

Diagnostic Approach and Management of *Clostridioides difficile* Infection

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ABSTRACT

Clostridioides difficile infection (CDI) was first viewed as a nosocomial infection as it is associated with antibiotics administration. But since antibiotics are more frequently to be prescribed in the community setting, clinicians should investigate the probability of all antibiotics-associated diarrhea as CDI.

Diagnostic of CDI should be conducted cautiously as the manifestation of CDI varies from asymptomatic to fatal consequences and is associated with morbidity, mortality, recurrence risk, outbreak possibility, and low quality of life. Management of this infection should include infection prevention and control, stopping the offending antibiotics, and administration of specific antimicrobials.

Clinicians should also recognize the risk of recurrence and the higher probability of less efficacious specific antimicrobials in each episode of recurrence.

Keywords: antibiotics, *Clostridioides difficile*, diagnosis, management

ABSTRAK

Infeksi *Clostridioides difficile* awalnya dinilai sebagai infeksi nosokomial, karena hubungannya dengan administrasi antibiotik. Namun karena penggunaan antibiotik cukup luas pada komunitas di luar rumah sakit, klinisi harus mengevaluasi kemungkinan seluruh kondisi diare yang berhubungan dengan antibiotik ke arah infeksi *C difficile*.

Diagnosis infeksi *C difficile* sebaiknya dilakukan secara saksama karena manifestasinya yang bervariasi mulai dari asimtomatik hingga kondisi fatal, yang berdampak pada morbiditas, mortalitas, risiko rekurensi, kemungkinan kejadian luar biasa, dan rendahnya kualitas hidup. Oleh karenanya, penatalaksanaan infeksi *C difficile* seharusnya mencakup pencegahan infeksi dan kendali, penghentian administrasi agen antibiotik, dan administrasi antimikroba yang spesifik.

Dalam menangani kasus infeksi *C difficile*, klinisi juga wajib menilai risiko rekurensi dan mengetahui bahwa seiring semakin sering rekurensi, semakin kurang efektifnya antimikroba yang diberikan

Kata kunci: antibiotik, *Clostridoides difficile*, diagnosis, penatalaksanaan

INTRODUCTION

Clostridioides difficile is a Gram-positive bacterium that has the potential to cause infection along the intestinal tract, with variability clinical symptoms, ranging from asymptomatic to fatal consequences. Due to its variable presentation, clinical approach to diagnose this condition should be done cautiously.¹

Clostridioides difficile infection (CDI) poses 2-sided health issues, as it causes a burden both on the individual aspect (regarding its morbidity, mortality, and its impact on quality of life) and on the community aspect (regarding the recurrence risk, outbreak possibility, and socioeconomic burden). CDI was reported to be associated with the higher cost of healthcare, up to \$30,049.²⁻⁵

CDI was first viewed as a nosocomial infection as it first was found more prevalent in the hospital environment where antibiotics were frequently prescribed. But as the prescription of antibiotics became more deliberately used in the community, the paradigm where CDI was placed among nosocomial infections had to be shifted. Hensgens et al reported that CDI was predicted to cause 390–730 cases of diarrhea in the community annually in the Netherlands. While Bartlett et al reported that CDI was responsible as the third most cause of community diarrhea (causing about 30% of community diarrhea). In 2011, CDC predicted that CDI might cause about 29,000 cases of death. These epidemiological findings had to be taken seriously in the clinical setting as the recent report regarding CDI could not exclude bias and the probability of misdiagnosis.²⁻⁵

This study was written to bring another perspective to better diagnose and manage CDI in the appropriate clinical setting.

Microbiological Aspect of *Clostridioides difficile*

Clostridioides difficile is a Gram-positive bacterium that can produce toxins, associated with colitis. The colonization of *C. difficile* is reported to be associated with antibiotics usage. The virulence factor of these obligate anaerobic bacteria was identified in 1935, determined by the production of its toxin: Clostridial toxin A (TcdA) and toxin B (TcdB). *C. difficile* is differentiated from other species based on its ability to decarboxylase parahydroxyphenylacetate acid, creating p-cresol, which enables *C. difficile* to produce porcine scent.^{2,3}

C. difficile is transmitted via oral-fecal route. The spore of these bacteria is formed as a dormant cell,

highly resistant to environmental conditions, such as disinfectant and antimicrobial agents. Ingested spore then travels through the stomach into the duodenum. In the duodenum, spore develops due to exposure of primary bile acids, produced by liver, such as taurocholic. On the other hand, secondary bile acid, which is produced by intestinal bacteria, has a restrictive property against *C. difficile* growth. While these bacilli can grow along the intestinal tract, colon is the most frequent site of development of *C. difficile*.¹⁻³

The ability of the spore to grow and colonize the intestine is influenced by the imbalance and dysbiosis of gut microbiota and metabolomics of normal flora. The usage of antibiotics causes this dysbiosis, creating an environment suitable for *C. difficile* to grow. Several studies also reported that ampicillin and clindamycin were associated with stimulating the production of colonization factor of bacteria, surface protein Cwp84, and SlpA.¹⁻³

Pathological Aspect of *Clostridioides difficile*

The mechanism of host immune response to CDI is initiated by the production of antimicrobial compounds, such as lysozyme and cationic antimicrobial peptides. The further involvement of innate immune response is the production of proinflammatory cytokines and chemokines via nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) pathway and transcription factor AP-1. The affecter of innate immune response is triggered by *C. difficile* toxin, flagellin protein of the bacilli, surface protein (SlpA), and bacteria cell wall.^{2,3}

The clinical manifestation of CDI is mainly influenced by the PaLoc locus containing the bacteria genomic profile. PaLoc is the pathogenic locus that encodes clostridial toxin, both TcdA and TcdB, along with 3 other proteins, associated with the regulation of production and secretion of that two-toxin homolog (TcdR, TcdE, and TcdC). The mechanism of these three proteins influencing the regulation of production and secretion of clostridial toxin has not yet been elucidated.^{2,3,6}

When TcdA and TcdB are secreted into the intestinal lumen, these two-homolog toxins will attach to the epithelial cells, inducing immune response to produce chemokine, proinflammatory cytokines, inflammatory cells migration, tight junction disruption, and epithelial cell death. Though TcdA and TcdB are homologs, TcdA is reported to be more potent in the small intestine, while the latter shows more potency in the colon segment.^{2,3}

Besides these two toxins, several strains of *C. difficile* can produce *C. difficile* transferase (CDT or binary toxin). Unlike the two former toxins, CDT is encoded by 2 genes, *cdtA* and *cdtB*, which are located in different loci. Although this binary toxin is reported to be associated with severe manifestation of CDI, the mechanism by which this toxin causes such impact has not been well understood. CDT is thought to be related to the disruption of actin cytoskeleton causing epithelial cell death, bacilli adherence, and *C. difficile* colonization.²

Epidemiology of *Clostridioides difficile* Infection (CDI)

CDI was first viewed as a nosocomial infection as it is associated with antibiotics usage. But as antibiotics were more deliberately used in community settings, CDI was found more frequently in the community. A study in the US reported that the incidence of this infection reaches up to 120 cases per 100,000 population annually. In the Netherlands, the incidence was reported to reach 730 cases per 100,000 population annually. CDI was also reported to be the third most frequent cause of community diarrhea (causing 30% of diarrhea cases). This number of cases should be viewed as an iceberg phenomenon because CDI is likely to go underdiagnosed.^{5,7,8}

Although CDI is closely related to antibiotics-associated diarrhea, a prospective study reported that *C. difficile* caused about 30% of antibiotics-associated diarrhea cases. In addition to this bacillus, *Staphylococcus aureus*, *Clostridioides perfringens*, *Clostridioides sordelli*, and *Klebsiella oxytoca* were reported to be the pathogenic causes of antibiotics-associated diarrhea.^{1,5,7,8}

Clinical Manifestation of *Clostridioides difficile* Infection (CDI)

Clinical manifestation of CDI varies from self-limiting diarrhea, fulminant colitis, pseudomembranous colitis, toxic megacolon, bowel perforation, and sepsis with/without multiple organ dysfunction syndrome. Several risk factors reported to be associated with CDI were history of hospital admission, underlying bowel condition, elderly, and antibiotics administration. Every class of antibiotics should be suspected to cause CDI, but among them, clindamycin, cephalosporin, and quinolone were the most frequently reported antibiotics to be associated with. In addition to antibiotics class, dosage and duration administered were reported to influence the manifestation of CDI. This finding was

supported by the observation that dysbiosis of gut microbiota could occur and sustain for more than 3 months after antibiotics treatment. Aside from antibiotics, proton pump inhibitors (PPI) were reported to be associated with CDI, though the mechanism was still under investigation.^{1,2}

Table 1. Clinical severity of *Clostridioides difficile* infection (CDI)

Severity	IDSA criteria	ACG criteria
Mild to moderate	WBC \leq 15,000 cells/mL and SCr $<$ 1.5 mg/dL	Diarrhea with any additional sign or symptoms not meeting severe or complicated
Severe	WBC \geq 15,000 cells/mL or SCr $>$ 1.5 mg/dL	Alb $<$ 3 g/dL with either WBC \geq 15,000 cells/mL or abdominal tenderness
Complicated	Associated with hypotension, shock, ileus, or megacolon	Associated with admission to ICU, hypotension, fever \geq 38.5°C, altered mental status, ileus/significant abdominal distention, WBC \geq 35,000 cells/mL or $<$ 2,000 cells/mL, serum lactate $>$ 2.2 mmol/L, or end organ failure

IDSA: Infectious Disease Society of America; ACG: American College of Gastroenterology; WBC: white blood cell; SCr: serum creatinine; Alb: albumin

Special attention is needed in the case where *C. difficile* causes asymptomatic colonization, as asymptomatic individuals are still able to transmit the clostridial spore into their environment. This asymptomatic colonization can be caused by both toxin-producing strains and negative toxin-producing strains. Asymptomatic colonization of non-toxicogenic *C. difficile* was reported to be a protective factor against other *C. difficile* isolate infections. However, this finding has to be interpreted cautiously as non-toxicogenic *C. difficile* strains can become toxicogenic through horizontal gene transfer.^{1,2,6}

Diagnostic Approach to *Clostridioides difficile* Infection (CDI)

Diagnosis of CDI has to be built upon clinical manifestation and microbiological study. Available diagnostic tests of CDI are *C. difficile* product test (glutamate dehydrogenase/GDH, aromatic fatty acid, TcdA and/or TcdB), culture (toxicogenic culture), and nucleic acid amplification test (NAAT) to *C. difficile* gene (detecting 16S rRNA, toxin gene, gene encoding GDH).⁹⁻¹¹

Diagnostic tests detecting bacteria components are possible to indicate colonization, while tests detecting toxins are methods with a higher probability to assess CDI. Thus, diagnostic effort built solely upon microbiological study is deemed to be irrational and generally ends up in overdiagnosis and overtreatment.^{2,8,10}

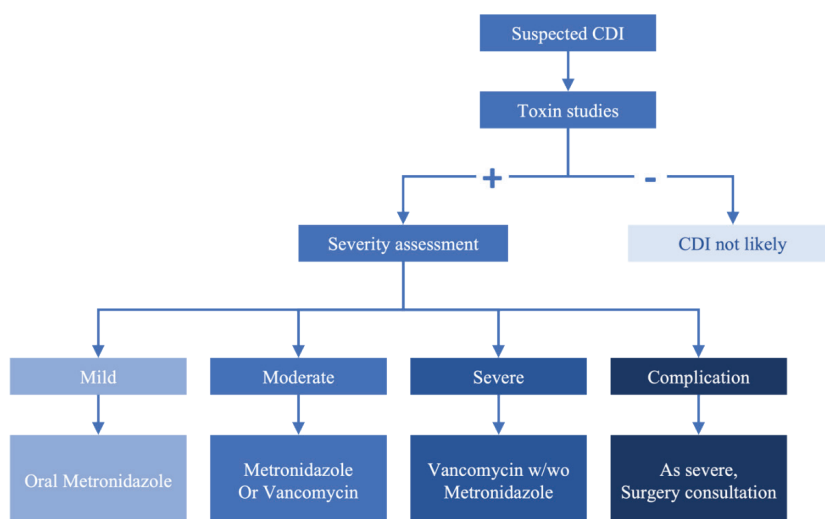


Figure 1. Clinical approach to suspected CDI cases

Table 2. Specific antimicrobials for CDI (adopted from IDSA)

Clinical definition	Recommended treatment	Strength of recommendation/ quality of evidence
Initial episode, non severe	VAN 4 x 125 mg for 10 days	Strong/high
	FDX 2 x 200 mg for 10 days	Strong/high
	Metro 3 x 500 mg PO for 10 days	Weak/high
Initial episode, severe	VAN 4 x 125 mg PO for 10 days	Strong/high
	FDX 2 x 200 mg for 10 days	Strong/high
Initial episode, fulminant	VAN 4 x 500 mg PO	Strong/moderate (oral VAN)
	Metro 3 x 500 mg IV and rectal VAN if ileus	Weak/low (rectal VAN)
		Strong/moderate (IV Metro)
First recurrence with history of Metro	VAN 4 x 125 mg PO for 10 days	Weak/low
First recurrence with history of VAN	VAN 4 x 125 mg PO for 10–14 days, 1 x 125 mg for the next 7 days, and every 2–3 days for 2–8 weeks (prolonged tapered and pulsed VAN regimen)	Weak/low
	FDX 2 x 200 mg for 10 days	Weak/moderate
Second or subsequent recurrence	Prolonged tapered and pulsed VAN regimen	Weak/low
	VAN 4 x 125 mg PO for 10 days followed by rifaximin 3 x 400 mg for 20 days	Weak/low
	FDX 2 x 200 mg for 10 days	Weak/low
	FMT	Strong/moderate

CDI: *Clostridioides difficile* infection; IDSA: Infectious Disease Society of America; VAN: vancomycin; FDX: fidaxomicin; Metro: metronidazole; PO: per oral; IV: intravenous; FMT: fecal microbiota transplantation

Evaluation of treatment using toxin studies is not recommended as toxins may remain detected during treatment, and sometimes until the patient has reached clinical cure. If the toxin is not detected from a stool sample, CDI is highly unlikely. However, if bacteria material is found in the stool sample while the toxin study is negative, CDI still cannot be excluded. Therefore, diagnosis of CDI must be built upon a 2-step algorithm, where toxin study and microbiological study have to be performed simultaneously.^{3,11,12}

Management of *Clostridioides difficile* Infection (CDI)

Management of CDI has to be initiated by infection prevention and control, which includes antibiotics stewardship, patient isolation, universal precautions, active disinfection, and education. Stopping offending

antibiotics is the mainstay treatment of CDI. Antibiotics currently available to eliminate *Clostridioides difficile* are metronidazole, vancomycin, and fidaxomicin. Patients with mild to moderate symptoms of CDI may be treated with oral metronidazole, while oral vancomycin is necessitated by those with severe symptoms or those with complications. This choice of antibiotics is reported to be supported by clinical trials, which showed that metronidazole was inferior to vancomycin in intention to treat analysis (clinical cure rate 72.7% in those with metronidazole and 81.1% with vancomycin). Concomitant antibiotics administration is not recommended in the setting of CDI as it is associated with a lower clinical cure rate, higher recurrence rate, and longer duration of diarrhea.^{10–13}

Aside from stopping offending antibiotics and administration of specific antimicrobials,

pharmacological management in the setting of CDI should include stopping anti-motility and evaluation of PPI. In patients with ileus or toxic megacolon indication, where oral antibiotics cannot reach the site of infection, rectal vancomycin combined with intravenous metronidazole may be recognized.^{7,11}

In fulminant CDI, surgical management by total abdominal colectomy may be recognized, especially when the patient is present with septic, severe organ dysfunction, acute abdomen, ileus, leukocytosis, and hyperlactatemia (> 5.0 mM).³

Recurrence of *Clostridioides difficile* Infection (CDI)

Those with CDI are reported to be prone to relapse up to 15–25% in 8 weeks after the first episode. Those with the first and second recurrences of CDI face the risk of the third recurrence of up to 65%. This recurrence is reported to be associated with immune response dysregulation due to clostridial toxin and/or dysbiosis of gut microbiota. The recurrence rate is reported to be lower in those treated with oral fidaxomicin (13%) compared to oral vancomycin (25%). Factors attributed to recurrence are age > 65 years old, concomitant antibiotics use, renal failure, history of CDI, antacid usage, and CDI severity.^{2,3}

Alternative Treatment of *Clostridioides difficile* Infection (CDI)

Probiotics administration was reported as the alternative therapy in treating recurrence CDI as CDI is caused by dysbiosis of gut microbiota, but clinical evidence supporting its prescription is still limited.^{7,14}

Another alternative in the management of recurrent CDI is fecal microbiota transplantation (FMT), especially in the setting where the episode of CDI occurs more than twice, in which the efficacy of specific antibiotics drops below 30%. Van Nood et al reported that FMT was efficacious in treating CDI with multiple recurrences. British Society of Gastroenterology (BSG) recommended that FMT could be an optional treatment in patients with a history of at least two episodes of CDI.^{2,7,14,15}

CONCLUSION

Clinicians should shift their view about *Clostridioides difficile* infection as solely a nosocomial infection to antibiotics-associated diarrhea which can be found in the community setting. Therefore,

diagnostic evaluation to confirm CDI in patients with antibiotics-associated diarrhea is important to avoid underdiagnosis and undertreatment. However, the diagnostic approach must be conducted cautiously as the implication of CDI affects not only individual aspects but also community aspects. Management should include infection prevention and control, stopping offending antibiotics, and administration of specific antimicrobial agents to achieve clinical cure and reduce the risk of recurrence.

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