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The Role of Diagnostic Stewardship in *Clostridioides difficile* Testing: Challenges and Opportunities

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Abstract

Purpose of Review—Accurate and timely diagnosis of *Clostridioides difficile* infection (CDI) is imperative to prevent *C. difficile* transmission and reduce morbidity and mortality due to CDI, but CDI laboratory diagnostics are complex. The purpose of this article is to review the role of laboratory tests in the diagnosis of CDI, and the role of diagnostic stewardship in optimization of *C. difficile* testing.

Recent Findings—Results from *C. difficile* diagnostic tests should be interpreted with an understanding of the strengths and limitations inherent in each testing approach. Use of highly sensitive molecular diagnostic tests without accounting for clinical signs and symptoms may lead to over-diagnosis of CDI and increased facility CDI rates. Current guidelines recommend a two-step, algorithmic approach for testing. Diagnostic stewardship interventions, such as education, order sets, order search menus, reflex orders, hard and soft stop alerts, electronic references, feedback and benchmarking, decision algorithms, and predictive analytics may help improve use of *C. difficile* laboratory tests and CDI diagnosis. The diagnostic stewardship approaches with the highest reported success rates include computerized clinical decision support (CCDS) interventions, face-to-face feedback, and real-time evaluations.

Summary—CDI is a clinical diagnosis supported by laboratory findings. Together, clinical evaluation combined with diagnostic stewardship can optimize the accurate diagnosis of CDI.

Introduction

Clostridioides difficile infection (CDI) is the most common cause of healthcare associated diarrhea in the United States [1, 2]. It can be either a community or a healthcare acquired pathogen capable of causing clinical syndromes ranging from asymptomatic colonization to fulminant colitis, and death [3, 4]. In the early 2000s, the incidence of CDI steadily increased, but more recently rates have leveled off, with 15–25% of health care-associated diarrhea attributable to CDI [4–7]. In 2017, 223,900 cases and 12,800 deaths were associated with CDI, and the health care costs of CDI are estimated to be $10,000 per CDI case and $1 billion attributable healthcare cost annually [1, 8, 9].

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Conflict of Interest

All other authors declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Given the staggering morbidity and mortality associated with CDI, the accurate and timely diagnosis of CDI is imperative to prevent transmission, start appropriate therapy, and improve patient outcomes. CDI is a clinical diagnosis that is supported by laboratory and imaging findings [10, 11]. It is estimated that 4–15% of hospitalized patients and close to 50% of long-term care patients are colonized with toxigenic *C. difficile*, meaning that the organism is present without any clinical signs and symptoms consistent with actual CDI [12]. Laboratory testing can indicate the presence or absence of *C. difficile* or its toxin, and should be taken into consideration with the clinical presentation [13]. Further complicating the clinical scenario, many hospitalized patients commonly develop diarrhea for non-infectious reasons, making the clinical decision to test for, and diagnose CDI, a complex one. An important challenge is determining which patients do, and do not have infection, given that *C. difficile* colonization is reported to be five to ten times more common than actual CDI [13]. The purpose of this article is to review the role of laboratory testing in the diagnosis of CDI, and the role of diagnostic stewardship to optimize *C. difficile* testing.

C. difficile Diagnostic Tests: Overview

Currently, there are many possible options for testing for *C. difficile.* A summary can be found in Table 1. Cell culture cytotoxicity neutralization assay (CCCNA) and toxigenic culture (TC) have long been considered the standards for *C. difficile* identification [3, 7]. CCCNA detects toxin B as well as toxin A, to an extent, in the stool. It involves the application of stool filtrate on a monolayer of cells and observation of a toxin-induced cell cytopathic effect (CPE) [3]. If CPE is observed, then a neutralization assay is performed to ensure that cytopathic effect is secondary to *C. difficile* and not a nonspecific toxicity [3]. TC relies on isolating the *C. difficile* organism from stool, growing it in culture, and determining whether it is toxin producing using either CCCNA or toxin immunoassays [3]. Enzyme immunoassays (EIA) detect toxin A and B using monoclonal or polyclonal antibodies against the toxin [14]. Early EIAs solely detected toxin A; however, recommended assays now detect both toxin A and B [3]. Glutamate dehydrogenase (GDH) is an antigen that is produced by all isolates of *C. difficile* whether they are toxin producing strains or not [3]. Both EIAs and GDH assays can be performed directly on stool. Nucleic acid amplification testing (NAAT) using PCR was approved by the FDA in 2009 [3]. Gene detection depends on the specific NAAT used. Currently available assays can detect *tcdA*, *tcdB*, *cdt*, and the deletion at nucleotide 117 on *tcdC*. This deletion is a surrogate marker for the identification of 027/NAP1/B1 strains [3].

Current Challenges in CDI Diagnosis

Currently available tests have the ability to detect *C. difficile*; however, because CDI is a clinical diagnosis, all results must be interpreted in conjunction with the clinical scenario and pre-test probability for CDI [10]. Each of the available laboratory tests *for C. difficile* has notable strengths and weaknesses, and thus there continues to be controversy about the optimal method for diagnosing CDI. The sensitivity and specificity vary among each test modality, but it is important to focus on the positive predictive value (PPV) and negative predictive value (NPV) as well. Positive predictive value is the likelihood that patients with a positive test truly have the disease and negative predictive value is the likelihood that

patients with a negative test do not have the disease. The PPV of a test is affected by the prevalence of CDI. The prevalence of CDI in hospital settings is higher than in the community. Increased awareness of CDI may lead to increased testing without an increase in the prevalence [5, 15]. This can lead to increases in false-positive results and difficulty identifying colonization versus actual disease [15–18].

CCCNA and TC are laborious and have long turnaround times; these drawbacks limit their use clinically where timely diagnosis of CDI is necessary in order to initiate appropriate therapy. Additionally, the sensitivity of CCNA is considered low, ranging from 65–90%, with a PPV of 50–87%, and NPV of 97–99% [3, 19]. By contrast, TC is extremely sensitive, has a PPV ranging from 57–91%, and NPV of 87–97% [3]. TC does not, however, detect the actual presence of toxin but only of the presence of toxin producing genes [3].

For many years, EIA toxin testing was favored by hospital laboratories over culture given the faster turnaround times and the detection of toxin correlated with clinical disease [20, 21]. Its PPV ranges from 50–92% but the NPV ranges from 78–100%, making false-negative results unlikely [3, 5, 15] The primary concern with exclusive use of toxin EIAs for CDI diagnosis is the potential that CDI cases may be missed due to the low sensitivity of the test. While reported EIA sensitivity is often high, it also has been reported to be as low as 40% [3].

The remaining *C. difficile* diagnostic tests, GDH and NAAT, are both fast and sensitive, and their use (particularly NAAT) has increased dramatically in recent years. Since 2009, NAAT testing for the toxin gene is now the most commonly used methodology, after concerns that patients with CDI were being missed by toxin tests [20, 22]. Both tests have high sensitivity and NPV (sensitivity 80–100% for GDH and 98–99% for NAAT; NPV 97–100% for GDH and 95–100% for NAAT). [3]. The primary limitation to both GDH and NAAT is the potential for over-diagnosis of CDI due detection of asymptomatic *C. difficile* colonization. GDH detects the presence of the organism but does not distinguish between toxigenic and non-toxigenic strains. Similarly, NAATs detect the presence of a toxin-producing gene but not necessarily production of toxin itself. Thus, neither test is able to distinguish between asymptomatic colonization and clinical disease. While GDH has not been widely used as a stand-alone test for CDI, NAAT certainly has.

Importantly, the current IDSA/SHEA guidelines do not recommend the use of NAATs alone unless institutional policies are in place to ensure appropriate selection of patients for *C. difficile* testing. The primary concern regarding use of stand-alone use of molecular *C. difficile* diagnostic tests such as NAATs is the potential for patients asymptomatically colonized with *C. difficile* to be diagnosed with CDI and treated as such as a result of a positive laboratory test. In the absence of clear clinical requirements for *C. difficile* testing (e.g., clinically significant diarrhea with no alternate cause), use of a standalone NAAT for *C. difficile* diagnosis may result in significantly higher CDI rates. Moehring et al quantified the increased incidence of CDI after switching to molecular testing at nonteaching community hospitals [23]. In the study, 10 hospitals switched to PCR and 22 control hospitals continued using nonmolecular testing. They noted a 56% increase in CDI incidence among hospitals that switched to PCR [23]. This finding was also supported in a

study from a tertiary care teaching hospital in Quebec City that found an increase in CDI incidence of greater than 50% when PCR alone was used for diagnosis as opposed to a 3-step algorithm [24].

Besides the problem of over-reporting CDI with NAAT testing, there are also patient safety concerns. Treating patients who are colonized can lead to the development of multidrug-resistant organisms, reduced gut microbial diversity, and increased risk for CDI after completing treatment [20, 25, 26]. Contact precautions are also associated with anxiety and depression as healthcare workers have been found to interact less with those in isolation [13]. Thus, the accurate diagnosis of CDI is imperative to direct patient care.

The accurate reporting of CDI rates is a high priority for hospitals, as this is publicly reportable data. The CDC's National Healthcare Safety Network (NHSN) began the laboratory-identified (LabID) reporting module for HO-CDI in 2009 [25]. HO-CDI for purposes of LabID reporting is defined as a positive laboratory test for *C. difficile* toxin from an unformed stool specimen greater than 3 days after admission and greater than 8 weeks after most recent CDI LabID event [25]. Although this definition of HO-CDI had the advantage of being clear and easy to use, it may have led to overreporting of CDI because it was likely including colonized patients in hospitals using NAATs. NHSN now utilizes a risk adjustment formula depending on the diagnostic method used that was designed to address this issue [27]; however, Marra et al evaluated this risk-adjustment formula at an academic center and found that the standardized infection ratio (SIR) for HO-LabID-CDI was almost double for NAAT (0.95) compared to EIA (0.50) [28].

The accurate diagnosis is also important when used for research and immunotherapy standpoint. One study noted that clinical trials of new therapies for CDI could have failed to meet the primary outcomes based on diagnostic issues associated with PCR use alone [29]. The authors cautions that the poor predictive value of *C. difficile* PCR may be undercutting the actual therapeutic benefit of new therapies in clinical trials [29]. The importance of accurate diagnosis of CDI cannot be understated.

Because of the complexities of the issues surrounding *C. difficile* diagnostics, international and United States (US) guidelines currently recommend the use of a multi-step algorithm for *C. difficile* testing [30, 31]. This algorithm includes the use of GDH plus a toxin EIA, GDH plus a toxin EIA followed by NAAT if discordant results, or NAAT plus toxin rather than NAAT testing alone [30]. The purpose of these two-step algorithms is to maximize the strengths of each test and minimize the risk of either over-diagnosis of CDI due to detection of asymptomatic colonization or under-diagnosis due to low sensitivity of some tests.

The use of two-step diagnostic algorithms begs the obvious question of how clinicians should interpret discordant results (primarily patients whose stools is NAAT positive, EIA negative). Some data indicate that patients with positive EIAs may be at increased risk of severe CDI and negative outcomes compared with patients whose stool was NAAT positive but EIA negative [10, 20, 32]. Polage et al found that outcomes in patients who were PCR positive but toxin negative, were comparable to patients without CDI (no positive laboratory test for *C. difficile*). These patients also had milder symptoms and shorter duration of

diarrhea than patients who were positive for both PCR and toxin EIA [20]. This finding has also been supported by other studies including other tertiary care, university affiliated centers [10, 32]. Kwon et al evaluated 111 patients for the pretest probability of CDI in relation to the assay result at a single site academic center. Seven patients were EIA negative but TC positive; none of these patients developed CDI or died within 90 days of testing [10]. In a multisite study, 4878 cases of CDI were diagnosed using GDH and EIA toxin followed by PCR only for GDH and toxin discordant results, and it was found that toxin positivity when compared with NAAT positivity was associated with prior antibiotic exposure in the preceding 12 weeks, prior hospitalizations, long-term facility stays, and more virulent *C. difficile* strains. Toxin positivity was also more likely than NAAT positive patients to have pseudomembranous colitis, white blood cell counts greater than 15 cells/μL, and albumin less than or equal to 2.5 g/dL. [33]. Other studies have shown mixed results in regard to mortality. Some report higher mortality in toxin positive patients, but in these cases there was no adjustment for potential confounders [20, 34]. Other studies have also found no difference in mortality between toxin positive and NAAT positive patients [24, 35].

However, better outcomes have not been observed in all patients with positive PCR and negative toxin tests. The two-step algorithm has also been assessed in immunocompromised individuals including those with a history of transplant, malignancy, active chemotherapy or immunosuppression, and decompensated cirrhosis. Some studies have reported low toxin positivity rates in immunocompromised individuals for unclear reasons but have hypothesized that this could be secondary to microbiome disruption from immunosuppressive and chemotherapeutic agents [36]. One study of patients from a tertiary care center and a cancer care center sought to evaluate the algorithmic approach in immunocompromised patients by testing with either PCR or GDH/toxin combination lateral flow assay. Their results showed that GDH has a sensitivity of 85% when used for screening [37]. Evaluation of these patients who were GDH-negative and PCR-positive still showed that they had diarrhea and other risk factors for CDI. They therefore were hesitant to adopt the 2-step algorithm and completely exclude NAAT only positive patients as colonized [37].

Key Areas of Focus for CDI Diagnostic Stewardship

Diagnostic stewardship modifies the process of ordering, performing, and reporting diagnostic tests to improve treatment of infections [38]. The goal of diagnostic stewardship for *C. difficile* testing is to encourage the rational use of *C. difficile* testing, improving the appropriate diagnosis of true CDI and reducing inappropriate testing and false positive results. Given the limitations associated with currently available *C. difficile* diagnostics and the challenge of differentiating between *C. difficile* colonization and CDI, diagnostic stewardship is necessary to optimize patient care. False positive tests for *C. difficile* can lead to inappropriate antibiotic use, prolonged hospital stays, increased healthcare costs, patient harm, and a paradoxical increase in the risk for true CDI [20, 39, 40]. The negative consequences of treating patients who are asymptomatically colonized or have a noninfectious cause for their diarrhea includes inducing CDI, increasing spore shedding which leads to increased transmission, unnecessary antibiotic use, antibiotic resistance, and decreased patient satisfaction with contact precautions [41]. Diagnostic stewardship

interventions take many forms, as noted in Table 2, and some key targets for stewardship are discussed below.

Patient Selection for Laboratory Testing

Healthcare facilities should ensure that patients whose stool is tested for *C. difficile* meet appropriate clinical guidelines, which include the presence of new onset, clinically significant diarrhea (≥3 unformed stools in 24 hours) that cannot be otherwise explained [30]. Laboratory testing should only be done on liquid stool and formed stool should not be tested. Ensuring appropriate selection of patients for *C. difficile* testing can be challenging, both for individual clinicians and for institutions. One study from an academic center retrospectively evaluated all cases of hospital onset *C. difficile* infections (HO-CDI) for one year to determine appropriateness of *C. difficile* testing. Only 19.6% could be classified as appropriate based on their criteria, with 14.8% classified as inappropriate and 65.5% as indeterminate. During that year, the HO-CDI standardized infection ratio (SIR) was 0.962, but if those tests classified as inappropriate were removed, the SIR would have been 0.819 [42]. Another study from an academic center found that on retrospective review, only 58% of HO-CDI were able to be classified as true infection [43]. They determined that reasons for non-true HO-CDI were lack of clinically significant diarrhea, laxative use, and delayed testing [43]. Some of the primary issues surrounding diagnostic stewardship and selection of patients for testing are discussed in more detail below.

Laxative Use

Laxative use is one of the most common alternate causes of diarrhea among patients tested for *C. difficile*. Some studies report laxative use in 14–50% of specimens submitted for *C. difficile* testing [5, 9, 10, 44]. Although some patients who are on laxatives may also have concurrent CDI, many patients may have diarrhea due to laxative use and are only colonized with *C. difficile*, without true CDI [10]. Given this, laxative use is an optimal target for intervention to prevent unnecessary testing. A case-control study at 5 hospitals noted that 9.8% and 13% of *C. difficile* testing was done on patients receiving laxatives 24 and 48 hours prior to testing [41]. Laxatives were continued for 24 hours after a sample was submitted for *C. difficile* testing 7.6% of the time and 11% of the time 48 hours after testing [41]. Similarly, Ahmad et al found that 39% of patients receive laxatives within 7 days of *C. difficile* testing, 14% received laxatives within 24 hours of testing and 52% continued to receive laxatives greater than 24 hours after testing [9].

Repeat Testing

Due to concerns of the low sensitivity of some *C. difficile* EIA tests, a common clinical practice is the “repeat x3,” or consecutively repeating *C. difficile* EIA testing in attempt to increase diagnostic yield [11, 15]. Repeat testing for *C. difficile* has been common for decades but is not recommended due to the lack of diagnostic value, risk of over diagnosis, and increased costs as a result [30]. This occurs because with each repeat test, the prevalence of CDI in the population decreases, and the PPV of the test decreases with each repeat test. Furthermore, studies have indicated that repeat testing within 48 hours had low diagnostic yield [15, 45–49]. Cardona et al reported that 0.9% of cases had a positive response if performed on the same day and 1.8% were positive if performed on the next day [45]. In a

study prompted by a pseudo-outbreak at an academic center, the investigators found that repeat testing led to increases in false positive test results because of a decrease in prevalence [50]. The PPVs of the second and third *C. difficile* tests were 30% and 4% [50]. In light of these studies, repeat testing was not found to be clinically helpful and was discouraged [51].

Sending repeat stool testing for PCR after a negative result has also been evaluated and is not recommended given the high sensitivity associated with NAAT [49, 52]. A study from an academic center noted that only 1% of repeat testing was positive [53]. The only variable in the study that was independently associated with a positive NAAT result within 7 days was a history of prior CDI [53]. Other studies have also noted similar results [54]. A common theme that reemerges with unnecessary testing is also the concern of cost [52]. One study evaluated the cost of repeat PCR and oral vancomycin therapy and found that out of 5,027 PCR tests in 3 years, 4,213 were negative and 97 patients were retested two or more times after a negative result with only 0.05% later being positive [55]. In the 97 patients, a third were also continued on empiric oral vancomycin for a mean of 8 days [55]. The costs of these repeat tests and antibiotic treatment was combined to be $94,624 [55]. As the value of repeat PCR testing has clearly not been shown to be beneficial and is associated with increases costs to the patient and healthcare system, and potentially unnecessary exposure to antibiotics, this is an area for a diagnostic stewardship intervention.

Strategies to Improve Diagnostic Stewardship

Given the importance of the accurate and timely diagnosis of CDI, interventions to improve diagnostic stewardship are of utmost importance. Interventions may be targeted towards clinicians, laboratories, or both. The main types of interventions includes education, order sets, order search menus, reflex orders, hard vs. soft stop alerts, electronic references, feedback and benchmarking, decision algorithms, and predictive analytics [56]. A summary of the literature of interventions used can be found in Table 2.

Interventions to Improve Documentation of C. difficile Symptoms in the Electronic Medical Record (EMR)

As previously discussed, CDI is a clinical diagnosis supported by laboratory findings. However, the frequency, consistency, and quantity of diarrhea is not always clear, and is dependent on the patient's ability to recall bowel movements. Furthermore, it is not uncommon that diarrhea is poorly documented in the EMR. This poor understanding and documentation of stool consistency leads to confusion and can lead to inappropriate testing [5, 42]. Improving documentation of stool characteristics can be leveraged for *C. difficile* diagnostic stewardship.

Tuong et al reported a successful intervention that reduced laxative use and unnecessary *C. difficile* testing [57]. Nursing staff were trained to record consistency of stools in the EMR. Real-time data tracking was done for dates and times of bowel movements, stool consistency, and recent laxative use. Laboratory personnel were allowed to cancel tests for patients who did not meet criteria for diarrhea related to CDI [57]. This intervention led to significantly reduced HO-CDI and frequency of oral vancomycin use without differences in

complication rates between patients who had cancelled tests and those who tested negative for *C. difficile* [57].

Interventions to improve documentation would require EMR infrastructure to support such documentation, paired with educational programs to encourage documentation. Limitations associated with interventions to improve documentation include limited care provider time and potential lack of adherence to documentation.

Use of Electronic Decision Support Tools

Many interventions to improve adherence to *C. difficile* testing guidelines may involve the use of electronic support tools. Many studies have tried the use of a computerized clinical decision support (CCDS) tool incorporated into the EMR [58, 59]. CCDS tools may be either "soft stop," which may provide education and guidance about *C. difficile* testing best practices but allow clinicians to bypass the recommendations, or "hard stop," which do not allow a *C. difficile* test to be ordered under pre-set, specified guidelines [56].

Studies that involved CCDS using a "hard stop" intervention or financial incentives have reported more success in reducing inappropriate *C. difficile* testing [60–62]. Mizusawa et al noted that providers tended to not follow a "soft-stop" but did follow a "hard-stop" [62]. Kwon et all noted that a hard stop for repeat *C. difficile* EIA testing within 96 hours of a prior negative test led to significant decreases in CDI testing rates and mean number of tests per admission [11]. Quan et al performed a pre- versus post-intervention study to evaluate clinician *C. difficile* testing habits. The intervention involved computer physician order entry (CPOE) alerts if patients did not meet appropriate testing criteria (diarrhea, no alternative cause for diarrhea, no laxative use within 24 hours, no previous CDI testing within 7 days, and age >1 year). The authors found that the CPOE alert resulted in a decreased rate of *C. difficile* testing and a decrease in tests ordered on patients receiving laxatives [60]. This highlights that fact that passive alerts from the electronic health record (EHR) can easily be ignored, however, CPOE alerts prevent overrides without appropriate approval from infectious disease or GI consultants.

Madden et al performed a quasi-experimental cohort study to evaluate the rates of CDI testing also using a soft stop CCDS tool. The 2-part CCDS tool notified providers when *C. difficile* had been tested for previously within 28 days and then listed a series of questions with the intent of helping the provider decide whether testing was appropriate. CDI testing decreased by 41% after the tool was implemented, duplicate results were significantly reduced, and hospital-onset CDI decreased by 31% [63]. These authors also performed a cost analysis and documented a savings of $61,524 annually due to reductions in unnecessary treatment and testing [61].

There have been several studies evaluating tools to reduce testing in the setting of laxative use [12, 44, 57, 64, 65]. Buckel et al utilized education along with pharmacist feedback for each patient who had a positive PCR or was receiving anti-CDI antibiotics [44]. Overall laxative use within 48 hours prior to sending the stool sample significantly decreased from 44% to 27% [44]. In a study of a multihospital academic health system, providers were required to use an order set for CDI testing [59]. This order set identified patients receiving

laxatives within the prior 36 hours. Clinicians then could discontinue laxatives and not continue order, discontinue laxatives and proceed with order, or proceed with order without discontinuing laxatives. This tool was associated with a significant decrease in the proportion of inappropriate *C. difficile* tests and increases in the proportion of patients with laxatives discontinued at the time of order placement [59]. Sperling et al were also able to reduce *C. difficile* testing by 42% without adverse patient impacts using EMR clinical decision support that required clinicians to answer questions about number of loose stool in 24 hours, laxative use in the prior 24 hours, and whether the patient was on tube feedings and had abdominal pain, fever, or elevated white blood cell count [65].

Another strategy that has been employed is using best-practice alerts (BPA). However, this strategy has not been associated with much success and failure has been attributed to “alert fatigue” [66]. Given the high volume of alerts a clinician can received during the day, there is risk that they will not be able to distinguish more important alerts from those that are less so [67]. One study reported that providers chose to override the BPA 75% of the time which was consistent with other studies [67–69]. BPAs have been found to be more successful when consultation by and infectious disease physician is required to override unnecessary testing [70].

Given that CCDS interventions may be a change in practice, they are frequently paired with educational campaigns to ensure proper awareness among clinicians and/or laboratory personnel about the purpose of the intervention. CCDS interventions should also be designed with some degree of flexibility. There are certainly times that repeat testing can be indicated, especially with worsening diarrhea or clinical syndromes consistent with CDI. For any hard stop limitation, measures should be in place to allow tests to be ordered in the appropriate clinical scenario. For example, a clinician may be able to call the laboratory or appropriate personnel to bypass the hard stop if clinically indicated. Information on who to contact or how to bypass the hard stop should be clearly noted on the hard stop alert.

Education, Feedback, and Collaboration

Education and feedback are equally important interventions. They provide clinicians with the necessary background and reasoning for why changes are being implemented. A multicenter study from Catalonia noted concern for low diagnostic suspicion of CDI in Europe with varying incidence and diagnostic methods across different countries [71]. They evaluated CDI rates and appropriate diagnostic methodology using online courses, in-person workshops, and dissemination of CDI recommendations on prevention and diagnosis. They found an increase in HO-CDI, non-nosocomial healthcare-related CDI (defined as infection starting in the community or within 48 hours of admission, in patients admitted to a health center in the 4 weeks prior to symptom onset), and community-acquired CDI (indicating poor knowledge and under testing of CDI prior to the intervention). They also noted a significant increase in the use of optimal diagnostic algorithm defined as a two- or three-step algorithm in hospitals that were previously using non-optimal testing [71].

The importance of education regarding appropriate testing is highlighted in a study by Kavazovic et al [72]. A nurse-driven protocol consisting of 4 criteria for *C. difficile* testing (three or more watery stools within 24 hours, no laxatives within 24 hours, no alternative

explanation, and zero positive *C. difficile* tests within 7 days) was implemented at an academic center. All stool specimens were testing using PCR and test fidelity was determined retrospectively. They found that 321/3474 *C. difficile* tests were ordered via the protocol and 10% were positive. Of the positive cases, 72% met the NHSN LabID definition of HO and 70% of these HO cases did not meet testing criteria [72]. Because of poor test fidelity this intervention was discontinued after one year. This study is a clear example of the consequences of inappropriate *C. difficile* testing and why individual patient assessment and knowledge regarding who and who should not be tested for CDI is so important.

Other non-electronic strategies used to improve *C. difficile* diagnostic stewardship include didactics and in-person feedback [65, 71, 73, 74]. A study of face-to-face feedback for providers along with education noted significant improvement in bowel movement documentation, suboptimal use of antibiotics for non-*C. difficile* infections, and proton pump inhibitor (PPI) use [73]. However, treatment of *C. difficile* colonization (defined as positive NAAT without greater than or equal to 3 bowel movements per day or an alternative cause for diarrhea and no fever, abdominal pain, or leukocytosis) improved, but was not statistically significant, and laxative use remained unchanged [73]. Feedback was accepted by the treating physician in 43% of cases. The authors noted that face-to-face feedback was more effective than feedback via phone [73].

Schultz et al found significant success in reducing *C. difficile* testing and HO-CDI through the use of a multidisciplinary team that included representatives from hospital epidemiology, performance improvement and patient safety, clinical microbiology, antimicrobial stewardship, pharmacy, environmental services, nursing, patient equipment, and hospital administration [74]. In total they implemented eight categories of interventions including diagnostic stewardship, electronic tools, education, isolation precautions, hand hygiene, environmental cleaning, antimicrobial stewardship, and pharmacy, and found their HO-CDI Lab ID rate decreased significantly to 6.3 infections per 10,000 patient days from 11.0 infections per 10,000 patient days and estimated a cost savings of $300,600 [74]. While they were unable to attribute this success to one specific intervention, the multidisciplinary approach was likely more successful than if single interventions were employed. Sperling et al incorporated EMR support (prompting to answer yes or no questions about stool frequency, laxative use in the last 24 hours, if on tube feeds and abdominal pain, fever, or elevated white blood cell count) and real-time monitoring by laboratory and infection preventionists and also found a reduction in testing rate, HO-CDI Lab ID rates, and the days of oral vancomycin therapy, but note that generalizability is limited and long term sustainability of real-time monitoring is resource intensive [65].

Real-time physician evaluation is another strategy that has been tested. One academic center evaluated infectious diseases (ID) specialist-led approval for *C. difficile* testing [75]. This center reported that they had previously tried using a CCDS tool that discouraged inappropriate testing but found that the BPAs were frequently ignored. Thus, they created an intervention wherein all CDI testing on hospital day four or later required mandatory approval by an ID specialist. This study found that HO-CDI testing and rates significantly declined after the intervention [75]. As noted above, real-time monitoring can be resource

intensive, however; this study reported there was a mean of 1.3 pager approvals per day with a range of 0–4 and took on average three minutes per approval [75].

Emerging Areas for Diagnostic Stewardship: NAAT Cycle Threshold Value and Ultrasensitive Assays

Because of the continued struggle to accurately diagnose CDI and avoid diagnosing those who with *C. difficile* colonization but without true CDI, some studies have begun to evaluate the use of NAAT cycle threshold as a component of diagnostic stewardship. A study from the UK found that low cycle threshold (CT) value was independently associated with toxin EIA positivity, higher mortality, and CDI severity [21]. Findings of lower CT values associated with the presence of toxin and increased CDI severity were also supported by Kamboj et al [76]. Because of this study, Madden et al decided to determine if CT values could identify patients with lower probability of disease. CT values for tests that were ordered appropriately were compared to those ordered inappropriately (based on their CCDS tool) [77]. They found that CT values were significantly higher in the inappropriate test group and the strongest predictor of an increased value was a repeat negative test [77]. However, not all studies have shown that CT value can adequately assess or predict negative outcomes and note that differences in mean CT values in patients with and without recurrence or a poor outcome were subtle, not generalizable, and should not override clinical decision making [78, 79]. Use of CT values in diagnostic stewardship is intriguing, but current studies have shown varying results and more definitive data is needed before promoting this as a testing modality.

A new diagnostic tool has also been developed to help with the continued dilemma regarding which patients truly have CDI and which are colonized. An ultrasensitive assay for quantification of *C. difficile* toxins with single molecular array is capable of detecting and quantifying *C. difficile* toxins A and B with an analytical cutoff of 1pg/μL and a clinical cutoff of 20pg/μL [80, 81]. These assay sensitivities are magnitudes higher than any other commercial assay and were thought to have the potential to be a standalone test and replace multistep algorithms [82]. One study hypothesized that using this technology, concentrations of toxin A and B would be higher in stool samples from patients with CDI than those who are colonized. However, this was not found to be the case. Toxin concentrations could not distinguish between CDI patients diagnosed with NAAT versus EIA and had substantial overlap [80]. Sandlund et al sought to evaluate the diagnostic accuracy of ultrasensitive *C. difficile* toxin assays. 298 patients with suspected CDI were tested using NAATs and ultrasensitive assays and discordant results were tested with CCNA. They reported that the ultrasensitive assay had a specificity of 97.4% and PPV of 78.1% and NAAT had 89% specificity and 54.7% PPV if assumed that all NAAT negative patients did not have CDI [83]. The proportion of overdiagnosis was three times higher in the NAAT positive and toxin negative group that in the NAAT and toxin positive group [83]. The use of ultrasensitive toxin detection has the potential to reduce overdiagnosis of CDI that has been associated with NAAT use, however, further studies are needed to evaluate this hypothesis.

Conclusions

Despite years of debate and investigation regarding the best testing strategy to diagnose CDI, there is no laboratory test alone that can distinguish between CDI and *C. difficile* colonization [21]. We know that the first step in appropriately diagnosing CDI relies on identifying patients with clinical symptoms consistent with the disease, but identifying the appropriate clinical syndrome is not a straightforward task. Given the importance of making an accurate diagnosis of CDI, diagnostic stewardship is necessary to ensure the rational use of *C. difficile* tests.

The backbone of diagnostic stewardship interventions include education to healthcare personnel regarding the pathophysiology of CDI and published guidelines for *C. difficile* testing. Of the interventions in the literature that have been discussed, CCDS interventions, face-to-face feedback, and real-time evaluations have been the diagnostic stewardship interventions with the best reported success rates.

CDI results in significant morbidity, mortality and cost to patients and the healthcare system. Therefore, the accurate diagnosis of CDI is of the utmost importance. While it is important to keep CDI on a differential for diarrhea, especially in the healthcare setting, attention should be focused on timing of clinical symptoms, frequency and consistency of stool, and thorough evaluation of noninfectious causes for diarrhea. Only once the appropriate clinical syndrome is identified should testing for CDI be carried out. Together, the clinical evaluation combined with diagnostic stewardship interventions can optimize the accurate diagnosis of CDI.

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Table 1.

Strengths and Weakness of *C. difficile* Tests [3, 7]

Test	Strengths	Weaknesses	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cell culture cytotoxicity neutralization assay	Detects presence of toxin	Poor sensitivity Prolonged turnaround time	65–90%	96–100%	50–87%	97–99%
Toxigenic Culture	Commonly considered the gold standard in method comparison	Detects toxin gene Prolonged turnaround time	80–100%	93–97%	57–91%	87–97%
Enzyme-linked immunosorbent assay	Detects presence of toxin Low cost Fast turnaround time	Variable sensitivity	40–100%	84–100%	50–100%	78–99%
Glutamate Dehydrogenase	Detects presence of antigen	Produced by both toxigenic and nontoxigenic strains	87–100%	76–98%	71–91%	97–100%
Nucleic acid amplification test	Detects presence of gene	Concern for overdiagnosis and detection of *C. difficile* colonization	83–100%	87–98%	46–94%	96–100%

Table 2.

Clinical Decision Support Diagnostic Stewardship Interventions

Category	CDS Intervention	Example	Intervention	Reported Results/Outcomes
Education	Electronic references	Sopena et al [71]	Online course for healthcare personnel on epidemiology and clinical manifestations of CDI, diagnosis of CDI, transmission, prevention, treatment.	Statistically significant increase in overall incidence of HO-CDI and community acquired CDI. Statistically significant increase in use of optimal diagnostic algorithm.
	Preanalytical/ Laboratory based	Truong et al [57]	Laboratory personnel rejected formed stool, repeat orders within 7 days, laxative use within 48 hours, and less than 3 unformed stools in 24 hours.	Statistically significant decrease in HO-CDI rates and vancomycin utilization. No increase in CDI-related complications for patients with cancelled tests.
		Yen et al [39]	NAAT orders cancelled by laboratory if stool sample not received within 24 hours of order placement, or if the stool was formed.	HO-CDI-SIR significantly lower statistically. Average number of total tests decreased.
		Lin et al [75]	All CDI testing on hospital day four or later required mandatory approval by an ID specialist.	HO-CDI testing and rates significantly declined statistically after the intervention. There was a mean of 1.3 pager approvals per day, with a range of 0–4. Each call took on average three minutes.
Test Ordering	Order set modification/ reflex orders and cascade ordering	Revolinski et al [66]	Order set for guidelines for treatment of CDI based on mild, moderate, severe, severe-complicated, and recurrent disease.	Only noted one use of the order set within 6 months so BPA added when ordering oral vancomycin or NAAT testing. After BPA order added, use increased but guideline compliance unchanged.
		White et al [59]	Providers required to use order set to order *C. difficile* testing. Providers were alerted to laxative use in the prior 36 hours.	Statistically significant decrease in inappropriate testing. Increase in discontinuation of laxatives in patients with diarrhea. Proportion of patients tested for *C. difficile* did not change.
		Madden et al [63]	2-part CCDS tool showing duplicate orders and questions to ensure appropriate testing.	41% reduction in overall testing. 31% fewer HO-CDI events. Percentage of positive CDI result did not significantly change.
	"Hard" or "soft" stop alerts	Bilinskaya et al [67]	Soft stop BPA for *C. difficile* PCR order if laxative use within 24 hours.	75.4% of alerts immediately overridden. 13.8% initially cancelled then reordered.
		Friedland et al [64]	Soft stop alerts based on stool documentation, laxative use, prior *C. difficile* testing placed in EMR and gave provider decision to cancel testing.	Patients who had *C. difficile* testing were significantly more likely to have diarrhea, less likely to have laxative use, more likely to have documented reason for testing. Clinically indicated testing significantly improved statistically. No change in CDI rates.
		Kwon et al [11]	Hard-stop intervention to limit repeat EIA testing within 96 hours of prior negative and within 10 days of prior positive.	Statistically significant decreases in CDI testing rates and mean number of tests per admission. Overall rate of positive tests did not change. No increases in 30-day mortality. No change in *C. difficile* targeted antibiotics.
		Quan et al [60]	Automated real-time computer order alert for appropriate testing. Any contraindication resulted in a hard stop requiring ID or GI consult.	CDI testing decreased 56%. Testing on laxatives decreased 64%. HO-CDI decreased 54%. Reordered CDI tests decreased by 64%.
		Mizusawa et al [84]	2 step BPA in the setting of laxative use within 48 hours, negative *C. difficile* testing within 7 days, or positive test within 14 days. If first BPA bypassed by clinician, then lab approval required as second BPA.	After CCDS, all hospitals saw significantly reduced testing orders. 15.4% followed the initial BPA and 57.7% followed the second BPA. Fellows and attendings more likely to follow BPA.
		Otto et al [70]	Four hospital information system alerts that *C. difficile* testing was not recommended within 7 days of positive, *C. difficile* testing not recommended within	

Category	CDS Intervention	Example	Intervention	Reported Results/Outcomes
			48 hours of prior negative, stool testing for O&P not recommended after hospitalized for 72hrs. Hard stop for ID consult required to override orders.	Overall volume of *C. difficile* orders increased, but noncompliant orders decreased, and repeat orders decreased.
Diagnostics	Decision support algorithms	Fleming et al [12]	Decision support embedded in EMR. Appropriate testing defined as 3 or more stool in 24 hours, watery diarrhea on days 1–3, no laxative use within 24 hours, and confirmation of fever, abdominal pain, white blood cell count >15/mm^3.	Significant (27%) decrease in total *C. difficile* testing. Significant improvement in appropriateness of CDI testing. Significant reduction in HO-CDI-IR.
		Sperling et al [65	Clinicians had to complete yes/no questions on stool frequency, laxative use in past 24 hours, tube feedings, and abdominal pain, fever, elevated white blood cell count. Clinicians could continue with order regardless of responses. Lab and IP also performed review to make sure stool unformed and patient not on laxatives.	*C. difficile* testing reduced by 42%. HO-CDI LabID rates decreased by 59%. HO-CDI-SIR decreased below CMS threshold. No adverse events noted.
		Madden et al [85]	2-part CCDS with duplicate alert and algorithm questioning regarding presence of diarrhea, symptoms of CDI, or risk factors for infection to encourage appropriate testing.	33% reduction in rates of *C. difficile* testing. Nonsignificant reduction in LabID CDI events. During the intervention, 22.5% were prevented by CCDS and 7.1% rejected by the lab.
	Feedback and benchmarking	Buckel et al [44]	Education to nursing and pharmacy on CDI testing indications prior to intervention involving pharmacy recommendations on testing and CDI treatment.	Laxative use within 48 hours prior to testing and in those with a positive test result showed statistically significant decrease. Overall documentation of stool frequency was not different. Significantly decreased CDI testing and overall CDI rate. Recommendations for not treating asymptomatic colonization deemed unsuccessful.
		Christensen et al [26]	Pre-intervention education on appropriate testing. Intervention included antimicrobial stewardship program prospective clinical review with recommendation to cancel or proceed with testing. Intervention followed by two-step CCDS tool for documentation of diarrhea and prior testing within 7 days.	Mean monthly number of positive NAAT results significantly decreased. HO-CDI-IR and SIR significantly decreased. Decrease in oral vancomycin use.
		Fabre et al [73]	Face-to-face feedback for nurses (stool documentation) and providers (colonization, CDI treatment optimization, stopping unnecessary antibiotics, stopping laxatives and PPIs).	Significant improvement in stool documentation. Suboptimal antibiotic and PPI use significantly decreased. Treatment of *C. difficile* colonization did not significantly change. Laxative use similar.
		Jakharia et al [86]	Weekday review of *C. difficile* orders placed. Samples that did not meet inclusion criteria were discussed with ordering provider. Providers were allowed to override recommendations.	Whole genome sequencing detected a diverse population that lacked clonality. The rate of testing and HO-CDI decreased during intervention. No change in rate of CA-CDI.
		Schultz et al [74]	Eight categories of interventions: diagnostic stewardship, electronic tools, education, isolation precautions, hand hygiene, environmental cleaning, antimicrobial stewardship, and pharmacy intervention.	Significantly reduced HO-CDI, CD testing. HCP compliance with gowning and gloving decreased.