Current Diagnostic and Treatment Approach of *Clostridioides difficile* Infection

Bella Yunita[1], Achmad Fauzi[2]*

[1] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Achmad Fauzi, MD. Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 70. Jakarta 10430, Indonesia. Email: bellaaabellss@gmail.com

ABSTRACT

C. difficile infection is related to wide spectrum of disease, from self-limiting diarrhea to fulminant disease that can cause toxic megacolon or pseudo-membrane colitis. Difficult approach to diagnose this disease is also problem. C. difficile infection is diagnosed when diarrhea occurred in high risk patient with positive result of GDH or NAAT test that was confirmed by positive result of toxin test. Nevertheless, there is limited choice of treatment in Indonesia. Thus, the main priority of C. difficile infection in Indonesia is associated with its prevention, by implementing standard precaution and use of rational antimicrobial.

Keywords*: C. difficile infection, colitis, diagnosis, diarrhea, treatment.*

INTRODUCTION

Clostridioides difficile (*C. difficile)* infection causes wide spectrum of disease; it may cause self-limiting diarrhea to severe and fulminant infection such as pseudo-membrane colitis and toxic megacolon. Several risk factors are reported to contribute for this infection: older age, history of hospitalization, people who lived in healthcare facilities, or history of antimicrobial use.[1] *C. difficile* infection is defined as *C. difficile* colonization that causes diarrhea, with positive result of *C. difficile* toxins or toxigenic *C. difficile* is detected from feces specimen, or pseudo-membrane colitis found by colonoscopy and/or histopathology examination. In the patient with risk factors and experienced diarrhea 3 times/day, this patient should undergo *C. difficile* examination.[2-3] Nevertheless, prevalence of community acquired *C. difficile* infection increased, because it can also occurred in patient without prior history hospitalization.[4]

In the United States, *C. difficile* infection is associated with 15,000-30,000 deaths/year, while in Indonesia, studies related to *C. difficile* infection is limited.[1,4] *C. difficile* infection is often undetected in Indonesia, yet higher use of over the counter (OTC) antimicrobial in Indonesia can lead to higher prevalence of *C. difficile* infection. Study from Collins, et al (2017) that was conducted in hospital located in Central Java reported positive glutamate dehydrogenase (GDH) results in 20.6% patients with detected toxins in 5.6% patients. From culture, toxigenic *C. difficile* was detected in 10.9% and non-toxigenic was detected in 10.6%. Other results from this study: ribotype 017 was detected in 24.3%, non-toxigenic QX 224 in 9.5%, and QX 238 and QX 108 was detected in 8.1%. This

prevalence was higher than in neighbor countries such as Australia (7%), Singapore (7-11%), and Malaysia (13.7%).[1] Because high prevalence of *C. difficile* infection and difficult diagnostic and treatment approach of this disease, this review article intend to explain current diagnostic and treatment approach of *C. difficile* infection.

CLOSTRIDIOIDES DIFFICILE VIROLOGY

C. difficile is gram positive rod, anaerobic bacteria that produces pathogenic spores for gut.[4-6] Transmission of *C. difficile* infection occurred as fecal-oral transmission. Once the *C. difficile* spores infected stomach, this spores can not be disintegrated even when exposed to acid secretion of stomach. The bacteria then enters small gut, and exposed to bile acid that can induce vegetative state of this bacteria. Prior exposure to antimicrobial decreased number of normal flora of the gut, thus induce colonization of *C. difficile* in colon. This colonization then produces *C. difficile* toxins.[5,6] *C. difficile* toxins inhibits polymerization of actin from host cell and then causes cell death. In colon, this bacteria produces spores that will exit with feces. *C. difficile* is reported can withstand heat and ethanol based disinfectant.[5]

There are three types of toxins produced by *C. difficile* bacteria, toxin A, toxin B, and CDT. Toxin A is enterotoxin, while toxin B is cytotoxin, thus both of these toxins play the role to impair gut mucosa and acute inflammation that causes colitis and diarrhea as the main clinical manifestation.[1,4] The third toxin, CDT, which is a binary toxin is rarely detected in host cell, yet it is associated with inflammation and water loss from colon.[1,7] Host immunity to fight the toxin is associated with severity of clinical manifestation and recurrent infection. Risk factors for *C. difficile* consist of history of hospitalization, history of antimicrobial use (clindamycin, cephalosporin, carbapenem, fluoroquinolone, and monobactam), and older age. Study from Smilings, et al.[8] (2014) reported that antimicrobial that is associated with *C. difficile* infection are third generation cephalosporin (OR 3.2; 95% CI 1.8-5.71), clindamycin (OR 2.9; 95% CI 2-4), forth generation cephalosporin (OR 2.14; 95% CI 1.3-3.52), carbapenem (OR 1.8; 95% CI 1.3-2.7), cotrimoxazole (OR 1.8; 95% CI 1.3-2.7), and fluoroquinolone (OR 1.7; 95% CI 1.2-2.4). Other risk factors are *inflammatory bowel disease* (IBD), heart disease, chronic kidney disease, and white race.[3] Table 1 explains clinical characteristic of *C. difficile* infection.[4]

Once *C. difficile* enters the body, it causes innate immune system by four virulence factor, TcdA/TcdB (or toxin A and toxin B), flagellin, protein A (SlpA), and PG fragment. All of this virulence factor then inducing production of nuclear factor κβ (NF-κβ) and AP-1 protein to release chemokine and pro-inflammatory cytokine.[7] *C. difficile* infection is different from *C. difficile* colonization. Toxigenic *C. difficile* always consists of toxin B and usually consists of toxin A. Nontoxigenic *C. difficile* does not cause infection. Nevertheless, toxigenic strain of *C. difficile* can cause colonization in asymptomatic patient. For diagnosing *C. difficile* infection, we need to obsereve diarrhea as clinical manifestation of *C. difficile* infection with positive result of toxin A and/or toxin B from feces specimen.[1]

DIAGNOSTIC APPROACH AND CLASSIFICATION

Active infection of *C. difficile* is marked by new onset of 3 times/day diarrhea with unknown cause. Other clinical manifestation that can occur

Table 1. Clinical characteristic of C. difficile infection.[4]

Characteristic	Hospital-acquired	Community-acquired	Recurrent
Age (median)	72	50-51	56-75
Risk factors	Prior use of antimicrobial, PPI, IBD	Prior use of antimicrobial, heart disease, CKD, IBD	Older age, female, CKD, IBD, prior use of corticosteroid, immunocompromised
Strain	078, 106	Ribotype 002, 020, 014, 015, 027, 078, 106	Ribotype 027
30-day mortality rate	10.6%	3-17%	7.8-9.3%

is fever, nausea and vomiting, and abdominal pain. Every patient with flare of IBD and diarrhea as clinical manifestation is recommended to undergo *C. difficile* examination. Normal result of colonoscopy and histopathology excludes *C. difficile* infection in patient with diarrhea.[3] **Table 1** explains clinical manifestation of *C. difficile* infection.[6]

Patient with clinical manifestation of *C. difficile* infection (diarrhea ≥ 3 times/day) should undergo *C. difficile* examination. *C. difficile* examination consists of GDH or NAAT examination. Negative results excludes *C. difficile* infection, yet if the result is positive it means the patient is recommended to undergo toxin examination. NAAT or GDH examination alone can not distinguish *C. difficile* infection from *C. difficile* colonization. Repeat examination within 7 days in the same diarrhea episode and in asymptomatic patient are not recommended.[2] **Table 3** explains choices for diagnostic examination with each sensitivity and specificity.[3] Picture 1 explains algorithm for diagnosing *C. difficile* infection.[3]

Table 2. Clinical manifestation of C. difficile infection.[6]

Spectrum of disease	Diarrhea	Other symptoms	Physical examination	Colonoscopy and other finding
Asymptomatic carrier	None	None	Normal	Normal
Simple antibiotic associated diarrhea	Mild	Absent	Usually normal	Normal
Early colitis	Profuse	Nausea, anorexia	Low grade fever, with/ without mild abdominal tenderness	Nonspecific patchy erythema
Pseudo-membranous colitis	Profuse	Nausea, malaise, abdominal discomfort	Fever (sometimes high); abdominal distension and tenderness	Pseudo-membrane (raised yellow plaque), leukocytosis (> 50,000/µl) with shift to the left pattern
Fulminant colitis	Usually profuse and sever, may be absent in ileus or toxic megacolon	Nausea, abdominal discomfort	Toxic appearance, high fever, abdominal distension, tenderness and peritoneal sign	Endoscopy is contraindicated in severely ill patient, leukemoid reaction, radiographic may show colonic dilatation, mucosa; thickening or perforation

Table 3. Choices for diagnostic examination of C. difficile infection.[3]

Examination	Sensitivity	Specificity	PPV	NPV	Comment
Toxigenic culture	94	99	-	-	Detect toxigenic strain Not differentiate colonization from active infection
Glutamate dehydrogenase (GDH)	94-96	90-96	34-38	100	Not differentiate toxigenic and non-toxigenic strain Not differentiate colonization from active infection
Cell cytotoxicity neutralization assay (CCNA)	93	98	-	-	Detect free toxin B Differentiate colonization from active infection
Nucleic acid amplification testing (NAAT)	95-96	94-98	46	100	Gene detection for toxin B Not differentiate colonization from active infection
Enzyme immunoassay (EIA) toxin A and toxin B	57-83	99	69-81	99	Detect free toxin Differentiate colonization from active infection

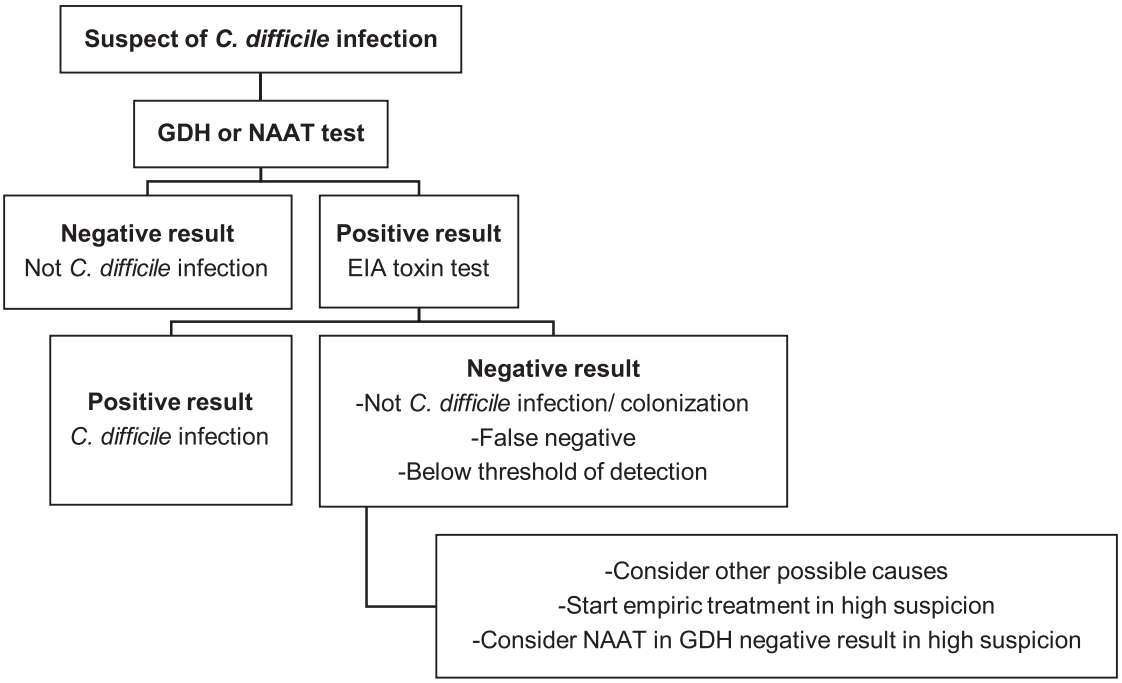

Figure 1. Diagnostic Algorithm for C. difficile Infection.[3]

Classification of *C. difficile* infection consists of severe disease, fulminant disease, and recurrent disease. Severe *C. difficile* infection is characterized by leucocyte ≥ 15,000/µl or SCr > 1.5 mg/dl. From post hoc analysis of RCT study, it was reported that leukocytosis (RR 2.29; 95% CI 1.63-3.21) and renal failure (RR 2.52; 95% CI 1.82-3.5) that occurred in *C. difficile* infection were associated with failure of fidaxomicin and vancomycin therapy.[9] Other definition of severe disease comes from European Society of Clinical Microbiology and Infectious Diseases (ESCMID), which defines severe *C. difficile* infection as infection with fever > 38.5°C, leukocytosis with leucocyte count of > 15,000/µl, and rise in SCr > 50% above baseline.[10] Fulminant *C. difficile* infection is characterized by criteria of severe disease and hypotension or shock or ileus or toxic megacolon. Fulminant disease is associated with needs of colectomy, increased risk of mortality after procedure, or increased risk of death. Other predictor for poor prognosis includes hypoalbuminemia, eosinophilia, fecal calprotectin > 2,000 µg/g, and fever > 38.5°C. Hypoalbuminemia is marker of protein loss in the condition of colopathy and host defense mechanism to bind toxin A or B, thus it promotes proteolytic formation to gut epithelial and avoid cytotoxic effect of infection.[3]

Recurrent infection is characterized as recurrent episode of diarrhea with positive result of confirmation test (NAAT or EIA) within 8-12 weeks after initial treatment of *C. difficile* infection. Outcome of recurrent infection divides into 2 categories: clinical recover (no diarrhea episode and no recurrent diarrhea) and bacteriologic recover (clinical recover and negative result from feces test).[3]

PRIMARY AND SECONDARY PREVENTION

Prevention of *C. difficile* infection includes standard precautions such as use of gloves (handschoen) and gown, wash hands with water and soap and implementation of hand hygiene for health workers, family, or caregiver who treat *C. difficile* infection patients.[2-3] Other primary prevention of *C. difficile* infection includes rational use of antimicrobial.[6] Patient with *C. difficile* infection room and bathroom should be separated with other patient, until 48 hours after diarrhea resolved. Asymptomatic patient is carrier of *C. difficile* infection, yet this group of patient does not have to be isolated from other patient.[2,5] Probiotic (living microorganism

with good effect for health, due to colonization of this microorganism is related to inhibition of pathogenic microorganism, modulation of immune system, and protect gut mucosa integrity) is not recommended as primary and secondary prophylaxis for *C. difficile* infection.[3]

Fecal microbiota transplantation (FMT), a new prevention approach of *C. difficile* infection, is recommended to prevent recurrent infection. Gut has normal flora that can inhibits or as competitor for pathogenic microorganism. In patient with proliferation of *C. difficile*, reduced number of normal gut flora is observed; thus FMT is thought to be a better option to increase number of normal gut flora that comes from healthy person.[11] FMT is administered during colonoscopy procedure or by capsule. Both of this administration of FMT is not different statistically from studies, but if it can not be done other approach is by enema administration. From RCT study, enema administration of FMT is not different statistically with placebo, thus it is better if FMT was administered by capsule or colonoscopy. Enema FMT can be considered in children with *C. difficile* infection. Repeat dose of FMT can be given 8 weeks after the first dose.[3]

Adverse effect of FMT administration is abdominal cramp, bloating, abdominal pain, nausea, diarrhea, constipation, and sub-febrile fever. Risk of other pathogenic infection is also observed with FMT administration. From study, it was reported that bacteremia from extended spectrum beta lactamases (ESBL) *Escherichia coli* can occur in FMT administration. FMT administration can also causes perforation, gastrointestinal bleeding, and sedation complication. Failure of FMT is defined as recurrent diarrhea with positive result of *C. difficile*. Administration of FMT from colonoscopy procedure or antimicrobial can be given in this situation.[3] Donor candidate for FMT should be screened from HIV, hepatitis A, B, and C, viral, bacterial, and parasite infection.[11]

Medical treatment for prevention of *C. difficile* infection consists of antimicrobial use or bezlotoxumab (BEZ). Oral vancomycin with the dose of 125 mg daily can be offered in patient who is not FMT candidate, relapse after FMT administration, or high risk of recurrent *C. difficile* infection. This approach can be offered in older patient (age ≥ 65 years old) or immunocompromised patient.[3] BEZ is monoclonal antibody that can bind with toxin B of *C. difficile* and can inhibit the toxin from attachment to gastrointestinal cell thus it can prevent colon cell damage. BEZ should be considered in older age (age ≥ 65 years old) with other criteria that consists of severe infection, immunocompromised patient, or recurrent infection of *C. difficile* within 6 months. BEZ should be used with caution in patient with heart failure or other heart comorbid. BEZ is administer in the dose of 10 mg/kg/day in 60 minutes, antibody can be detected 3 months after administration.[3,12]

MANAGEMENT

Based on newest guidelines from American College of Gastroenterology (ACG) 2021, management of *C. difficile* infection with antimicrobial consists of

- Initial treatment for non-severe infection: oral vancomycin 125 mg q.d.s. or oral fidaxomicin 200 mg b.i.d. for 10 days
- Initial treatment for low risk and non-severe infection: oral metronidazole 500 mg t.i.d. for 10 days
- Initial treatment for severe infection: oral vancomycin 125 mg q.d. or oral fidaxomicin 200 mg b.i.d. for 10 days
- Fulminant disease: fluid resuscitation followed by oral vancomycin 500 mg q.d.s. within 48-72 hours, or in combination with intravenous metronidazole 500 mg t.i.d.. FMT should be considered in patient that refractory from antimicrobial therapy and poor candidate of surgery procedure
- Ileus patient: enema vancomycin 500 mg q.d.s. IBD patient: oral vancomycin 125 mg q.d.s. for 14 days
- Immunocompromised patient: vancomycin or fidaxomicin as antimicrobial
- Pregnant or lactation: vancomycin as antimicrobial[3]

Table 4 explains antimicrobial recommendation from Infectious Disease Society of America (IDSA) 2021.[12]

Table 4. Antimicrobial recommendation from Infectious Disease Society of America (IDSA) 2021[12]

Clinical manifestation	Recommended treatment	Comments
Initial episode	Preferred: oral fidaxomicin 200 mg b.i.d. for 10 days Alternative: oral vancomycin 125 mg q.d.s. for 10 days Alternative for non-severe disease: oral metronidazole 500 t.i.d. 10-14 days	Non-severe disease: leucocyte < 15,000/µl and SCr < 1.5 mg/dl
First recurrent disease	Preferred: oral fidaxomicin 200 mg b.i.d. for 10 days or 200 mg b.i.d. for 5 days followed by once every other day for 20 days Alternative: oral vancomycin 125 mg q.d.s. for 10 days or in tapered and pulsed regimen Adjunctive: intravenous BEZ 10 mg/kg during antimicrobial administration	If metronidazole is given in the first treatment, consider oral vancomycin Tapered/pulsed vancomycin regimen: 125 mg q.d.s. for 10-14 days, followed by 125 mg b.i.d. for 7 days, 125 mg o.d. for 7 days, then every 2-3 days for 2-8 weeks
Second or subsequent recurrent disease	Oral fidaxomicin 200 mg b.i.d. for 10 days or 200 mg b.i.d. for 5 days followed by once every other day for 20 days Oral vancomycin in tapered and pulsed regimen Oral vancomycin 125 mg q.d.s. for 10 days followed by rifaximin 125 mg t.i.d. for 20 days FMT Adjunctive: intravenous BEZ 10 mg/kg during antimicrobial administration	Antimicrobial should be offered first then FMT
Fulminant infection	Oral or NGT administration of vancomycin 500 mg q.d.s. Combination with intravenous metronidazole 500 mg t.i.d. should be considered in ileus patient Rectal instillation of vancomycin in ileus patient	Fulminant: hypotension or shock, ileus, toxic megacolon

Fidaxomicin is superior to prevent recurrent *C. difficile* infection, followed by vancomycin, and then metronidazole. Low risk patient (younger patient with less comorbid) can be treated with metronidazole; this treatment is also cost-effective in this group of patient. Other antimicrobial that is studied for *C. difficile* infection treatment are teicoplanin, nitazoxanide, surotomycin, cadazolid, and ridinilazole.[3,13,14] Other approach of antibody based therapy that has been studied for treatment of *C. difficile* infection beside BEZ, included intravenous immunoglobulin (IVIG). Yet, current study regarding use of IVIG in *C. difficile* infection is not associated with improve mortality, colectomy, and hospital duration.[13]

Antimotility agent such as loperamide without antimicrobial administration in fulminant disease is not recommended, due to trapped of *C. difficile* toxin can increase risk of toxic megacolon. If the patient is already in antimicrobial therapy, antimotility treatment can be considered. Cholestyramine is not recommended as *C. difficile* infection treatment, moreover in patient with vancomycin administration due to drug interaction between this two drugs. high fiber diet should be considered in *C. difficile* infection, because it can increase gut microbiota and reduce *C. difficile*.[3]

Fulminant *C. difficile* infection should be treated in multidisciplinary approach, involving gastroenterologist, infection specialty, critical care, and surgeon. Supportive treatment with fluid resuscitation is administered with the target of normal urine output (0.5-1 ml/kg/hour) and renal function. Antimicrobial is recommended with option and dose as previously stated. In ileus patient, enema vancomycin is recommended, due to more effective delivery of treatment compared to oral administration of drug. Combination with metronidazole should be considered, because metronidazole has greater delivery to colon in ileus patient compared to oral vancomycin.[3]

Surgery should be done with colectomy and end ileostomy and stapled rectal stump or diverting loop ileostomy with colon lavage and intraluminal vancomycin for 10 days. Surgery is recommended in patient with fulminant disease and followed by toxic megacolon, ischemia, or perforation of the gut. FMT is also recommended in fulminant or severe infection, with colonoscopy approach, especially in pseudo-membrane disease. FMT can be administered 3-5 days until loss of pseudo-membrane. FMT administration is also associated with reduce risk of colectomy and sepsis. Recurrent infection should be treated with different antimicrobial with initial therapy. For patient with vancomycin and metronidazole as initial therapy, for recurrent infection this patient should be treated with fidaxomicin. Metronidazole is not recommended in recurrent infection. Anti-secretory agent such as proton pump inhibitor (PPI) should be continued once it is started.[3]

Patients with IBD exposed to higher risk of *C. difficile* infection due to corticosteroid and biological agent (infliximab, adalimumab) exposure, more comorbid, hospitalization history and repeat visit to hospital to control their disease. *C. difficile* infection in IBD increase risk of colectomy. In patient with IBD, oral vancomycin 4 x 125 mf should be given of minimal 14 days. In flare IBD, immunosuppressive agent should not be stopped, yet if the symptom does not improve after *C. difficile* infection treatment, escalation of immunosuppressive agent should be considered.[3]

In special population such as lactating or pregnant women, vancomycin is antimicrobial of choice, because higher risk of failure with metronidazole therapy. Fidaxomicin should be avoided in lactating or pregnant women, while FMT should be avoided in pregnancy. Vancomycin is not transferred in breast milk, thus it is safe to give to lactating women. Immunocompromised patient can be given vancomycin or fidaxomicin. In immunocompromised patient, *C. difficile* is easier to occur, with high risk of severe and recurrent disease. This risk increased due to history of hospitalization, neutropenia, history of antimicrobial and immunosuppressive agent. Increased risk occurred in HIV patient with CD4 $\leq$ 50 cell/mm^3 and multiple organ transplantation.[3]

CONCLUSION

Due to high spectrum of disease, diagnostic and management approach of *C. difficile* infection should be noticed. For patient with high risk of this infection (older age, history of hospitalization, history of antimicrobial use) that experience diarrhea 3 times/day, GDH or NAAT test should be conducted. Negative result defined negative *C. difficile* infection, while positive result should be confirmed with toxin detection. If the toxin detection is positive, thus the patient is diagnosed with *C. difficile* infection. Antimicrobial agent should be administered based on initial or recurrent disease, severity of disease, with FMT, BEZ as adjunctive treatment to prevent recurrent infection. Unfortunately, choices of treatment is not much in Indonesia, because the only option of antimicrobial that is available is metronidazole. Thus, primary prevention by implementing standard precaution and rational use of antimicrobial should be primary priority in limited resource country.

REFERENCES

1. Collins DA, Gasem MH, Habibie TH, et al. Prevalence and molecular epidemiology of *Clostridium difficile* infection in Indonesia. New Microbe and New Infect. 2017;18:34-7.
2. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-48.
3. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol. 2021;116:1124-47.
4. Fu Y, Luo Y, Grinspan AM. Epidemiology of community-acquired and recurrent *Clostridioides difficile* infection. Therap Adv Gastroenterol. 2021;14:1-11.
5. Sandhu BK, McBride SM. *Clostridioides difficile*. Trends Microbiol. 2018;26:1049-50.
6. Guh AY, Kutty PK. In the clinic: *Clostridioides difficile* infection. Ann Intern Med. 2018;169:ITC49-64.
7. Liwang F, Sinto R. Pendekatan klinis terkini infeksi *Clostridium difficile* nosocomial. JPDI. 2021;8:104-9.
8. Smilings C, Riley TV. Antibiotics and hospital-

acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. J Antimicrobe Chemother. 2014;69:881-91.
9. Bauer MP, Hensgens MP, Miller MA, et al. Renal failure and leukocytosis are predictors of a complicated course of *Clostridium difficile* infection if measured on day of diagnosis. Clin Infect Dis. 2012;55:S149-53.
10. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on treatment guidance document for *Clostridioides difficile* infection in adults. Clin Microbiol Infect. 2021;27:S1-21.
11. Gupta A, Khanna S. Fecal microbiota transplantation. JAMA. 2017;318:1.
12. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis. 2021;73: e1029-44.
13. Cho JM, Pardi DS, Khanna S. Update on treatment of *Clostridioides difficile* infection. Mayo Clin Proc. 2020;95:758-69.
14. Guery B, Galperine T, Barbut F. *Clostridioides difficile*: diagnosis and treatments. BMJ. 2019;366:l4609.