Table 2: Included literature review articles for systematic review

Ref no.	Author, Year	Type of study	Sample (n)	Region	Purpose	Results
10	Guery et al., 2023	Review article	N/A	Switzerland	Evaluate diagnostic modalities of CDI in the ICU.	Clinical features and two step algorithms are considered as a gold standard diagnostic test for C.diff in the ICU.
11	Srisajjakul, 2022	Review article	N/A	Thailand	Imaging characteristics of associated with drug induced bowel complications.	Plain films may show large bowel dilation with thumbprint appearance and CT scan commonly show colitis with wall thickening >1.5cm. Imaging is used adjunctively when clinical diagnosis is in question.
12	Guery, et al. 2019	Review article	N/A	Switzerland	Up to date data on diagnostic strategies for CDI.	The ESCMID recommends a two step approach that allows for a high sensitivity (NAAT or GDH assay) followed by a specific test for toxin if positive (EIA or CCNAs).
13	Mileto, 2019	Review article	N/A	Australia	Overview of diagnostic testing for CDI	Current diagnostic options for C.diff include CCNAs, EIAs, bacterial culture, NAATs, and toxin detection tests.
6	Xiao, et al. 2019	Review article	N/A	N/A	Review of epidemiology, pathogenesis, and available testing	TC takes 3-5 days to results and needs complementary testing. GDH has high sensitivity and specificity, but needs EIA or NAAT as complimentary testing. NAAT-PCR based testing, high sensitivity, and specificity, but cannot differentiate between asymptomatic colonization and infection.
1	Kodadek, et al., 2018	Review article	N/A	United States	Review the prevention and diagnosis of CDI.	Diagnosis requires 3 or more unformed stools in 24 hours, or radiographic evidence of ileus or megacolon and a positive laboratory test. Testing should not be repeated within 7 days of to avoid decreasing specificity.

2	Martínez-Meléndez, 2017	Review article	N/A	Mexico	Laboratory testing, diagnosis, and prevention of CDI.	C.diff should be tested in Bristol scores of ≥5 with ≥3 stool movements. There are various testing methods that are employed for patients with C. diff including GDH, CCNA, TC, NAATs, and EIA.
14	Ong, 2017	Review article	N/A	United States	Overview of CDI diagnosis.	Patients with CDI have diarrhea with at least 3 unformed stools in the last 24 hours or evidence of ileus or toxic megacolon with positive testing. Patients that haveIBD are at a higher risk of developing CDI.
15	Usacheva et al, 2016	Review article	N/A	United States	CDI pathogenesis and molecular mechanisms of CDI-specific diagnostics.	Currently there is no gold standard test for diagnosis of CDI except for characteristic lesions visualized directly on colonoscopic. Patients with community acquired diarrhea tested for C.diff with PCR may falsely test positve due to colonization. New C.diff strains with altered genomics and toxins may skew test results on current available tests.
3	Smits, 2016	Review article	N/A	Netherlands, Australia, UK	Review the diagnosis of CDI	Mainstay diagnosis is clinical suspicion followed by a TC or detection of toxin. Other approaches include antigen and toxin assays followed by nucleic acid testing if there is discordant test results.
16	Bouza, 2016	Review article	N/A	Spain	Diagnostic testing of CDI.	TC is still the gold standard. Toxin EIAs have a short turnaround time but low sensitivity and high specificity and GDH EIA has a high sensitivity and low specificity. Newer PCR testing have high specificity and sensitivity and are faster but come with a cost.
17	Kaiser, 2015	Review article	N/A	United States	Risk factors of CDI in surgical patients	GI surgery, exposure to peri-operative antibiotics, and PPI exposure in surgical patients increase the risk for CDI. In these

						patients, C.diff can lead to recurrent pouchitis in ileo-pouch anal anastomosis and high volume ileostomy output in patients with ileostomy.
18	Korman, 2015	Review article	N/A	Australia	Diagnosis of C.diff in adults.	
19	Rineh, 2014	Review article	N/A	United States	CDI molecular pathogenesis and novel therapeutics	The normal microbiome of the colon acts as an inhibitor for C.diff colonization and certain bile salts can also inhibit C.diff germination. Approximately 10% of C.diff strains produce binary toxin which are clostridial iota-like toxins and have a higher rate of rCDI.
4	Stanley, et al., 2013	Review article	N/A	N/A	C.diff risk factors, diagnosis, and prevention in specific populations	The primary risk factors include age $\geq$65, antibiotic use within the last 3 months, hospitalization. Secondary risk factors include hypoalbuminemia, ICU admission, HIV, and autoimmune diseases.
20	Berg et al., 2013	Review article	N/A	United States	CDI diagnosis in IBD.	Patients with IBD are at higher risk of developing severe clinical symptoms and worse clinical outcomes. An independent risk factor is corticosteroids. C.diff can occur in the small bowel in this patient population, especially in patients that have an ileoanal anastomosis (J-pouch).
21	Bloukh, 2013	Review article	N/A	United Arab Emirates	CDI overview of diagnosis and prevention.	Diagnosis of C.diff is clinical but requires a high clinical suspicion in patients with diarrhea. Multistep algorithm involving GDH, EIA toxin, and NAAT-PCR is sometimes required.
22	Alrabaa, 2013	Review article	N/A	United States	CDI risk factors, prevention, and diagnosis	Risk factors for CDI include: antibiotic exposure, longer length of healthcare stay, higher acuity of care, and advanced age.
23	Kucharzik et al., 2023	Guideline	N/A	Europe	ECCO guideline on CDI in IBD.	IBD is known to be an independent risk factor for C.diff, even in the absence of other risk

						factors. Screening for C.diff is recommended during IBD flares. Suspected patients should be maintained under contact precautions until testing has confirmed the diagnosis. Two step algorithm should be employed for diagnosis
8	Abreu y Abreu, et al, 2019	Guideline	N/A	Mexico	Consensus on the prevention and diagnosis of CDI.	TC has the highest sensitivity and specificity followed by CCNAs. In patients that have ileus or stool sample is difficulty to collect, a rectal swab with NAAT-PCR can be implemented.
5	Surawicz, et al., 2013	Guideline	N/A	United States	Clinical guideline for diagnosis and prevention of rCDI and CDI.	The main risk factors for this disease is exposure to antibiotics and the organism. Other risk factors include GI surgery, gastric acid suppressing medications, IBD, hypogammaglobulinemia, increased age, and poor health.
24	Lee et al., 2021	Retrospective cohort	23	Taiwan	Diagnosis of CDI in critically ill patients with diarrhea and ileus	In this ICU, 23 cases of CDI were included with 6 cases having ileus and 17 with diarrhea. The ileus group had a higher mortality rate, severe presentation, and shorter ICU stay.
25	Gupta et al., 2019	Retrospective cohort	92	United States	Evaluate toxin testing in escalation of CDI therapy in IBD patients.	The toxin neg PCR+ IBD group had a significantly higher rate of antibiotic response and required lower rate of escalation of therapy compared to only toxin+ patients.
26	Sheitoyan-Pesant, 2015	Retrospective cohort	1527	Canada	Diagnose rCDI within 14-60 days with repeat toxin testing.	This type of disease occurs commonly in females and the median age was 73. The probability of developing a first rCDI was 25% and second rCDI 38% with increasing incidence from 2010-2013.
27	Spadao, 2014	Retrospective cohort	2119	Brazil	Diagnosis of CDI in hospitalized hematological patients.	The incidence of CDI in this population was 3.1%. The rate of incidence of CDI per 1,000 days of neutropenia varied from 0.78 to 5.45 and per 1,000 patient-days varied from 0.78 to 10.24 during

						the study period. Risk factors associated with death were severe form of the disease, and the use of linezolid.
28	Mostafa, 2022	Cross-sectional study	80	Egypt	Compare sensitivity and specificity of PCR in comparison to toxigenic culture for diagnosis of CDI in patients taking antibiotics.	Out of 80 patients with AAD included in the study 12 (15%) were positive and 68 (85%) were negative for Toxigenic culture. Out of 80 patients with AAD included in the study, 32 (40%) were positive and 48 (60%) were negative for PCR.
29	Lanis, 2013	Experimental study	N/A	United States	C.diff exotoxin, TcdB variant B027 in comparison to other forms of exotoxin variants.	C.diff exotoxin TcdB especially from 027/B1/NAP1 variant is potent and causes symptoms. It talks about variants of TcdB especially B027 and B003. Both epitomes are potent but B027 is more potent given its resistant genes to antibiotics. These variants also had brain hemorrhage in mice due to acting on high brain microvascular endothelial.

CDI, clostridioides difficile infection; IBD, inflammatory bowel disease; C. diff, clostridioides difficile; PMC, pseudomembranous colitis; CT, computed tomography; TC, toxigenic culture; GDH EIA, glutamate dehydrogenase enzyme immunoassay; NAAT, nucleic acid amplification test; CCNAs, cytotoxicity neutralization assays; USA, United States of America; PCR, polymerase chain reaction; CDC, Centres for Disease Control; WBC, white blood cell count; FMT, fecal microbiota transfer; IBD, inflammatory bowel disease; CMV, cytomegalovirus. rCDI, recurrent clostridioides difficile infection; CDI, clostridioides difficile infection; IBD, inflammatory bowel disease; PCR+IBD, polymerase chain reaction positive inflammatory bowel disease; NAAT-PCR, nucleic acid amplification test-polymerase chain reaction; ICU, intensive care unit; CDAD, clostridium difficile associated diarrhea. AAD, antibiotic associated diarrhea; PCR, polymerase chain reaction; CDI, clostridioides difficile infection; TcdB, toxin B gene; C.diff, clostridioides difficile.