Clostridium difficile infection

Stephen A. Geller[a,b,c], Fernando P. F. de Campos[d]

Picture provided by Dr. Stephen A. Geller - personal archive.

Clostridium difficile infection (CDI) is a significant and increasing medical problem, surpassing methicillin-resistant *Staphylococcus aureus* as the most common hospital-onset or facility-associated infection,[1-3] and a key element in the challenging battle against hospital-acquired infections. This Gram-positive, anaerobic, spore-forming colonizes the intestinal tract after antibiotics have altered the normal intestinal flora. CDI may be life-threatening; the death rate has dramatically increased from 3,000 per year in 1999-2000 to 14,000 per year in 2006-2007.[4] The use of antibiotics, although not the only risk factor, is the most significant triggering event, increasing in incidence with prolonged antibiotic use.[2,3,5] Many antibiotics have been implicated in the etiopathogenesis of CDI, especially ampicillin, amoxicillin, clindamycin, cephalosporin (particularly third generation cephalosporins) and quinolones.[2,3,6-8] However, not all cases of CDI are associated with

[a] Department of Pathology and Laboratory Medicine – David Geffen School of Medicine – University of California, Los Angeles/California – USA.
[b] Department of Pathology and Laboratory Medicine – Weill Cornell Medical College, New York – USA.
[c] Department of Pathology and Laboratory Medicine – Cedars-Sinai Medical Center, Los Angeles/California – USA.
[d] Department of Internal Medicine – Hospital Universitário – Universidade de São Paulo, São Paulo/SP – Brazil.

antibiotics or their prolonged use. In 24% of cases of CDI there was no history of previous use of antibiotics and 9% had less than 3 days of use.[9] Most of these were hospitalized individual who had close contact with patients with diarrheal diseases. Other risk factor includes administration of antineoplastic agents like doxorubicin, cisplatin, cyclophosphamide, fluorouracil and chlorambucil, methotrexate.[10] Immunocompromised patients, either from cancer chemotherapy or, especially, after transplantation, also were prone to develop CDI. Other risk factors include: preceding inflammatory bowel disease (IBD) and other comorbidities, advanced age, enteral feeding (especially post pyloric), prior gastrointestinal surgery, and proton pump inhibitor users.[2,3,11]

Clinical presentation varies widely (Table 1). Asymptomatic (culture positive) carriers can have mild colitis without the characteristic inflammatory ("pseudo") membrane formation or fulminant toxic megacolon. Watery diarrhea is a cardinal manifestation accompanied by cramps and lower abdominal pain. Acute abdomen, requiring emergency surgery, has been described.[11,12] Symptoms generally start 2-10 days after antibiotic use. Although frankly bloody diarrhea is uncommon, occult blood is present in 26% of cases. As many as 50% of patients have a low-grade fever. When the temperature is greater than 38.5 °C there is usually severe disease. Leukocytosis, with increased band forms is frequent, as is hypoalbuminemia. Creatinine value elevations are seen with increasing severity of the diarrhea. Acute inflammatory exudate may be present in as many as 40% of stool samples.[11,13-15] Imaging studies are of little use in detecting CDI and endoscopy is indicated when rapid diagnosis is required. Findings may vary: normal mucosa (in mild cases), mild erythema, and friability can be seen before the appearance of the characteristic multiple, raised and centrally ulcerated, yellowish-white plaques (pseudomembranes).[16] The entire colorectal mucosa can be affected in the most severe cases but, most often, the lesions are patchy and separated by unremarkable mucosa, as in the image above. With effective therapy the mucosa heals completely.

Symptom recurrence may be due to reinfection by a different strain or can represent relapse with the original strain, and may be characterized by one or several episodes, starting days or weeks after treatment. Relapse may be more severe than the first episode.[17]

Currently, many laboratory assays have been used to diagnose CDI, but no single "gold standard" has been recognized.[2,3,11] *C. difficile* toxin is obtained from stool samples, which should be maintained at temperature under 4 °C if not immediately processed since the toxin is heat sensitive (a frequent cause of false-negative result). For this purpose the available tests are: Polymerase chain reaction (PCR), Enzyme immunoassay (EIA) for *C. difficile* glutamate dehydrogenase (GDH), Enzyme immunoassay (EIA) for *C. difficile* toxins A and B, Cell culture cytotoxicity assay and selective anaerobic culture.

Histologic examination is characteristic but, in biopsy samples, may be indistinguishable from acute ischemic colitis.

Less severe CDI may be treated with oral metronidazole or vancomycin with 90-98% cure rates. As the results are considered similar, metronidazole has been favored over vancomycin to limit the spread of vancomycin-resistant enterococci. Other treatment choices include fidaxomicin and rifaximin. Recently, fecal transplantation to either the upper or lower gastrointestinal tract has been shown to be dramatically effective in many cases of severe CDI.[18-20]

Table 1. Patterns of clinical presentation[2,3]

Carrier stage (asymptomatic)
C. difficile associated diarrhea (CDAD)
C. difficile associated colitis (CDAC)
Pseudomembranous colitis
Fulminant colitis
C. difficile associated enteritis (rare)
Acute appendicitis (rare)

REFERENCES

1. Miller BA, Chen LF, Sexton DJ, Anderson DJ. Comparison of the burdens of hospital-onset, healthcare facility associated *Clostridium difficile* infection and of healthcare-associated infection due to methicillin-resistant Staphylococcus aureus in community hospitals. Infect Control Hosp Epidemiol. 2011;32(4):387-90. PMid:21460491. http://dx.doi.org/10.1086/659156

2. Burke KE, Lamont ST. *Clostridium difficile* infections: a worldwise disease. Gut Liver. 2014;8(1):1-6.

PMid:24516694 PMCid:PMC3916678. http://dx.doi.org/10.5009/gnl.2014.8.1.1

3. Kazanski M, Smolark S, Kinnarney F, Grzebeniak Z. *Clostridium difficile*: epidemiology, diagnostic and therapeutic possibilities: a systematic review. Tech Coloproctol. 2014;18(3):223-32. PMid:24178946 PMCid:PMC3950610. http://dx.doi.org/10.1007/s10151-013-1081-0

4. Hall AC, Curns AT, McDonald LC, Parashar UD, Lopman BA. The roles of norovirus and Clostridium difficile among gastroenteritis deaths in the United States, 1997-2007. In: 49th Annual Meeting of the Infectious Disease Society of America; 2011 Oct 22; Boston, MA.

5. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium* difficile infection after exposure to antibiotics. J Antimicrob Chemother. 2012;67(3):742-8. PMid:22146873. http://dx.doi.org/10.1093/jac/dkr508

6. Pépin J, Valiquette L, Alary ME, et al. *Clostridium* difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171(5):466-72. PMid:15337727 PMCid:PMC514643. http://dx.doi.org/10.1503/cmaj.1041104

7. Riley TV. Antibiotic-associated diarrhea: a costly problem. Pharmacoeconomics. 1996;10(1):1-3. http://dx.doi.org/10.2165/00019053-199610010-00001.

8. Thomas C, Stevenson M, Williamson DJ, Riley TV. *Clostridium difficile*-associated diarrhea: epidemiological data from Western Australia associated with a modified antibiotic policy. Clin Infect Dis. 2002;35(12):1457-62. PMid:12471563. http://dx.doi.org/10.1086/342691

9. Centers for Disease Control and Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. MMWR Morb Mortal Wkly Rep. 2005;54(47):1201-5. PMid:16319813.

10. Anand A, Glatt AE. Clostridium difficile infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis. 1993;17(1):109-13. http://dx.doi.org/10.1093/clinids/17.1.109.

11. Oldfield EC 4th, Oldfield EC 3rd, Johnson DA. Clinical update for the diagnosis and treatment of Clostridium difficile infection. World J Gastrointest Pharmacol Ther. 2014;5(1):1-26.

12. Drapkin MS, Worthington MG, Chang TW, Razvi SA. Clostridium difficile colitis mimicking acute peritonitis. Arch Surg. 1985;120(11):1321-2. http://dx.doi.org/10.1001/archsurg.1985.01390350097021.

13. Wanahita A, Goldsmith EA, Musher DM. Conditions associated with leukocytosis in a tertiary care hospital, with particular attention to the role of infection caused by clostridium difficile. Clin Infect Dis. 2002;34(12):1585-92. PMid:12032893. http://dx.doi.org/10.1086/340536

14. Dansinger ML, Johnson S, Jansen PC, Opstad NL, Bettin KM, Gerding DN. Protein-losing enteropathy is associated with Clostridium difficile diarrhea but not with asymptomatic colonization: a prospective, case-control study. Clin Infect Dis. 1996;22(6):932-7. http://dx.doi.org/10.1093/clinids/22.6.932.

15. Marx CE, Morris A, Wilson ML, Reller LB. Fecal leukocytes in stool specimens submitted for Clostridium difficile toxin assay. Diagn Microbiol Infect Dis. 1993;16(4):313-15. http://dx.doi.org/10.1016/0732-8893(93)90081-H.

16. Bartlett JG. Clinical practice: antibiotic-associated diarrhea. N Engl J Med. 2002;346(5):34-9. PMid:11821511. http://dx.doi.org/10.1056/NEJMcp011603

17. Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis. 1997;24(3):324-33. http://dx.doi.org/10.1093/clinids/24.3.324.

18. Smits LP, Bouter E, de Vos WM, Borody TJ Nieuwdorp M. Therapeutic potential of fecal microbiota transplantation. Gastroenterology. 2013;145(5):946-53. PMid:24018052. http://dx.doi.org/10.1053/j.gastro.2013.08.058

19. Cammarota G, Ianiro G, Gsbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. J Clin Garoenterol. 2014, Jan 16 [Epub ahead of print; cited 2014 May 10]. Available from: http://journals.lww.com/jcge/pages/articleviewer.aspx?year=9000&issue=00000&article=98691&type=abstract

20. Sha S, Liang J, Chen M, et al. Systematic review:fecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. Aliment Pharmacol Ther. 2014;39(10):1003-32. PMid:24641570. http://dx.doi.org/10.1111/apt.12699

Stephen A. Geller, M.D.
Department of Pathology and Laboratory Medicine
David Geffen School of Medicine, UCLA
Los Angeles/CA – USA
geller16st@gmail.com

Fernando P. F. de Campos, PhD
Department of Internal Medicine
Hospital Universitário – USP
São Paulo/SP – Brazil
fpfcampos@gmail.com