Clostridium difficile infection: a review article

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Abstract: Clostridium difficile is definitely increasing in incidence, severity and mortality CD is the lbading cause of infection nosocomial diarrhea in developed countries as well as being responcible for outbreaks of infection diarrhea in hospitals all over the word. In many European countries diagnosis is probably suboptimal.

Recurrent disease is especially challenging Fecal micriobiota is suggesting as a safe, inexpensive and effective treatment.

Key words: CDI clostridium difficili infection, Management of CDI, FMT, Fecal Microbota Transplatation.

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Introduction

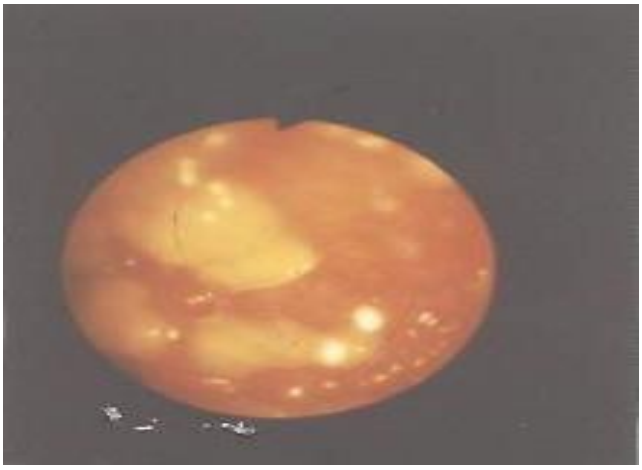
Clostridium difficile (*CD*) owns its name from the Greek word "kloster" which means spindle and from the word difficile that means difficult, as it was difficult to be isolated and cultured. *Clostridium difficile* is an anaerobic, spore-forming, Gram-positive bacillus, widespread in the environment, especially in the soil. It was first introduced in 1935. However, its effect in human health was not well known, until the early 1970, when Cohen and his colleagues found that it is responsible for diarrhea and pseudomembranous colitis (picture 1) (**1,2,3**). Nowadays, it is well known that *Clostridium difficile* is the most commonly recognized cause of antibiotic-associated diarrhea in humans. *Clostridium difficile* infection (CDI) is the most frequently encountered nosocomial infection in the United States and more importantly is an emerging cause of community-associated disease (**4-8**).

Pathophysiology

The bacterium is part of the human normal microbiota in a small percentage in the adult population (0-3%) and 15-20% of infants. *CD* can be found in two forms: the vegetative form and the spores. The vegetative form is able to produce toxins and cause clinical symptoms. On the other hand, the spores can survive in difficult circumstances, are resistant to antibiotics, and can be found either in the environment or in the gut (**9**).

Clostridium difficile infection can be divided in endogenous and exogenous. Endogenous infection arises from the carrier strains, while exogenous infection is caused via the oral-fecal route of infected individuals, contaminated health care workers, nosocomial sources, and contaminated environment (**9**). The spore of the bacterium can be orally ingested, survive in the gastric acidity and return back to the vegetative form in the small intestine.

The infection process includes the colonization and the production of toxins. The colonization process is assisted by the reduction of the normal intestinal microbiota as a consequence of broad-spectrum antibiotics use (**10, 11**). In addition, it is consisted of the implementation and the multiplication of *CD* in the gut lumen. For the colonization, *CD* uses surface proteins, and many adhensins have been discovered (**12**). The production of toxins is responsible for the clinical symptoms. *CD* produces two toxins: an enterotoxin (toxin A) and a cytotoxin (toxin B). The genes encoding these toxins are located on a region, called the Pathogenicity Locus (PaLoc) (**13**). Toxin A (308kDa) attracts neutrophils in ileum, resulting in cytokines production. In addition to that, it breaks down the intracellular junction in enterocytes leading to increased permeability and diarrhea (**14**). Toxin B (269kDa) causes depolarization of actin in enterocytes and therefore enterocytes' cytoskeleton is destroyed. Although these two toxins act synergistically, it appears that species that are not producing toxin A can still lead to symptomatic manifestation of the disease. Apart from this, the production of one or both toxins, it does not seem to be the only factor responsible for the disease (for example, in children high toxins levels are present but the disease is absent) (**1**). In addition to the major toxins, C. difficile may produce a number of other putative virulence factors, including CDT binary toxin, fibronectin binding protein FbpA, fimbriae, SlpA S-layer, Cwp84 cysteine protease, and Cwp66 and CwpV adhesions (**9**). In 2003, attention was drawn by a CDI reported in Canada, USA, and Europe that it was caused by an extremely virulent pathogen, the NAP1/BI/027. This strain is responsible for severe disease, increased complications and mortality, and is resistant to fluoroquinolone (**1, 2, 13**).



Picture 1: Pseudomembranous colitis in large intestine.

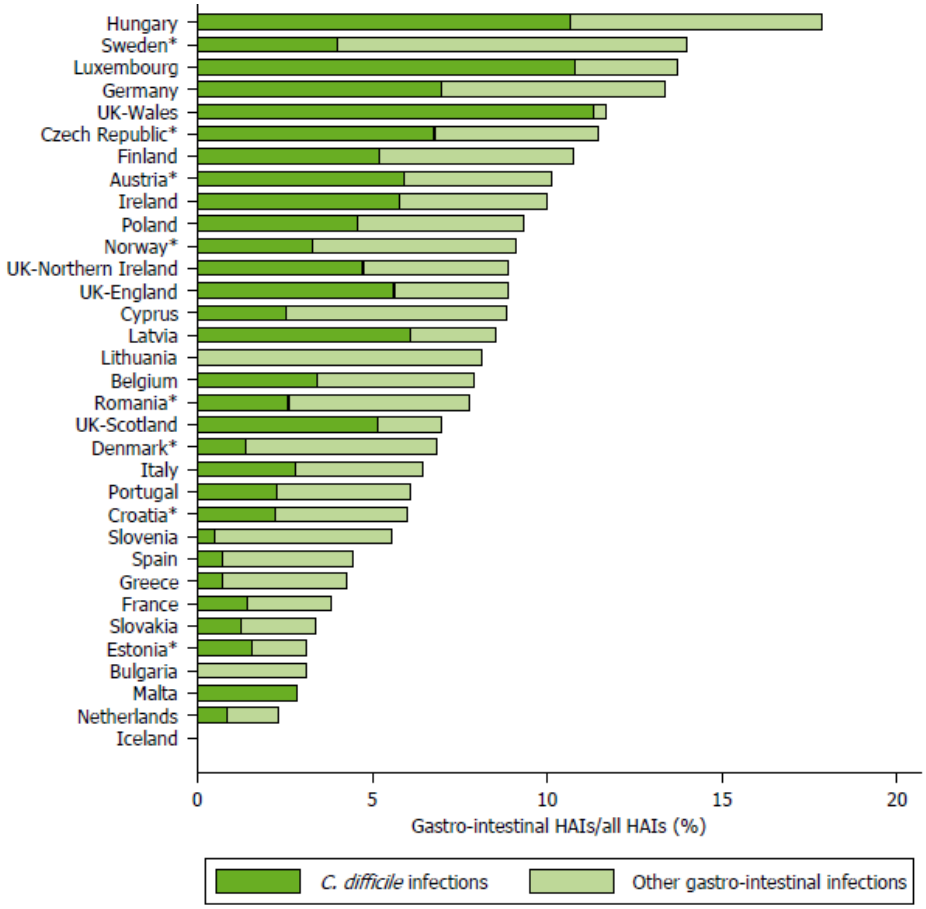
Epidemiology of CDI in Europe

In 2012, a study contacted by European Centre for Disease Prevention and Control (ECDC) indicated that *CD* infection was responsible for 48% of all gastrointestinal infections (Figure 1) (**15**) . A year earlier, Braver et al. (European Study Group of C. difficile (ESGCD)) performed a survey in 34 European countries with 509 patients participating. The mean incidences of CDI was 4.1/10000 patients. 65 different PCR ribotypes were identified, of which 014/020 (16%), 001 (9%), and 078 (8%) were the most common. Most patients had a previously identified risk profile of old age, comorbidity, and recent antibiotic use. At follow up, 22% of 455 patients had died, and C. difficile infection was responsible for the 40% of those deaths (**16**).

As mentioned before, ribotype 027 strains were first reported in Canada in 2003, and later in the UK. In Europe, toxin type III, which is released by the newly virulent strain ribotype 027, has been recognized in 75 hospitals in England, 16 hospitals in The Netherlands, 13 healthcare facilities in Belgium and 9 healthcare facilities in France. This type is really difficult to be controlled (**17**)

Assuming that the population in Europe is approximately 457 million, the cost of *Clostridium difficile*-associated disease (CDAD) is about 3000 million euro/year and more significantly is expected to be doubled over the next 4 decades.

It is important to highlight that European countries have reported an increase of CDI (**17**), and more significantly it appears to become more and more common in the community, and in people who used to belong in the low risk categories (e.g patients without previous exposure to antibiotics or young individuals). Community-aquired CDI was known since 1980, and since then it is increasingly significantly (**18**). Wilcox and his colleagues estimated that in Leeds there were 20.2 incidences of community CDI/100000 patients annually, while in Truro there were 29.5 incidences of community CDI /100.000 patients annually (**19**).



difficile infections and other gastro-
excluding hepatitis) as a percentage of
ated infections, by country, ECDC (**15**)

Clinical Manifestations of CDI

The clinical manifestations of infection with toxin-producing strains of *Clostridium difficile* range from asymptomatic colonization to severe pseudomembranous colitis (PMC), toxic megacolon and death (**20,21**). The severity of disease is related to the toxicity of *Clostridium difficile* strains and patient's risk factors, such as the presence of neutralizing antibody against TcdA and TcdB **(21,22,23,24,25)**. The symptomatic manifestations of CDI can be stratified into mild to moderate, severe and complicated disease (**26**,**22**,**25**).

Mild disease is defined as CDI with watery, nonbloody diarrhea as the only symptom (**26**). The onset of diarrhea is typically during or shortly after administration of a course of antibiotic therapy. It may also occur from a few days after the initiation of therapy to as long as 8 weeks after the termination of the antibiotic therapy (**23**).

Other clinical features of CDI are fever, abdominal cramps, leukocytosis, and hypoalbuminemia. Systemic symptoms are usually absent in mild disease but are common in moderate or severe disease (**21,23,26**). The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA) guidelines define severe disease as colitis associated with the serum concentration of leukocyte up to 15,000 cells/μl and the serum creatinine level higher than 1.5 times the normal level (**24**). Other characteristics of severe disease include PMC, fever with the temperature sometimes reaching 40°C, mental status changes, serum lactate levels greater than 2.2 mmol/l and hypoalbuminemia with serum albumin levels less than 2.5 mg/dl (**23,24**).

Severe and complicated disease may cause paralytic ileus which can evolve into toxic megacolon with nausea, vomiting, dehydration, lethargy, or tachycardia in addition to fever and abdominal pain. Severe and complicated disease may also includes hypotension, renal failure, systemic inflammatory response syndrome, sepsis, and if untreated, death (**21,26,24**).

It is important to be noted, that on rare occasions, patients with severe or complicated CDI may not have diarrhea. This occurs when the infection causes paralytic ileus, preventing the passage of stool (**23**).

Diagnosis of CDI

The diagnosis of CDI is based on a combination of signs and symptoms, confirmed by microbiological evidence of *Clostridium difficile* toxin and toxin-producing *Clostridium difficile* in stools (**25**). Colonoscopic or histopathological findings demonstrating pseudomembranous colitis (PMC) can also be helpful in the diagnosis of the disease.

Imaging studies

Having in mind that in up to one-third of patients PMC will involve the right colon only, colonoscopy is the most preferable procedure for its detection (**23,27**). Detection of PMC with endoscopic visualization can be used for the diagnosis of CDI, although there are many other causes of PMC, they are very rare. However the sensitivity of these studies is relatively low considering that PMC is often not present. Also in cases of fulminant colitis there is the risk of perforation during this procedure (**23**). Nevertheless, CT imaging can be valuable in the diagnosis of PMC and complicated CDI. Characteristic features of PMC's CT include colonic-wall thickening, pericolonic stranding and ascites, which suggest hypoalbuminemia (**23,27**). Also include the "double-halo sign" (which is seen with intravenous contrast material and shows varying degrees of attenuation attributable to mucosal hyperemia and submucosal inflammation), and the "accordion sign" (which shows oral contrast material with high attenuation in the colonic lumen alternating with an inflamed mucosa with low attenuation (**23,27**).

Laboratory testing

Diagnostic tests for CDI include: cell culture cytoxicity assay (CCCA), glutamate dehydrogenase (GDH) and Toxins A and/or B, toxigenic culture of *Clostridium difficile*, and nucleic acid amplification tests (NAAT) including 16S RNA, toxin genes, and GDH genes.

Cell culture cytotoxicity neutralization assay (CCCNA):

This assay aims to the detection of the presence of *CD* toxin in fecal samples. It is performed by preparation of a filtrate of stool sample, which is then inoculated onto a monolayer of an appropriate cell line. If *CD* toxin is present in the filtrate, toxin-induced cytopathic effect (CPE) will be observed after 48 hours of incubation. A neutralization assay is then performed to verify that the CPE is caused by *CD* toxins rather than nonspecific toxicity. The neutralization assay is performed by using either C. sordellii or C. difficile antiserum (**21,28,29**). Although CCCNA is a test with high specificity and moderate to high sensitivity, it is not considered as a gold standard diagnostic method for CDI as it is technically demanding and has a relatively long turnaround time (**21,23,26,29**).

Toxigenic culture:

This method based on the isolation of *CD* from fecal specimens and the determination if the recovered isolate is a toxin-producing strain. First step aims to inhibit the overgrowth of other fecal flora to isolate *CD* strains (**21**). There have been many different methods reported for this purpose including using anaerobic agar or broth culture with selective and differential agents, (such as cycloserine-cefoxitin mannitol broth with taurocholate and lysozyme (**30**)), or/and employing a heat shock or alcohol shock. After the isolation of the colonies suspicious for *CD* , the organism has to be identified (**21**). Lots of different biochemical methods can be used for the identification of *CD* such as detection of hydrolysis of L-proline-naphthylamide ("PRO Disk" positive), RapidANA (Remel, Lenexa, KS) test and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (**21**). When *CD* has been identified, it must be determinate if the isolates are toxin-producing strain or not. Usually, this is performed by growing the *CD* isolates in broth and performing CCCNA on the culture or by using Enzyme immunoassays (EIAs) (**21**).

Although toxigenic culture is not clinically practical because of its slow turnaround time, the sensitivity and specificity of it are relatively high. Therefore, is considered as a reference method rather than a diagnostic method (**21,26,24**).

Enzyme immunoassays (EIAs):

EIAs use monoclonal or polyclonal antibodies against *CD* toxins. There are a number of commercially available EIAs for *CD* toxins such as rapid immunochromatographic/lateral flow membrane immunoassays and microwell and solid-phase assays (**21**). Rapid commercial EIAs give results within hours rather than days, however, this method is considered as a suboptimal alternative approach for diagnosis due to the fact that it has a lower sensitivity than a toxigenic culture or cell cytotoxicity assay (**23,26,24**).

Glutamate dehydrogenase (GDH):

This test is a antigen test which detects GDH, a metabolic enzyme produced at high levels in all isolates of *Clostridium difficile*, including both toxigenic and non-toxigenic strains (**21,23**). Although GDH is high sensitivity test with a turnaround time of 15–45 min, it only indicates the presence of the organism and not the toxicity of it' s strains. Furthermore, *CD* is not the only organism that produced this enzyme therefore, the specificity of this test is low. It is considered as a screening test for CDI of which positive assays require further testing by cell cytotoxicity assay, EIA for toxins, or toxigenic culture (**23,31,32**).

Combination testing—GDH detection and toxin EIA:

Enzyme immunoassays that combine GDH detection and a toxin EIA in one test (**23**)

Nucleic acid amplification techniques (NAATs):

NAATs are the newest diagnostic method for the direct detection of *Clostridium difficile* in clinical specimens. These assays use conventional Polymerase chain reaction (PCR) methods and targeted a variety of genes, including the tcdA, tcdB, and 16S rRNA genes (**21**). Some of them are the BD GeneOhm Cdiff

assay, the ProDesse ProGastro *Cd* assay, the Xpert *C. Difficile* Epi assay, the Illumigene assay, the Simplexa *C. difficile* Universal Direct assay, the Portrait Toxigenic *C. difficile* assay, the AmpliVue *C. Difficile* assay and the Verigene *C. difficile* test (**21,33,34,35**). PCR assays appear to be rapid, sensitive, and specific and evidence suggests that NAATs are good stand-alone diagnostic tests for toxigenic *Clostridium difficile* (**26,24,35**). However, more data on utility are necessary before this methodology can be recommended for routine testing.

Guidelines

Preferably a two- or three-stage algorithm is performed to diagnose CDI, in which a positive first test is confirmed with one or two confirmatory tests or. Fecal samples could be investigated with an GDH, an enzyme immunoassay detecting toxins A and B, or NAAT detecting Toxin B (TcdB). Samples with a negative test result can be reported as negative. Fecal samples with a positive first test result should be re-tested with a method to detect free fecal toxins, or with a method to detect GDH or toxin genes, dependent on the assay applied as first screening test. If free toxins are absent but *CD* TcdB gene or GDH are present, CDI cannot be differentiated from asymptomatic colonization (**24,25,36,37**).

Testing should only be performed on unformed stool sables (as the positive result in a formed stool only signifies colonisation), unless ileus is present (rectal swabs are suitable specimens in this case) (**24,25,38**). It also should only be performed at patients with potential infective diarrhea and negative tests for common enteropathogens, irrespective of age, prior antibiotic use, co-morbidity, co-medication, and onset of diarrhea (**25**). Repeat testing during the same episode of diarrhea is of limited value and it is not recommended (**24,25,38**).

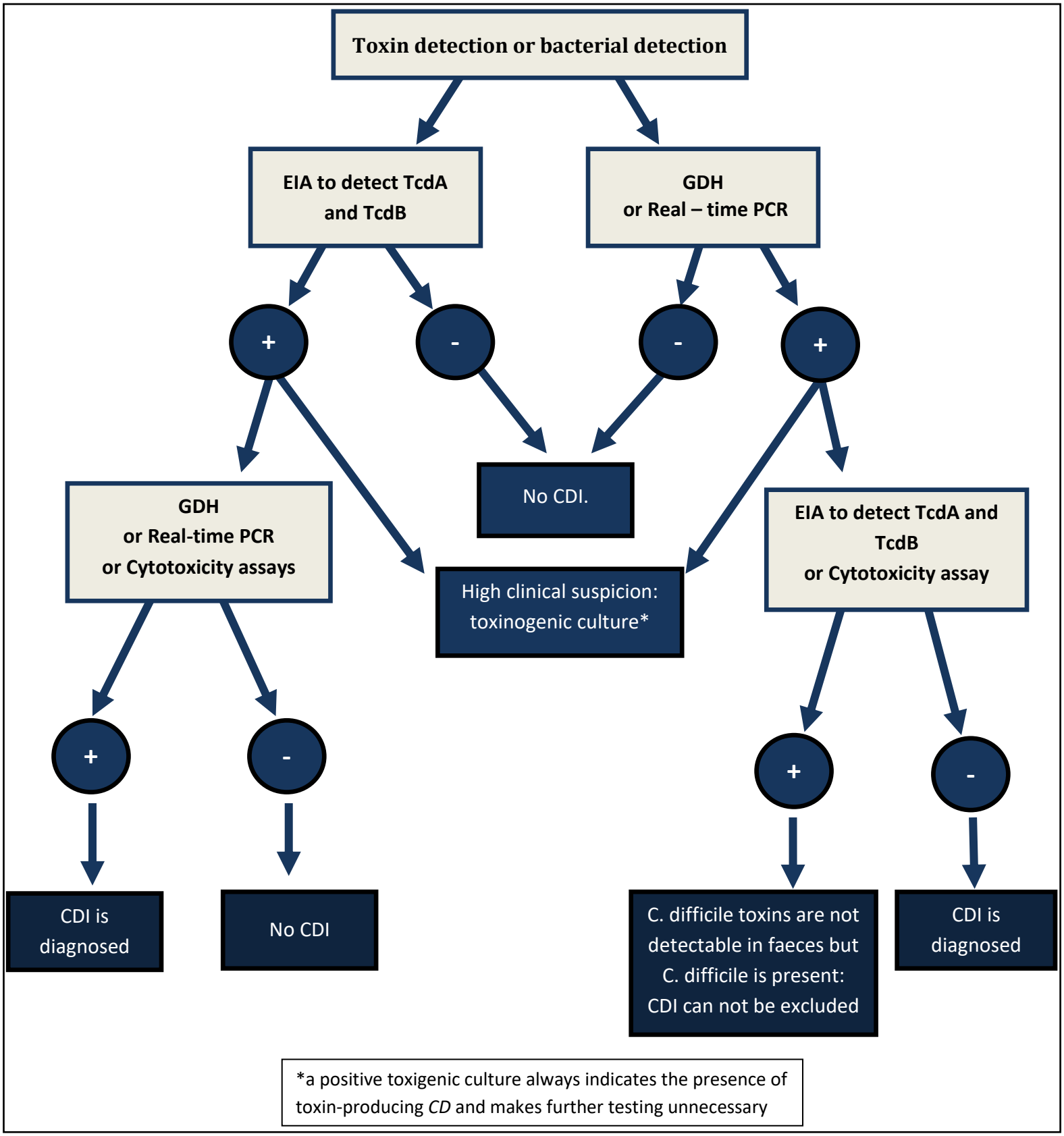


Figure 2: Algorithm to diagnose CDI (25)

Clostridium Difficile Infection Treatment / Management of CDI

All Clostridium Difficile Infection (CDI) treatment plans are based on the disease severity and whether it is an initial or a recurrent infection. As mentioned before, severity is classified in mild to moderate/ non severe, severe, and severe with complications. This classification is of great importance in order to ensure appropriate clinical decisions. Treatment could be either conservative or surgical. (39,40,41)

Empiric therapy should be considered for patients whose symptoms strongly indicate CDI even if the laboratory test results are pending (42, 43). On the other hand, carriers with no clinical symptoms should not be treated (40,44). Any antimicrobial agent(s) being used to treat any other infections than CDI should be ceased as their administration increases the susceptibility to recurrent. Although, if antibiotics are essential for the management of the primary infection, they should be substituted with other agents whose propensity to induce CDI is significantly lower such as tigecycline or tetracycline (40, 45, 46, 47, 48, 49). Moreover, it is of clinical importance to avoid any usage of antimobility/antiperistaltic agents with the intention of reducing the risk of obscuring other symptoms or triggering toxic megacolon (39, 41, 46, 50, 51). Also, a correlation between Acid-suppressing medications [especially Proton Pump Inhibitors (PPIs)] and CDI has been reported. Therefore, PPIs should be reviewed if CDI is suspected. (42, 46, 47). As stated, diarrhea is one of CDI's main symptoms which results in remarkable volume depletion and electrolyte imbalance. Thus, supportive care including intravenous fluid resuscitation, and restoration of electrolyte balance, is required (39, 42, 44, 45, 52, 53).

In the case of an initial episode, the optimal treatment plan consists of either metronidazole, vancomycin or fidaxomicin depending on the infection's severity (39, 44, 53, 54, 55, 57). Generally, metronidazole is recommended for treatment of mild to moderate infections, whereas vancomycin is recommended for treatment of severe infections. Moreover, fidaxomicin can be applied as an alternative for vancomycin or for patients with high risk for recurrent episodes (44, 50, 55, 56, 57).

Mild to moderate CDI.

Metronidazole and vancomycin are equally effective for treatment of non-severe CDI(58, 59). However, metronidazole is considered to be the first line drug due to its lower cost. Furthermore, vancomycin is not recommended for mild-moderate CDI therapy due to the risk of spreading of vancomycin-resistant enterococci (VRE). (39, 44, 50, 52, 59)

Metronidazole should be prescribed at a dose of 500 mg orally 3 times per day or 250 mg 4 times per day for 10-14 days (39, 41, 42, 52). Vancomycin can be used as an alternative, at a standard dosing of 125 mg orally 4 times per day for 10 days, for patients who cannot tolerate metronidazole, do not respond to the initial treatment for 5-7 days or develop signs or symptoms of severe CDI(39, 44, 53, 60). In addition, vancomycin should be administrated in the case of pregnant, and breastfeeding women (39). Metronidazole can be administrated intravenously in patients unable to take oral medication in contrast with vancomycin which is ineffective on CDI therapy when given intravenously (as it cannot be excreted into the colon) (42, 44, 52, 53).

Severe CDI.

Metronidazole is considered inferior to vancomycin for the treatment of severe CDI based on their pharmacokinetic parameters(44, 53, 61). The full dose of vancomycin reaches the large intestine (the site of infection in this case) as it is poorly absorbed from the gastrointestinal tract when given orally. In contrast, metronidazole is usually absorbed entirely and promptly after oral intake. Therefore, vancomycin is the first line drug for severe CDI therapy. (40, 44, 52, 53) The recommended dose of vancomycin is 125 mg 4 times daily for 10 days. Fidaxomicin, at a dose of 200 mg 2 times daily for 10days, can be applied to patients that present vancomycin intolerance or no signs of improvement (45, 46, 47). In patients whom oral antimicrobials cannot reach an infected segment of the colon, vancomycin can be delivered via enemas, at a dose of 500 mg in 100-500 ml of normal saline 4 times a day, as an adjunctive therapy (39, 44, 50, 60). Administration of oral metronidazole is strongly contraindicated in severe CDI (44, 52).

Severe and Complicated CDI.

For the management of severe and complicated CDI, vancomycin is recommended at a high oral dose (or by nasogastric tube) of 500 mg 4 times daily, plus intravenous metronidazole at a dose of 500 mg 3 times daily. In complicated CDI with ileus, or toxic megacolon and/or significant abdominal distention, vancomycin per rectum (at a dose of 500 mg in a volume of 100-500 ml 4 times daily) is also highly recommended. (39, 41, 44, 37, 50, 52, 53, 60)

Surgical intervention can be life-saving for patients that progress to fulminant CDI or patients that do not respond to medical therapy. Although, there are no clear guidelines to establish when medical therapy has failed. Consequently, early surgical consultation to all patients with complicated CDI is of crucial importance. There is enough evidence to support that earlier operative management before the aggravation of the infection and irreparable organ damage, leads to improved survival. (39, 45, 47, 50, 53)

Treatment failure, rectal toxicity(toxic megacolon), intestinal perforation, acute abdomen, septic shock, hypotension requiring vasopressor therapy, mental status changes, necrosis of the intestine, systemic inflammation, and multiple organ failure are the main indications for surgical management (39, 41, 46, 47, 52).

Two different surgical approaches are used to manage complicated CDI: (1) Subtotal colectomy, and (40) Diverting loop ileostomy with colonic lavage. (62)

Subtotal colectomy with end ileostomy is the operation of choice. During this procedure, the entire colon is been removed, and an ileostomy is been created leaving the rectum in place. As subtotal colectomy has high mortality rate, it is vital to diagnose infected patients early enough in order to reduce the risk of progressing to fulminant colitis and organ failure (40, 62).

Diverting loop ileostomy with colonic lavage has been proposed as a substitute to colectomy. During this procedure, an ileostomy is being created and the colon is being flushed with warm polyethylene glycol. This procedure is less extensive, therefore reduced morbidity and mortality rates have been reported. (40,62)

Recurrent CDI (RCDI).

According to the Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) Recurrent CDI is defined as "an episode of CDI that occurs less than or equal to 8 weeks after the onset of a previous episode, provided that CDI symptoms from the earlier episode resolved after completion of initial treatment, and other causes have been excluded" (43, 44, 53, 63). One to five (1:5) CDI patients present a recurrent episode. After the first recurrence, the risk for multiple relapses escalates to 40-65% (39,41). The infection relapse may be due to the same strain as the initial episode or a different one (41, 52, 53)

The management of RCDI can be challenging since no alternative treatment is available. The treatment of the first recurrence is the same as the treatment of the initial episode. Despite the fact that Vancomycin and fidaxomicin are considered to be equally effective in the treatment of first RCDI, fidaxomicin seems to be superior to vancomycin in preventing further recurrences (expect from the case of PCR ribotype 027). (39, 42, 52, 63) Fidaxomicin's cost is significantly higher than vancomycin's or metronidazole's cost. Therefore, cost should always be in consideration when defining the optimal treatment plan. (Treatment Strategies for Recurrent *Clostridium difficile* Infection - Christine Leong and Sheryl Zelenitsky). Vancomycin administrated at a tapered and/or pulsed regimen, at a dose of 125mg 4 times daily, is recommended for the treatment of the second recurrence (39, 52, 63, 64). Whether a third recurrent episode ensues, Fecal Microbiota Transplantation(FMT) is strongly recommended(39, 44,48, 50, 53, 63, 64, 65, 66).

Regimen	*Subclass*	*Mechanism of Action*	*Pharmacokinetics*	*Clinical Application*	*Adverse Effects – Toxicities*
Metronidazole	Nitroimidazole	Bactericidal activity: Disruption of electron transport chain	Oral or IV	Mild-moderate CDI, first RCDI	Gastrointestinal disturbances, taste disturbances, neuropathy, seizures etc.
Vancomycin	Glycopeptide	Bactericidal activity: Inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of nascent peptidoglycan	Oral or IV	Mild-moderate CDI, severe CDI, severe and complicated CDI, Recurrent CDI	"Red man" syndrome, nephrotoxicity etc.
Fidaxomicin*	Macrocyclic	Bactericidal activity: Inhibits bacterial RNA Polymerase	Oral	Severe CDI, Recurrent CDI	Nausea, vomiting, constipation

Table1: Properties of antimicrobial agents used to treat CDI (57,67,68)

**Fidaxomicin was approved by the US Food and Drug Administration (FDA), for the treatment of CDI, in May 2011.*

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is considered to be an alternative therapeutic technique use to treat recurrent CDI, and it is defined, as the introduction of normal fecal microbiota from a health donor to a patient.(53, 65, 66, 69, 70, 71, 72) This donor, who is usually a family member of the CD infected patient, should meets specifics criteria such as no antibiotic use for the last three months, no history of infectious or bowel inflammatory diseases.(66, 70, 72) The efficacy and safety of stool transplantation have been shown to be equally, either administered using the upper part (e.g. nasoduodenal tube) or the lower part of the gastrointestinal tract (e.g. colonoscopy enema)(48, 53, 66, 69). Donor's stool are taken on the day of FMT and diluted in with normal seline (50 grams of stool to 200ml-250ml of seline). (66, 72,73) The solution is stored until the procedure, which should take place no more than 6hours after the the donor voiding. (72,73) Positioning the solution via colonoscopy ensures that distribution's positioning is adequate to the colon.(72) As for the preparation of the patients, they should stop any antibitiotic treatment before the transplantation and be administered a proton pump inhibitor last day prior to procedure.(70, 73, 74)

A*gents other than metronidazole, vancomycin, and fidaxomycin.*

Rifaximin. Rifaximin is a wide-spectrum rifamycin characterized by gastrointestinal-selectivity as it is poorly absorbed from the GI tract when administrated orally. The administration of rifaximin raises concerns for development of resistance against ramycins. Despite the fact that current guidelines discourage the use of rifaximin as monotherapy for CDI, it can be given in combination with oral vancomycin for RCDI therapy. Further investigations are needed to evaluate the efficacy of rifaximin in CDI treatment. (46,75,76,77)

Probiotics. Currently, there is insufficient evidence to recommend the use of probiotics for the treatment or prevention of CDI. Due to the potential risk of fungaemia or bacteremia, more studies are needed for the use of probiotics can be recommended.

Nitazoxanide, anion exchange resin, tigecyclin, fusidic acid, not-toxigenic C.difficile, rifampicin, or monoclonal antibodies, are currently not recommended since there is not enough evidence to prove their benefits to the treatment or prevention of CDI.

Discussion

Conclusion

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