Testing and diagnosis of Clostridioides difficile infection in special scenarios: A systematic review

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Abstract

Aim

To evaluate *Clostridioides difficile* testing and diagnosis in specific patient populations.

Background

*Clostridioides difficile* infection (CDI) is a biochemical and clinical diagnosis. Certain patient populations are at higher risk and testing must be interpreted correctly to avoid overdiagnosis and overtreatment. Consequently, we need to understand the limitations of the tests used to avoid increase morbidity and mortality due to false negative test results. Diagnostic assays should be ordered in a step wise approach in specific patient populations to confirm CDI.

Methods

Manuscripts were extracted from three different databases based on keywords. Data were extracted based on the PRISMA 2020 guidelines. Each manuscript was analyzed using appropriate critical appraisal tools.

Results

A total of 70 reports were evaluated. 18 review articles, 4 retrospective cohorts, 3 guidelines, 1 experimental, and 1 cross sectional study were eligible for inclusion. A total of 27 reports were included.

Discussion

CDI should be considered in all patients with traditional risk factors. Increased clinical suspicion of CDI is required in special populations such as hypogammaglobulinemia, transplant recipients, surgery, and inflammatory bowel disease. Testing should be limited to patients with the clinical manifestations of CDI to ensure a high pre-test probability for test interpretation. Diagnostic assays should follow a sequential, stepwise approach to accurately categorize the toxin expression status of the bacteria.

Introduction

*Clostridioides difficile* (formerly known as *Clostridium difficile*) is a gram positive, spore forming, strict anaerobic bacillus.(1, 2) The organism lives harmoniously in the colon with its growth and production suppressed by normal gut flora. This bacterium was discovered in 1935 and later the first case of antibiotic associated pseudomembranous colitis was diagnosed in 1978. At this time, the strain was
originally named *Bacillus diffciliis* due to its microscopic appearance and difficult cultivation. (3) This organism is a leading cause of gastrointestinal disease and costs the health system 4 billion dollars annually. (2) Since the 20th century, CDI rates have been increasing worldwide with increasing incidence in adults. In 2002, high mortality rates were attributed to a strain called ribotype 027/B1, also known as NAP-1. (3) There was a lack of systematic surveillance for CDI prior to 2003. After the worldwide outbreak of the NAP-1 strain, the Centers for Disease Control and Prevention (CDC) approximated that there were 500,000 CDI cases and 29,000 deaths in the America in 2011. (3) In 2010 study found that 97% of cases were related to healthcare and 75% of these patients had a history of previous hospitalizations. (4) Trends from another study demonstrated incidence increasing from 5.5/10,000 to 11.2/10,000, with more dramatic increases in adults aged adults aged ≥ 65 of age. (4) The emergence of NAP-1 variant of *Clostridioides difficile* (C.diff) has been as high as 30% in hospitalized patients, accounts for more than 300,000 newly diagnosed cases per year, and up to 40% of community acquired infections required hospitalization. (3)

Since the discovery of the NAP-1 strain, testing for C.diff has increased. The virulence of C.diff is from two clostridial toxins, enterotoxin (toxin A) and cytotoxin (toxin B). These toxins are encoded by genes, cdtA and cdtB, on the pathogenicity locus (PaLoc). (2) All strains of C.diff have the ability to ferment and produce glutamate dehydrogenase (GDH) irrespective of toxigenic properties. This has led to the test for GDH which has a sensitivity (Sn) ranging from 79.5–100%, specificity (Sp) of 82.7–100%, negative predictive value (NPV) of 100%. (5) GDH testing does not distinguish between toxigenic and non-toxigenic strains, therefore, a confirmatory test is required for toxin analysis. The best test for detecting toxin production is a toxigenic culture (TC) due to its high Sn and Sp, but due to its turnaround times, other assays are preferred in the modern era. (5–7) The toxin A/B enzyme immunoassay (EIA) is a common confirmatory test which detects antibodies directed against both virulent clostridial toxins. The Sn varies from 53–85% with a Sp of 91–98%. (6) Due to poor Sn, combination of rapid turn-over tests and a multi-step approach are considered to avoid false positives and false negatives. (8) In addition, sole reliance on molecular testing for toxins increases the likelihood of over-diagnosis and over-treatment of C.diff. This conclusion is most important in patients that have asymptomatic colonization or carriage of C.diff. This carriage is common in healthcare associated facilities and in the community and it is estimated that prevalence ranges from 7–18%. (9)

**Methods**

**Design:**

This systematic review was created to establish a comprehensive collection of current data from different databases to align with the most up to date evidence-based practice patterns for the workup of CDI. This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist. Our research was not registered online.

**Search strategy and selection:**
We evaluated studies that identified the roles of biochemical testing of *C. diff* and implications of disease severity and development of toxic megacolon in a subset of patient populations. On 2 February 2023 author CC searched the databases PubMed (1946-present), Scopus (1788-present), and the Cumulative Index of Nursing and Allied Health Literature (CINAHL Complete, 1937-present) to identify relevant reports. Search terms used included index and keyword terms for “clostridioides difficile”, “toxin assay”, and “toxic megacolon”. The search strategy is listed in Table 1. Inclusion criteria were English language articles published between the years 2012 to 2023, with eligibility based on population, type of study, and outcomes. Exclusion criteria were non-English language reports that were experimental (except for one study which was deemed necessary for this review) or basic science, poor quality appraisal, pediatric population, and outdated guidelines. All six investigators had to agree to including and/or excluding the studies based on these criteria before they were finalized into this paper. One experimental study was included in this systematic review for the purpose of identifying the hypervirulent strain NAP-1. After removing duplicates, the full text articles of the search results (n = 76) were uploaded to Rayyan, a Web-based platform used to organize and manage articles for systematic reviews.

**Data extraction:**

All five investigators (A.K, J.A, M.N, P.D, D.S) extracted five reports each and two investigators (K.S and G.M) extracted three reports from the eligible studies based on: last name of author, publication year, number of patients, purpose of the study, and results. All appropriate records and studies grouped based on study type and listed in Table 2 in descending year of publication.

**Quality appraisal:**

Two investigators (K.S and A.K) independently reviewed each of the thirty included reports for authenticity and quality. We utilized the JBI global website to methodologically assess the transparency of each included report. Review articles (18), retrospective cohorts (4), guidelines (3), experimental (1), and cross-sectional study (1) were criticized to have excellent appraisal. The following instruments were used: Text and opinion for review articles, the revised Appraisal of Guidelines for REsearch & Evaluation (AGREE) II for guidelines, diagnostic accuracy tool for the cross-sectional study, experimental study checklist for the experimental study, and cohort study checklist for the cohort studies.

**Results**

After identifying 85 records from Scopus, 24 records from PubMed, and 37 records from CINAHL we removed 70 duplicate records using an excel spreadsheet. We manually excluded 6 records based on publication year. Lastly, we excluded records based on abstract screening and not meeting eligibility criteria. Overall, 27 reports were eligible for inclusion in this systematic review as listed in Fig. 1.

**Discussion**

In this part of the manuscript, we discuss definitions, risk factors, emphasis on specific patient populations, diagnosis, and testing.
**Risk factors:**

### Table 3
Risk factor table for initial and recurrent *clostridioides difficile*.

<table>
<thead>
<tr>
<th>Increased risk</th>
<th>Reduced risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial CDI</strong></td>
<td><strong>rCDI</strong></td>
</tr>
<tr>
<td>Independent</td>
<td>Dependent</td>
</tr>
<tr>
<td>- Recent gastro-intestinal surgery (particularly colectomy, ileo-anal pouch, and ileostomy)</td>
<td>- Antibiotics</td>
</tr>
<tr>
<td>- Recent exposure to anti-neoplastic agents</td>
<td>- PPI in cirrhosis</td>
</tr>
<tr>
<td>- IBD</td>
<td>- Sharing room with CDI patient</td>
</tr>
<tr>
<td>- Previous hospitalization</td>
<td></td>
</tr>
<tr>
<td>- Advanced age (&gt; 60)</td>
<td></td>
</tr>
<tr>
<td>- Greater co-morbid conditions</td>
<td></td>
</tr>
<tr>
<td>- Solid and hematopoietic transplant</td>
<td></td>
</tr>
</tbody>
</table>

CDI, *clostridioides difficile* infection; PPI, proton pump inhibitors; IBD, inflammatory bowel disease; rCDI, recurrent *clostridioides difficile* infection; C. diff, *clostridioides difficile*.

**Antimicrobials:**

Predisposing risk factors for CDI are listed on Table 3 but, the two main risk factors for CDI are exposure to antibiotics and C.diff.(1, 3, 10–14) Antibiotic use is the strongest risk factor for development of CDI and the most common include clindamycin, fluoroquinolones, and cephalosporins. Optimization of antimicrobials and antibiotic stewardship have been shown to reduce CDI incidence by up to 60%.(4, 15) In the Netherlands, a three-year case control study studied the association between duration and dosage of antibiotics. Third-generation cephalosporins had the highest odds followed by carbapenems, and second-generation cephalosporins of developing CDI (OR 5.3, 4.7, 3.3, respectively).(16) Those currently on antibiotics and within 30 days of completion had the greatest risk (OR 6.7–10.4).(10) Interestingly, linezolid has conflicting data on C.diff risk as some research has shown a theoretical inhibition of exotoxin production and reduction in CDI inhibited.(17, 18) The study in Main Medical Center was primarily experimental in vitro gut model and the second study lacked external validity as the patient population of interests were principally heart transplant recipient and had a small sample size (n = 91). On the other hand, one study found patients who underwent HSCT more prone to developing CDI with linezolid.(12) Along depressed immune system due to multiple other comorbidities, these patients lose their protective gut microbiome from gastrointestinal inflammation.(3, 12)
Nonantimicrobial risk factors:

Proton pump inhibitors (PPIs) are common medications used in all clinical settings that have been associated to CDI. A meta-analysis of approximately 299,000 participants from 23 retrospective studies demonstrated CDI incidence of 64.9% in PPI users. The meta-analysis concluded with judicious PPI prescriptions. The study has limitations as the length of duration of PPIs was not defined. In addition, the study incorporated the ‘trim and fill’ method to adjust the asymmetrical funnel plot which can lead to over- or under-estimation of true measures in this meta-analysis. Other retrospective studies or systematic/meta-analysis that determined both PPIs and histamine receptor-2 blockers increase CDI. Although it is generally accepted by the Federal of Drug Administration (FDA) that PPIs increase CDI, there is considerable controversy based on the current available literature.

Reduced risk:

A detailed list of factors that decrease the risk of CDI are listed in Table 3. Binders that are commonly used for bile sequestration such as cholestyramine and colestipol have been shown to decrease risk of CDI. In lieu of these resins, vancomycin is highly efficacious and clinicians should be reminded to set a timing interval between oral vancomycin and bile resins. Currently, 4,000 mg of cholestyramine is given three to four times daily and two to three hours after oral vancomycin. Apart from medications, asymptomatic colonization is thought to be immunoprotective. Approximately 40% of patients with community care associated C.diff do not have antibiotic exposure. In fact, 10% of healthy adults, up to 50% of institutionalized patients, and neonates become asymptomatic reservoir and spread this bacteria throughout the healthcare system. Carriers have immunoglobulin G (IgG) antitoxin A and B antibodies against C.diff, thereby, inhibiting toxin production. It has been postulated that earlier colonization of asymptomatic C.diff may lead to a robust memory immunity until the later decades of life. As antitoxin A and B antibodies production weans with aging and apoptosis, this poses a risk factor for CDI in the elderly.

Special risk populations:

Hypogammaglobulinemia:

As forementioned, humoral immunity protects against toxicogenic colonization of C.diff. Patients with solid organ transplant(s) (liver, kidney, heart and lung), may benefit from passive immunization for C.diff. These immunosuppressed receipts receiving prophylactic antibiotics post-transplant have a prevalence of 1.0–30% for CDI. In addition, hypogammaglobulinemia has been found to be an independent risk factor for CDI and rCDI. In a prospective study, 235 patients underwent heart transplant and 35 developed CDI. Of these 35 patients, immunoglobulin levels were determined to be low in 6 of the 7 tested individuals. Although routine IVIG administration is not recommended, it should be considered in patients with hypogammaglobulinemia that have other conferring comorbid conditions for CDI.

Surgical:
In the surgical patient, there are multiple risk factors that both confound and modify the effect of CDI such as gastrointestinal surgery, emergent surgery, organ transplant, and nasogastric tube feeds. Gastrointestinal surgeons influence CDI both directly (by surgical treatment) and indirectly (by inadvertently contributing to CDI by an unrelated surgery). There is evidence that enteral tube feeding in patients with anatomical or dynamic obstructions increases the risk of CDI. The transit time of stool is decreased and allows for proliferation of toxins resulting in toxin proliferation. According to the 2017 Infectious Disease Society Association (IDSA), a match cohort study demonstrated enteral feeds increase the risk of CDI. Therefore, it is best practice to discontinue NGT early to reduce the possibility of cross-contamination from hospital instruments.

**Inflammatory bowel disease:**

Inflammatory bowel disease (IBD) harbors a pro-inflammatory state that causes physiological, anatomical, and immunological changes to the gastrointestinal tract. As opposed to HCO-HFA and CAO-HFA CDI, IBD specific populations present with CAA CDI. A national prevalence survey found CDI in ulcerative colitis (UC) to be 37 per 1,000, 11 per 1,000 in Crohn’s disease (CD) and 4 per 1,000 in general medical patients. IBD patients suffer from acute flares leading to increased hospitalizations, immunosuppression with corticosteroids, and increased prescription of antimicrobials. Of all the forementioned factors, corticosteroid administration has the greatest risk, with a threefold increase in CDI incidence. A study in British Columbia determined that corticosteroids to be an independent risk factor in IBD. Interestingly, it is unclear what risk immunotherapy poses in this population. The complications of CDI are much higher in UC (9.5%) than with CD (7%) partly due to more extensive involvement of the colonic mucosa in UC. Patients with colectomy and have ileo-anal pouch or ileostomy remain at an elevated risk of CDI as well. Symptoms such as increasing ostomy output, bleeding, changes in stool consistency and frequency, and along with systemic markers of inflammation should prompt evaluation of an infectious source. Healthcare professionals should have a low threshold to initiate therapy however should be aware of rising metronidazole resistance in this group of patients. In terms of testing, IBD patients are more likely to have toxin positive strains if there is one or more classic risk factor for CDI (antibiotic exposure, recent hospitalization, institutionalized, history of surgery) in comparison to toxin negative strains (68% vs 31%).

**Intensive care unit (ICU):**

Patients that are directly admitted to the ICU have been found to be colonized with toxicogenic C. diff strains. Approximately 15% of 5,300 admitted patients were confirmed to have CDI and this correlates to the increased incidence of community acquired CDI. Patients found to have CDI at the time of ICU admission were much more likely to have subsequent CDI in the future (p < 0.01). A retrospective study in Taiwan found that the diarrheal group had a longer length of ICU stay than the ileal group (28 vs 12 days, p < 0.01). A cohort study determined that the size of the unity and capacity of rooms were related to horizontal transmission. Therefore, hand hygiene is the cornerstone in the ICU to decrease transmission of spores. In the ICU, there is accumulation of co-morbid conditions, virulent organisms, and use of broad-spectrum antibiotic that increase CDI risk.
Diagnosis of Clostridium Difficile infection

CDI diagnosis requires a clinical syndrome accompanied by a biochemical test for confirmation. CDI is defined as the presence of detectable toxicogenic C.diff strain and clinical syndrome of acute diarrhea consistent with ≥ 3 unformed Bristol 5–7 stools in the last 24 hours without another explanation and prior exposure of antibiotics in the last 2 months. Each test must be accurate to diagnose the pathogen and timely to ensure rapid isolation for infection control and preventing progression. C.diff colitis can be a challenge to diagnose as symptoms can overlap with other general diarrheal illnesses and detection of nontoxicogenic strains of C.diff which do not require treatment.

To diagnose a clostridium difficile infection, patients must have acute diarrhea in addition to either toxigenic difficile strain or C.diff toxins in stool samples.(34) C.diff tests include toxigenic culture (TC), Glutamate dehydrogenase (GDH) detection assays, nucleic acid amplification tests (NAATs), cell cytotoxicity neutralization assays (CCNAs), and toxin detection tests (EIA). Each test is compared in details in Table 4. Patients who are at high risk for CDI are the ones that have received antibiotics in the last 3 months, hospitalized for more than 3 days, and atleast 65 years of age.(3)

<table>
<thead>
<tr>
<th>Type of tests</th>
<th>Turnaround (h)</th>
<th>Sn/Sp</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>48-120h (5,6)</td>
<td>87–100%/94–100% (7)</td>
<td>This is a gold standard test. Isolates toxigenic strains of C.diff from the stool culture or rectal swab.</td>
</tr>
<tr>
<td>GDH/EIA</td>
<td>&lt; 2h (6,14)</td>
<td>&gt;90%/80–100% (7,14,32,33)</td>
<td>Considered the first test to order for screening.(34) Quicker and more sensitive than toxin EIAs. Test uses antibodies to detect the presence of GDH, a cell wall-associated enzyme that is present in both toxigenic and nontoxigenic strains. Therefore, cannot be used alone in the diagnosis of CDI.</td>
</tr>
<tr>
<td>NAAT</td>
<td>&lt; 4h (6)</td>
<td>100%/70% (14,35)</td>
<td>Detects nucleic acid sequences through amplifications of the genes that produce toxins A and B (TcdA and TcdB respectively). Detects toxin genes instead of active toxin, it cannot differentiate between CDI and asymptomatic carriage.(35) NAAT can be done by PCR (polymerase chain reaction) or LAMP (loop-mediated isothermal amplification).</td>
</tr>
<tr>
<td>CCNAs</td>
<td>72-96h (34)</td>
<td>90–100%/98–99% (7)</td>
<td>This test works by inoculating a stool sample onto two sets of sensitive tissue culture cells, first set without C.diff anti-toxin and the second set with the anti-toxin. Positive if cytopathic effect in the first set.</td>
</tr>
<tr>
<td>Toxin ELISA</td>
<td>&lt; 2h (6)</td>
<td>53–85%/91–98% (7)</td>
<td>This test uses antibodies to detect the presence of C.diff toxins A/B. A negative toxin assay does not rule out toxigenic strains. Combining a high sensitivity test (like GDH) with EIA can make up for the low sensitivity of this test.</td>
</tr>
</tbody>
</table>
No stand alone test can distinguish between toxigenic/nontoxigenic strains and asymptomatic colonization as described in Table 5. Therefore, a 2-step or multi step diagnostic algorithms have been used to improve the diagnosis of CDI. The 2-step approach starts by a high sensitive test (GDH EIA or NAAT) followed by a high specificity confirmatory test (TcdA /TcdB EIAs) per the 2016 Europe and UK guidelines (ESCMID). (8, 36)

### Table 5

<table>
<thead>
<tr>
<th>Detection of C.diff</th>
<th>Detection of toxins A and/or B</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (toxigenic C.diff strain)</td>
<td>CCNAs: Detects TcdA and TcdB</td>
</tr>
<tr>
<td>GDH EIA (Toxigenic and nontoxigenic strains)</td>
<td>Toxin A B immunoassays (ELISA)</td>
</tr>
<tr>
<td>PCR-NAAT: Detects TcdA and TcdB genes (Toxigenic strains)</td>
<td></td>
</tr>
</tbody>
</table>

Most algorithms start with a GDH test followed by toxin EIA as shown in Fig. 2. Some algorithms start with NAAT instead of GDH followed by toxin EIA which is more expensive but has a higher diagnostic accuracy. Economic studies showed that starting with GDH costs approximately $10 per algorithm vs $30 per algorithm starting with PCR. (5) Therefore, many small community hospitals and long term care facilities perform GDH with toxin A/B EIA and subsequent NAAT for inconsistent results. This is referred to as the “multi-step approach” where the NAAT is used to differentiate if the positive GDH was due to toxigenic strain or nontoxigenic strain as illustrated in Fig. 3. (7) Another modification of the multistep algorithm is to combine step 1 and step 2 together by testing for GDH and toxins at the same time, followed by NAAT if inconsistent results as described in Fig. 4. The advantage of this modification is saving time by combining steps 1 and 2 together as described in Table 6. The disadvantage is the cost of the Toxins EIA test which is usually unnecessary if the GDH is negative. The previous 3 algorithms summarize the recommended testing by the ESGCD and ESCMID. (8)
### Table 6
Comparison of 2-step, multi-step, and modified multi-step algorithm

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>First test</th>
<th>Second test</th>
<th>Third test</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 step</td>
<td>NAAT</td>
<td>Toxin A/B EIA</td>
<td>N/A</td>
<td>Pros: Faster</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cons: More expensive</td>
</tr>
<tr>
<td>Multi-step</td>
<td>GDH</td>
<td>Toxin A/B EIA</td>
<td>NAAT</td>
<td>Pros: Most cost effective.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cons: Time consuming, Multiple steps.</td>
</tr>
<tr>
<td>Modified multi-step</td>
<td>GDH and Toxin A/B EIA</td>
<td>NAAT</td>
<td>Pros: Fast turn around time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cons: Unnecessary toxins test with GDH is negative</td>
</tr>
</tbody>
</table>

Nucleic acid amplification test (NAAT); Glutamate Dehydrogenase (GDH) Enzyme Immunoassay (EIA)

**Who should be tested?**

C. diff colonization has been reported to be between 0–15% in healthy and 10–15% in hospitalized patients.\(7, 37\) Therefore, it is important to only screen symptomatic individuals to avoid false positives as laboratory tests alone cannot differentiate between an actual infection and asymptomatic colonization.\(7\) Fecal swabs cannot be used for toxin detection (inadequate sample) due to inadequate sample, instead they can only be used for culture or NAAT.\(2, 5\)

Candidates for testing are those that are laxative free for 48 hours, Bristol 5 or more ≥ 3 bowel movements in 24 hours, abdominal pain/cramps, with no other clear cause of diarrhea.\(7\) Patients with findings of colitis, severe ileus, or megacolon on imaging should be prioritized.\(5\) Also, early surgery consult is recommended for those showing evidence of megacolon or ileus on imaging.\(4\)

Retesting individuals within 7 days of previous negative test is not recommended. Repeated testing can increase healthcare costs and false-positive results. Diagnostic yield of repeat testing is approximately 2%. It is also not recommended to repeat testing to check for cure, as greater than 60% of patients will remain positive after successful treatment.\(2, 25\)

**Limitation:**

Systematic review is limited by the inclusion and exclusion criteria. This systematic review was governed by testing and diagnosis in specific populations only. The majority of the included reports in this manuscript were review articles and guidelines. In addition, there is significant heterogeneity in different studies that evaluated the risk factors and correlation of CDI. More randomized controlled and blinded studies need to be conducted in the future for specific risk factor attributes that may increase and/or decrease CDI prevalence and incidence.
Conclusion

Clostridium difficile is a major cause of health care associated infections. There is an increased prevalence of this bacteria in the community from widespread contamination and transmission. The new emergence of the B1/NAP1/027 strain has caused widespread mortality and increased testing. The infection is a clinical syndrome that is defined by ≥ 3 unformed Bristol 5–7 bowel movements in the last 24 hours without another identifiable cause and positive stool testing. There are a wide variety of available diagnostic tests and the preferred tests are GDH antigen, toxin A/B EIA, and NAAT. These tests are accurate and make a timely diagnosis in the patient but it is imperative that we are aware of the limitations of each test. Toxin A/B EIA is not very sensitive while NAAT detects both toxigenic and non-toxigenic strains and does not differentiate between active disease or carrier state. The 2-step approach, multi-step approach, and modified multistep approach are the different algorithms used for testing and vary due to cost and institution. Specific populations are more predisposed to C. diff colitis due to dysregulation in the immune system, medications, and the acuity of care. There is a need for further research in specific disease groups as studies have numerous variables that produce heterogeneity and poor external validity.

Declarations

Author Contribution

K.S: The corresponding author, wrote the methodology and results section and created Table 2, . Proofread and double-checked the final manuscript.A.K: prepared diagnosis section in Discussion and created Figures 3-4.D.S: Prepared the abstract for the manuscript.J.P: Prepared the PRISMA 2020 flow diagram and Table 1.P.D: Wrote the ICU and IBD section in the discussion of this manuscript.C.C: Extracted all the files and removed duplicates in the result section of this paper and uploaded to Rayyan. Formated the references in APA.E.M: Dr. Morrison is an Infectious Disease physician and she provided edits to further clarify information throughout the manuscript from an infectious disease standpointW.S: Gastroenterologist and was the main mentor of this manuscript. Guided and provided assistance in edits to decrease the length of the manuscript. Also recommended this journal for submission.

References


### Tables

Tables 1 and 2 are available in the Supplementary Files section.

### Figures
Figure 1

PRISMA 2020 flow diagram for systematic review.
Figure 2

2 step diagnostic approach for C.diff

Figure 3

Multi-step approach of the original 2-step algorithm
Figure 4

Modification of the multi-step approach

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Table2.pdf