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The *C. difficile* puzzle:

Putting it all together

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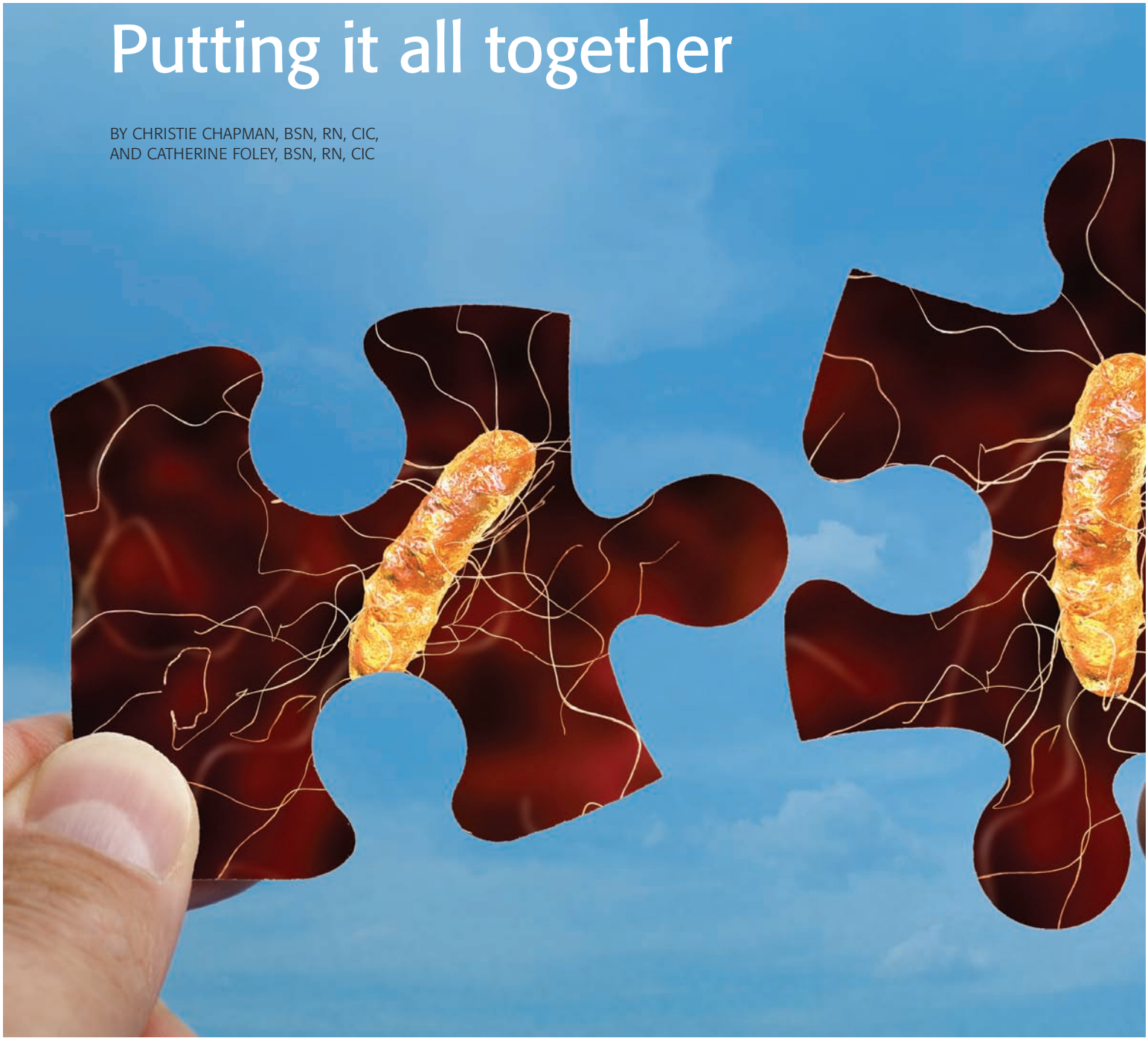

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Abstract: This article explores *Clostridium difficile* infection (CDI) versus colonization, regulations surrounding CDI reporting, the varied types of CDI testing methods available, and the important role nurses have in thoughtful submission of stool specimens for *C. difficile* testing.

Keywords: CDI, *C. difficile* colonization, *C. difficile* infection, *Clostridium difficile*, PCR, polymerase chain reaction testing

IDENTIFYNG AND PREVENTING *Clostridium difficile* infection (CDI) in hospitalized patients is a large and complex puzzle. The incidence of CDI has increased over 200% since 2000 and it is now one of the leading causes of healthcare-associated infections (HAI) in the US.[1] Reasons for the rise in CDI include an increase in older hospitalized adults with multiple comorbidities. In addition, more broad-spectrum antibiotics are being prescribed than ever before and healthcare settings are struggling to provide adequate infection prevention measures.[2]

Although preventing CDI is a top priority, the best way to do so is unclear. Since the introduction of fast, accurate molecular-based polymerase chain reaction (PCR) testing for CDI, research studies have raised concerns about overdiagnosis. Are rising rates a reflection of PCR capturing asymptomatic *C. difficile* colonization as well as true disease? Depending on their level of understanding about the implications of the testing method, clinicians may be erroneously diagnosing CDI in patients who are colonized with *C. difficile* but don't have signs and symptoms of infection or require treatment.[1]

In an attempt to find some of the hidden puzzle pieces that may help put together a clearer picture of true CDI in healthcare, this article explores what *C. difficile* infection really is, regulations surrounding CDI reporting, the varied types of CDI testing methods available, and the important role nurses have in thoughtful submission of stool specimens for *C. difficile* testing.

Overgrowth of normal gut flora

C. difficile is part of the community of normal gut flora in humans. Its overgrowth is usually kept at bay by more dominant bacterial anaerobes.[3] As discussed in detail below, CDI develops when an abnormal increase of *C. difficile* in the large intestine causes signs and symptoms of gastrointestinal (GI) infection.

In its infectious state, *C. difficile* produces toxins and spores that resist heat, acid, many antiseptics, and antibiotics. Spores from *C. difficile* bacteria are passed in feces and spread to food, environmental surfaces, and objects when people fail to perform effective hand hygiene with soap and water. In healthcare facilities, inadequate environmental cleaning of rooms and shared equipment compounds the risk to patients.[4,5]

CDI causes gut inflammation, secretion of fluid and mucus, and colitis.[6] Signs and symptoms can range from mild diarrhea to fulminant colitis. The patient may also have fever, abdominal pain, and leukocytosis. If untreated, CDI can lead to sepsis, toxic megacolon, colectomy, and death. Identifying and treating CDI as early as possible is imperative to prevent these devastating consequences.[4] However, a person can be colonized with *C. difficile* without having CDI.

Infection or colonization?

Colonization occurs when bacteria present in the body, such as on the skin or in the mouth, intestines or airway, accumulate without causing disease.[7] In their 2017 *Clinical Practice Guidelines for* Clostridium difficile *Infection in Adults and Children* update, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) reported that among adult inpatients in acute care hospitals, the prevalence of asymptomatic colonization with *C. difficile* is between 3% and 26%.[8]

Toxins A and B, the main virulence factors produced by the *C. difficile* bacteria, drive the signs and symptoms of infection in patients. These toxins will be present in the stool of a patient with a CDI. They will most likely *not* be found in stool of a patient who is colonized but not infected with *C. difficile*.[8] In one study, 21% (293 of 1,416) of hospitalized adults tested for *C. difficile* were positive on PCR testing, but toxins were identified in only 44.7% of those patients (131 of 293).[1]

Diagnosis of *C. difficile* without true infection leads to increased costs, unnecessary isolation precautions, and treatment with unnecessary antibiotics.[9] These all have the potential to cause unintended patient harm.

The regulatory piece of the puzzle

In the very worthy quest for improved patient outcomes, acute care hospitals and other healthcare facilities track large amounts of data around patient safety measures. In 2011, the Affordable Care Act/Value-Based Purchasing required that all acute care hospitals report lab-identified (LabID) versus clinically identified CDI through the National Healthcare Safety Network (NHSN) database.[10] In 2017, hospital-onset CDI became a performance measure that determines a portion of a hospital's Medicare reimbursement. These data are also available for public perusal via websites such as Hospital Compare and state-specific Departments of Health and Human Services.[11]

The definitions NHSN gives to determine CDI are epidemiologic (not clinical) and are built around only a single positive *C. difficile* lab test result. Positive lab results are submitted to NHSN and placed into three categories:[12]

- ***community onset (CO)***—positive *C. difficile* specimens collected in an outpatient or inpatient location 3 days or less after admission to the facility (days 1, 2, or 3 of admission). This category doesn't affect Medicare reimbursement or public reporting.
- ***community-onset healthcare facility-associated (CO-HCFA)***—collected in an inpatient location 3 days or less after admission to the facility (specifically, days 1, 2, or 3 of admission) or collected in an outpatient location in which the patient was not previously discharged from an inpatient location within the same facility 28 days or less prior to current date of specimen collection. This category also doesn't affect Medicare reimbursement or public reporting.
- ***healthcare facility-onset (HO)***—positive *C. difficile* specimens collected more than 3 days after admission to the facility (on or after day 4 of hospital admission). This is considered an HAI and is the focus of this article. This category does affect Medicare reimbursement and is reflected on public HAI websites.

CDI is the only HAI covered in NHSN reporting and surveillance where, despite public scrutiny, rates are not significantly improving. In some states, rates have actually worsened.[13]

In light of the narrow regulatory definitions for HO CDI and healthcare's responsibility to treat with medication only when necessary, we need to get CDI testing right. Understanding how facilities test for CDI might help with this piece of the puzzle.

Which test is best?

Healthcare has struggled with CDI testing for many years. Currently, no best practice in testing for CDI is generally accepted. Multiple factors determine the clinical usefulness of a CDI diagnostic test.

- Sensitivity: the ability of a test to correctly identify individuals who truly have a given disease or condition. In other words, does a positive result really indicate the presence of disease?

• Specificity: the ability of a test to correctly exclude individuals who do not have a given disease or condition. In other words, does a negative result really indicate lack of disease?
• Turnaround time (TAT): how labor intensive is it and how soon are the results available?
• Cost: how expensive is acquiring the equipment for the test and running the test?
• Availability: can the lab perform the test? Not all labs have the equipment or personnel needed to perform certain lab tests.[9]

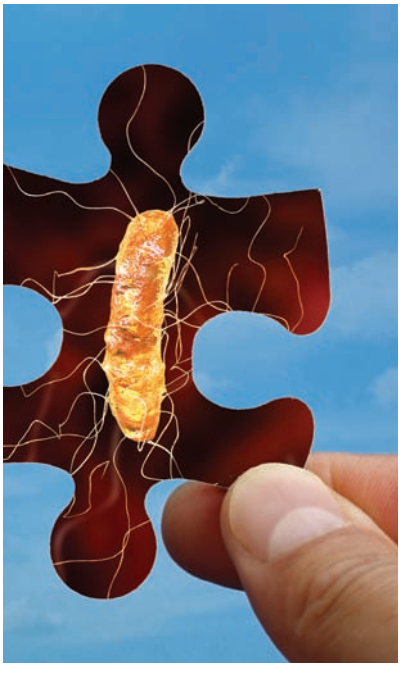
As discussed earlier, toxins A and B are the main virulence factors produced by *C. difficile* bacteria and will be present in the stool of a patient with a CDI. Accordingly, any effective CDI test method must target the presence of these toxins to identify true infection in a patient.[9]

The first tests for CDI were developed in the 1970s and 1980s. The *cell cytotoxicity neutralization assay* and *toxigenic culture* detected *C. difficile* toxins on a cell culture medium. While very sensitive, these tests lacked acceptable specificity, had a very long TAT, and were not available to all labs.[9]

In the early 1990s, the *enzyme immunoassay (EIA)* for *C. difficile* toxins A and B was developed. EIAs have a quick TAT and are inexpensive and widely available. However, recent studies have shown that the EIA for toxins A and B has a poor sensitivity (between 45% and 60%) and is not recommended as a stand-alone test for CDI.[9]

In 2006, an EIA for *glutamate dehydrogenase (GDH)*, an antigen produced by *C. difficile*, came to market. Although this test has good sensitivity and TAT, it detects all *C. difficile*, including nontoxin-producing strains, so isn't as specific in detecting true CDI.[14]

Some labs use the EIA and the GDH in a two-step method: first GDH for initial screening; then, if the GDH is positive, EIA to detect the presence of toxin. However, this type of testing can produce conflicting results that can be difficult to interpret and might require further testing to confirm a true CDI.[9]



Unnecessary isolation precautions and treatment with unnecessary antibiotics have the potential to cause unintended patient harm.

In 2009, *nucleic acid amplification tests (NAAT)*, which include PCR tests, became available commercially. NAATs detect one or more genes specific to toxigenic strains; the critical gene is tcdB, which encodes for toxin B. This test is quick, producing results in hours instead of days, highly sensitive (80% to 100%), specific (87% to 99%), and now widely available to all labs.[9] However, studies started to emerge possibly linking elevated reporting of incidence rates to this testing technology. The NAAT detects the presence of the genes responsible for potential toxin production but does not detect the presence of active toxin in stool specimens—meaning that if it's used as a stand-alone test for disease, it could be detecting *C. difficile* colonization as well as *C. difficile* infection.[9] The authors of one study found numerous false positives with the PCR, and the CDC discovered that CDI incidence increased by 43% to 67% in hospitals that changed from toxin EIAs to PCR testing for CDI.[15]

More recently, a fecal *gastrointestinal pathogen panel (GIP)* PCR has become clinically available. Requiring only one stool sample, the GIP tests for many GI infections, including CDI. The GIP can detect genetic markers of toxins A and B and appears to be highly sensitive and specific. However, the transport medium recommended for collection of stool specimens liquefies the stool sample, making it difficult to determine if the specimen collected was formed or liquid stool. (As discussed below, testing for CDI should be performed on unformed stool specimens.) In a 2014 study, Khare et al. recommended further study to determine whether positive GIP results indicate disease or colonization.[16]

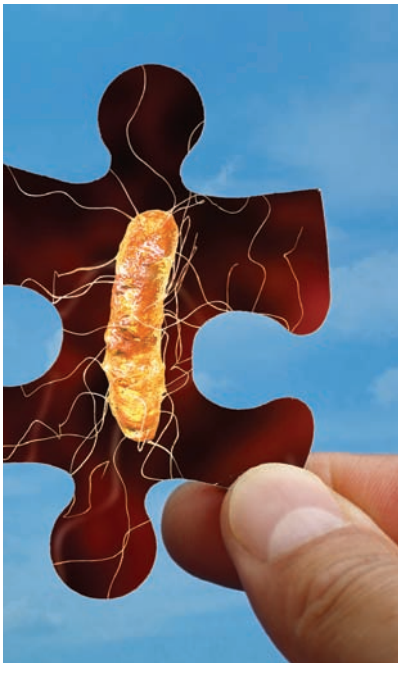
Clinical guidelines for CDI identification and testing have been published by SHEA, the IDSA, and the American College of Gastroenterology (ACG). Although they differ in the type of test they recommend, they all agree that CDI is a *clinical* diagnosis that is defined by a set of signs and symptoms (most often diarrhea) *and* (not "or") a positive lab test confirmation.[17] A study by Dubberke et al. concluded that clinical presentation is important when interpreting CDI testing and that validated criteria are needed to indicate when to test for CDI.[18]

Nurses drive appropriate testing

More healthcare facilities are finding that appropriate stool submission for CDI testing is the key needed to

correctly identify true CDI in their institutions. Many are turning to nurses to drive this effort.

For obvious reasons, nurses aren't usually decision-makers in choosing the type of lab test a facility will use for CDI. However, nurses can be a huge driver of what type of stool is submitted for testing. The nurse understands the day-to-day clinical picture of patients better than almost anyone else on the healthcare team and will probably be the first to make the connection between clinical signs and symptoms and potential CDI. As the missing piece of the CDI puzzle, nurses can be the facilitators of a timely and thoughtful approach to submission of stool specimens for *C. difficile* testing that is based on the patient's clinical history, current signs and symptoms, and recent medication history.



The nurse understands the day-to-day clinical picture of patients better than almost anyone else on the healthcare team.

What does diarrhea tell you?

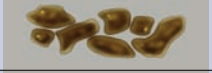
Many pharmacologic and nonpharmacologic interventions can cause a one-time diarrhea event. According to SHEA and IDSA, acute diarrhea is defined as 3 or more loose or watery stools in 24 hours.[8,17] This definition or a similar variation is being used by most researchers, the ACG, and the World Health Organization when collecting data or providing literature and/or guidance around identification and treatment of diarrheal illnesses.

So in practice, is *clinically significant* diarrhea being tested for CDI? A 2015 study suggests maybe not. This retrospective research showed that 36% to 50% of hospitalized patients tested for *C. difficile* did *not* have clinically significant diarrhea defined as 3 or more loose stools/24 hours.[6]

What about stool consistency? One source of clarity is the NHSN guidance around stool collection for CDI lab identification. Those experts tell us that the stool specimen submitted for testing should be "an unformed stool specimen that conforms to the container." This consistency of stool is more likely to indicate infection or inflammation rather than colonization.[10] The Bristol Stool Chart is a tool that can help guide nurses in identifying infectious stool consistency that warrants collection and lab identification. (See *Bristol Stool Chart*.)

The Bristol Stool Chart visually represents how defecation disorders relate to stool consistency. Nurses use this tool to prompt patients to describe the consistency of their stool with minimal embarrassment by asking them to "point to the one that looks most like your stool." This provides a consistent stool documentation guideline in the electronic health record to support appropriate submission of stools for CDI testing.

Bristol stool chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Water, no solid pieces, entirely liquid

Source: Gyawali CP. *Gastroenterology Subspecialty Consult.* 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. Adapted from Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 1997;32:920-924.

Consider a laxative vacation

Something else to consider is how laxative use may affect patients' stools. Many studies have shown that constipation is a challenge for the growing population of older adults; some research has shown between 50% and 74% of long-term-care facility residents are on a laxative regimen.[19] A laxative's type and dosage can alter stool

consistency. Are clinicians submitting loose or watery stools for CDI testing from patients whose diarrhea was triggered by laxatives? Two recent studies revealed that 20% to 44% of patients tested for CDI were on a laxative regimen, which may have been the true cause of their diarrhea.[15]

Many healthcare settings are now evaluating patient medications and stopping laxative administration for 24 to 48 hours to see if the diarrhea resolves before submission of stool for CDI testing. This laxative vacation could potentially decrease misidentifying noninfectious *C. difficile* colonization as CDI, which could lead to unnecessary treatment.

Take steps to prevent transmission

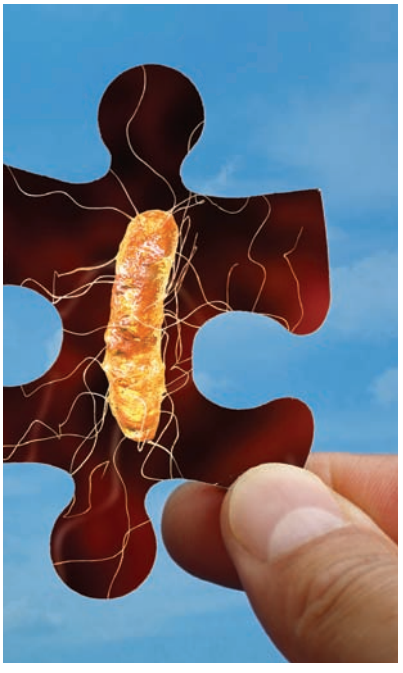
Optimal hand hygiene and appropriate glove use remain the cornerstone for preventing *C. difficile* transmission via the hands of healthcare workers. Before contact with a patient with CDI, nurses and other healthcare personnel should perform hand hygiene, then don gloves. Following contact with a patient with CDI, healthcare personnel should remove gloves, then perform hand hygiene. Follow these guidelines to reduce risks.[20-22]

- Because alcohol does not kill *C. difficile* spores, use of soap and water for hand hygiene is more effective than alcohol-based hand rubs. However, according to the CDC, some data suggest that even with soap and water the removal of *C. difficile* spores is more challenging than the removal or inactivation of other common pathogens. In addition, alcohol-based products are more effective than soap and water for inactivating nonspore-forming bacteria.[20]

Any theoretical benefit from instituting a soap-and-water hand hygiene protocol must be balanced against the potential for decreased compliance resulting from a more complex hand hygiene routine. Consequently, although performing hand hygiene with either soap and water or an alcohol-based product is acceptable in routine situations, soap and water is preferred during a *C. difficile* outbreak to prevent spore transmission. In addition, hand hygiene with soap and water is recommended after any nursing care that may involve fecal contamination.[20,21]

- Patients with known or suspected CDI should be placed on contact precautions in private rooms with dedicated toileting facilities. If private rooms are limited, patients with fecal incontinence should be prioritized. If private rooms are not available, patients can be placed in rooms with other patients with *C. difficile* infection (cohort). Dedicate or ensure proper cleaning of any shared medical equipment.
- Don gloves and gowns before entering patients' rooms and remove them before leaving the patient's environment. Perform hand hygiene after removing gloves.[22]

Continue these precautions until diarrhea ceases. Because patients shed the organism for days after diarrhea resolves, some institutions routinely continue isolation for several days beyond symptom resolution or until discharge depending upon the setting and average length of stay.[21]



Could you be holding the missing piece of the CDI puzzle in your facility?

Seeing the whole picture

Solving the puzzle of CDI in healthcare is complicated. Among the many challenges are a narrow and nonclinical lab identification, regulatory definition, varied CDI testing methods available, and the subjective assessment of CDI symptoms such as diarrhea. Accurate CDI lab identification increases the chances that patients are treated only for CDI infection, not colonization. It also creates an accurate picture of CDI in healthcare facilities, which will allow those examining and evaluating that data to react with interventions that are useful and meaningful.

Early recognition is sometimes a missing puzzle piece. However, astute nurses can recognize the signs and symptoms of CDI and advocate for submission of appropriate stool specimens for testing in a timely manner to assure early identification and treatment for patients. By carefully selecting stool for CDI testing and taking into account the patient's clinical status, clinically significant diarrhea, and laxative use before testing, nurses can help confirm true CDI in healthcare facilities with more accuracy.

Could you be holding the missing piece of the CDI puzzle in your facility? ■

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