of the high negative predictive value of these tests. Note: do not use Lactoferrin testing for Oncology patients as Lactoferrin may be false negative in neutropenic patients.
        - Lactoferrin is a stool (fecal) test that is used to detect inflammation in the intestines. Intestinal inflammation is associated with, for example, some bacterial

infections and, in people with inflammatory bowel disease (IBD), it is associated with disease activity and severity.

- Nucleic acid amplification tests (NAAT) for *C. difficile* toxin genes such as PCR may be used as a standard diagnostic test for CDI. However, it should be noted that false positives occur with PCR testing.
- At a minimum for laboratory-based diagnosis of CDI, rural facilities (where cost and staffing issues are paramount) should employ EIA rapid testing using the combination *C. difficile* common antigen and Toxin A/B methodologies. *C. difficile* antigen negative, Toxin A/B negative results provides a reliable, cost-effective and easy to perform *C. difficile* screen with a 90% or better, negative predictive value

Other issues to consider:

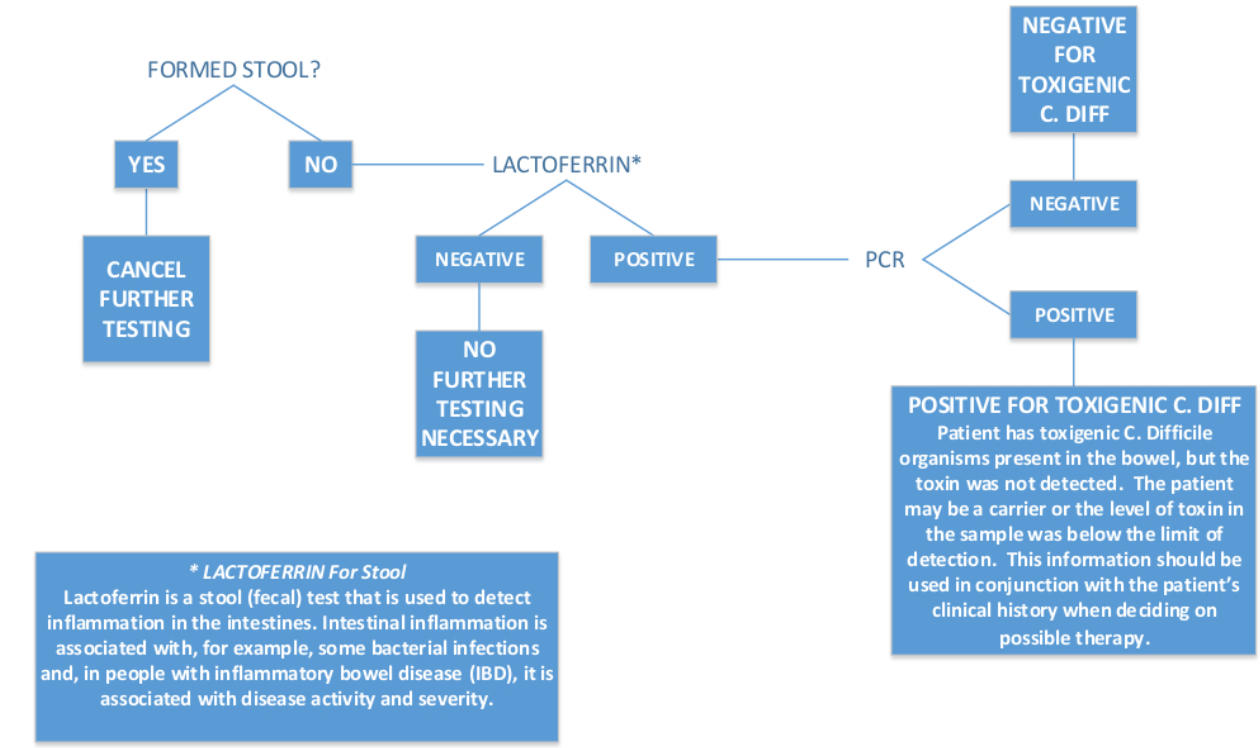
- Relapse CDI is very common, occurring 25% of the time, and is most likely to occur within 2 weeks of initial treatment. Relapse is a clinical diagnosis and does not require retesting. Consult an Infectious Disease Physician when multiple relapses (> 2) occur.
- Healthcare facilities should develop a policy to reject stool specimen for CDI testing if the specimen does not take the shape of the container (i.e. liquid stool specimen)
- According to the American Academy of Pediatrics, testing for CDI in children should only be performed in children with clinical diarrhea and the following age-related conditions:
    - Under 12 months – test only those with Hirschsprung disease or other severe motility disorders. Alternative etiologies should be sought even with a positive result.
    - 13 – 36 months – Seek alternative etiologies first as *C. difficile* results are difficult to interpret. A positive test indicates possible CDI.
    - Over 36 months – Increase the pre-test likelihood by testing children with the following risk factors: recent antimicrobial therapy, use of proton pump inhibitors, underlying bowel disease, renal insufficiency, or impaired humoral immunity. A positive test indicates probable CDI.
- Refer to Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) for additional information relating to testing, treatment and infection prevention measures. https://doi.org/10.1093/cid/cix1085

Examples of algorithms using 2- or 3- step testing methods (See Addendum 1-4)

The accurate laboratory diagnosis of CDI remains a work in progress. Examples of laboratory imperfections include the inability of C difficile toxin B gene PCR to distinguish between colonization and true infection, and toxin B EIA, although has excellent specificity, performs at best with 85-90% sensitivity (assumes 10-15% false negative rate). However, a reasonable approach to laboratory diagnosis of CDI overcomes the above issues by using a combination of clinical findings and laboratory results, as follows: stool studies are ordered only for patients with diarrhea and signs of infectious colitis (fever/chills, abdominal pain, etc.) and only liquid stool conforming to the shape of the collection container should be tested. Laboratory testing can include a combination of Lactoferrin, GDH/toxin EIA, and C. difficile toxin B gene PCR.

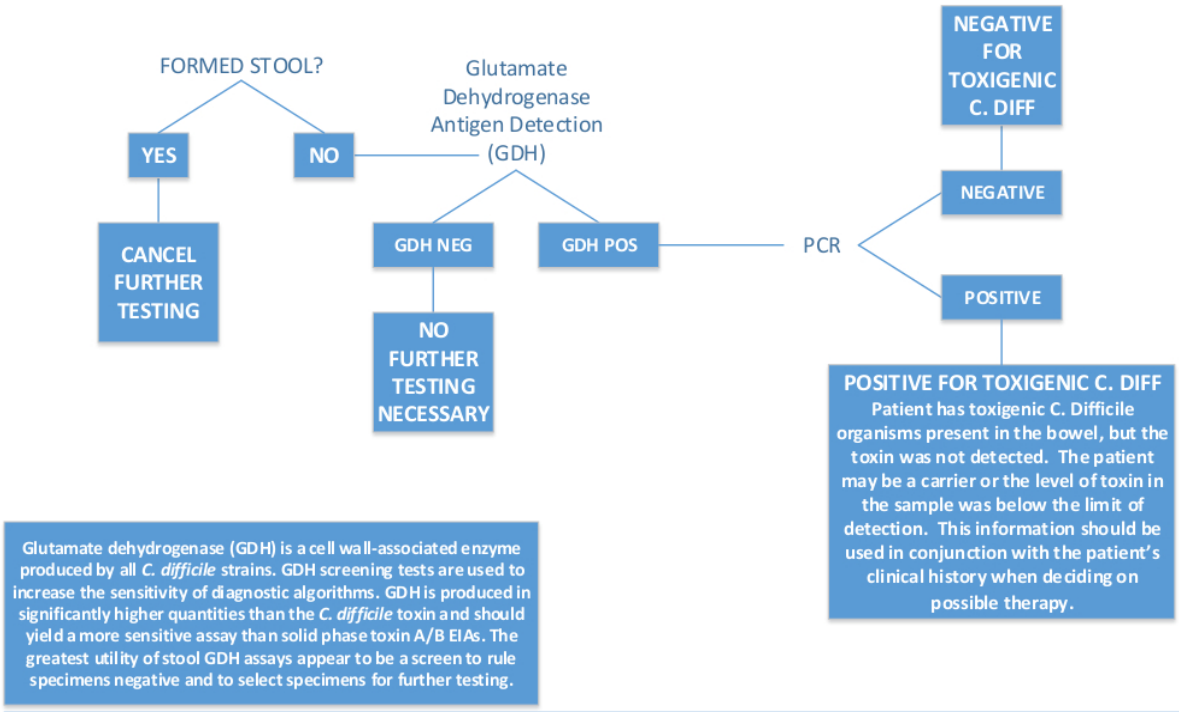
Four diagnostic algorithms are presented as examples but are not intended as “one size fits all”. The algorithms use a 2- and 3-tiered approach, using GDH, Lactoferrin, GDH & toxin EIA, and PCR when indicated. (Note- Lactoferrin may be false negative in neutropenic patients). The minimum laboratory diagnosis of CDI requires combination GDH/toxin EIA testing of liquid stool, with negative result indicating > 90% negative predictive value of disease.

Clostridium difficile TESTING ALGORITHM
Addendum 1: Example of a Two Step Testing Method Using Lactoferrin and PCR



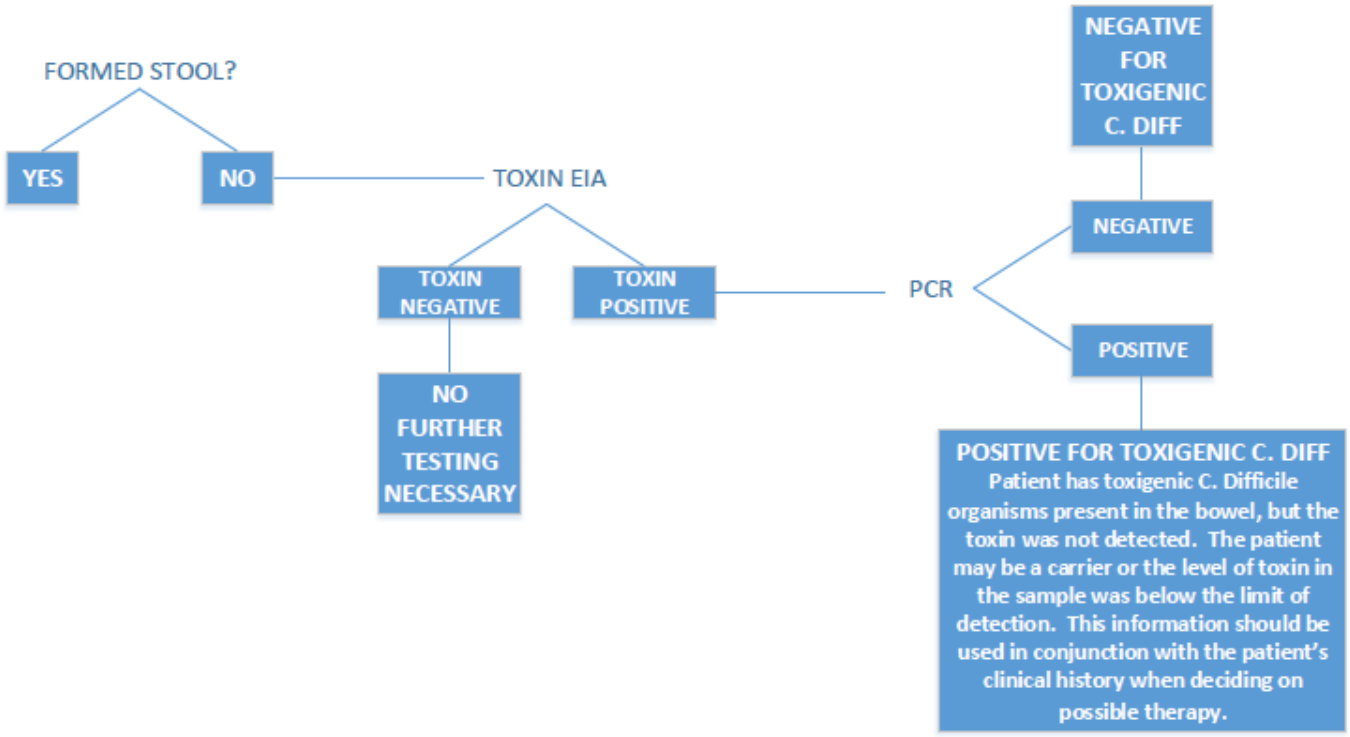
Clostridium difficile TESTING ALGORITHM

Addendum 2: Example of a Two Step Testing Method Using GDH and PCR

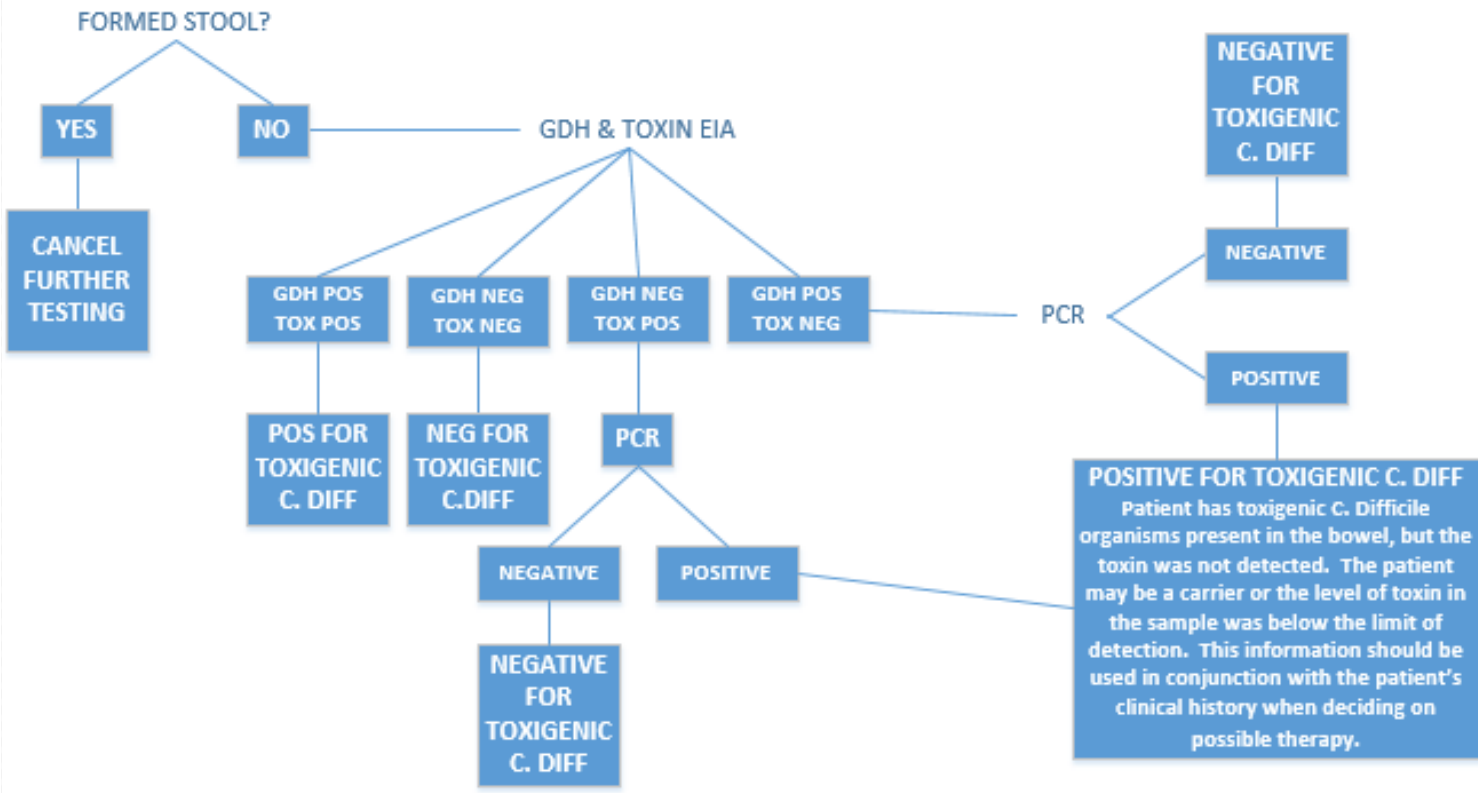


Glutamate dehydrogenase (GDH) is a cell wall-associated enzyme produced by all *C. difficile* strains. GDH screening tests are used to increase the sensitivity of diagnostic algorithms. GDH is produced in significantly higher quantities than the *C. difficile* toxin and should yield a more sensitive assay than solid phase toxin A/B EIAs. The greatest utility of stool GDH assays appear to be a screen to rule specimens negative and to select specimens for further testing.

CLOSTRIDIUM DIFFICILE TESTING ALGORITHM
Addendum 3: Example of a Two Step Testing Method Using Toxin EIA and PCR



CLOSTRIDIUM DIFFICILE TESTING ALGORITHM
Addendum 4: Example of a Three Step Testing Method Using GDH, Toxin EIA, and PCR



References

1. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* Infection in the Molecular Test Era. JAMA Internal Medicine 2015; 175(11):1792-1801. September 8, 2015. Retrieved from: http://archinte.jamanetwork.com.
2. Dubberke ER, Burnham CD. Diagnosis of *Clostridium difficile* Infection. Treat the Patient, Not the Test. JAMA Internal Medicine November 2015; Vol. 175, Number 11. Retrieved from: http://archinte.jamanetwork.com.
3. A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*. Guidance Document. American Society for Microbiology. 21 September 2010.
4. APIC. An APIC Guide: Guide to the Elimination of *Clostridium difficile* in Healthcare Settings. 2008.
5. APIC. APIC Implementation Guide: Guide to Preventing *Clostridium difficile* Infections. 2013.
6. Cohen et al. Clinical Practice Guidelines for the *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiology 2010; 31(5):431-455.
7. Dubberke et al. Development and Validation of a *Clostridium difficile* Infection Risk Prediction Model. Infection Control and Hospital Epidemiology. 32;4:360-366. April 2011.
8. Dubberke et al. Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals. Infection Control and Hospital Epidemiology. 2008; 29(supplement 1).
9. Eastwood et al. Comparison of Nine Commercially Available Clostridium difficile Toxin Detection Assays, a Real-Time PCR Assay for C. difficile tcdB, and a Glutamate Dehydrodgenase Detection Assay to Cytotoxin Testing and Cytotoxigenic Culture Methods. Journal of Clinical Microbiology. 47;10:3211-3217. October 2009.
10. Jarvis et al. National point prevalence of *Clostridium difficile* in US health care facility inpatients, 2008. American Journal of Infection Control. Pgs 1-8. 2009.
11. McDonald et al. *Clostridium difficile* Infection in Patients Discharged from US Short-stay Hospitals, 1996-2003. Emerging Infectious Diseases. Vol. 12, No. 3. March 2006.
12. Peterson et al. Detection of Toxigenic *Clostridium difficile* in Stool Samples by Real-Time Polymerase Chain Reaction for the Diagnosis of C. difficile-Associated Diarrhea. Clinical Infectious Diseases. 2007;45:1152-1160.
13. Peterson and Roblcsek. Does My Patient Have *Clostridium difficile* Infection? Annals of Internal Medicine. 2009;151:176-179.
14. Policy Statement: Clostridium difficile Infection in Infants and Children. American Academy of Pediatrics. DOI: 10.1542/peds.2012-2992. 2013.
15. Surawicz et al. Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. The American Journal of Gastroenterology. April 2013:108:478-497.
16. McDonald et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clinical Infectious Diseases, cix1085, https://doi.org/10.1093/cid/cix1085. Published 15 February 2018.