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Review

The burden of clostridium difficile infection in patients with liver cirrhosis

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Abstract

Clostridium Difficile Infection (CDI) has registered a dramatically increasing incidence in the general population over the past decades. Nowadays, Clostridium Difficile is the leading cause of hospital-acquired diarrhea in Europe and North America. Liver cirrhosis is the final stage of any chronic liver disease (CLD). The most common causes are chronic hepatitis C or B and viral co-infections, alcohol misuse, and nonalcoholic fatty liver disease (NAFLD).

CLD and cirrhosis are listed among the ten leading causes of death in the US. Cirrhosis due to any etiology disrupts the homeostatic role of the liver in the body. Cirrhosis-associated immune dysfunction (CAID) leads to alterations in both inherited and acquired systemic and local liver immunity. CAID is caused by increased systemic inflammation and immunodeficiency and it is responsible for 30% of mortality rates all over the world.

Clostridium Difficile infection frequently affects patients suffering from liver cirrhosis because of the high number of prolonged hospitalizations, regular use of antibiotics for the prevention or treatment of SBP, proton pump inhibitor (PPI) use, and an overall immunocompromised state. Clostridium Difficile is a Gram-positive bacterium responsible for the high morbidity and mortality rates in patients with cirrhosis, with an essential increase in a 30-day mortality.

Keywords : clostridium difficile, liver cirrhosis, anaerobic infection, immune dysfunction

Highlights

- ✓ Patients with liver cirrhosis are characterized by alterations of inherited and acquired immunosuppression, being an easy target for Clostridium Difficile, which is associated with significant morbidity and mortality.
- ✓ The latest guideline treatment recommendations for an initial episode of Clostridium Difficile have changed, either vancomycin or fidaxomicin now currently chosen over metronidazole.

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Introduction

Clostridium Difficile represents a common infection in healthcare settings, being responsible for severe diarrhea (1-3). Hall and O'Toole first isolated C. Difficile from the stool of a healthy infant. The given name of the bacterium resulted from the difficulty of isolation and culture by using the available methods at the time. The secondary pseudomembranous colitis associated with C. Difficile infection was first described in 1893. In 1978, researchers associated C. difficile with antibiotic-associated diarrhea (4).

The highest incidence is among those aged over 65 years, being more prevalent among females and whites. Clostridium Difficile is the most common pathogen in nosocomial and antibiotic-associated diarrheal diseases. It can also be a community-acquired Clostridium Difficile infection in patients with no risk factors (5). The frequency of the Clostridium Difficile infection (CDI) and its increased morbidity, which is associated with a prolonged duration of treatment, leads to a significant increase in hospital treatment costs.

Cirrhosis occurs when regenerative nodules surrounded by fibrous bands replace the healthy liver tissue. This deranged histologic architecture is responsible for the portal hypertension and end-stage liver disease. The cause of cirrhosis is easy to recognize by making a minute history anamnesis, and also by combining the serologic and histologic evaluation. According to the geographic area, the leading cause responsible for the occurrence of liver cirrhosis is different. For example, abusive alcohol intake and hepatitis C infection are the most common causes of liver cirrhosis in developed countries, while hepatitis B is common in endemic areas such as Asia and sub-Saharan Africa. Nonalcoholic steatohepatitis (NASH) in obese and diabetic patients is responsible for the development of liver cirrhosis when there is no other apparent cause. Knowing the etiology is essential in order to apply the correct treatment and to predict both evolution and prognosis (6-9).

The Clostridium Difficile infection is becoming an increasingly incident disease, with the highest risk of infection occurring in hospitalized patients and with unusually high mortality in immunosuppressed patients, responsible for high morbidity and mortality rates, being a substantial financial burden for healthcare providers (10, 11).

Discussions

Pathogenesis

Clostridium Difficile is an anaerobic, Gram-positive, spore-forming bacillus, which may be part of the normal intestinal microbiota in healthy newborns. The microorganism, first described in 1935, is transmitted through the oral-fecal route. CDI affects tissues through toxin production. The pathogenesis strains of C. Difficile produce two exotoxins: A (enterotoxin) and B (cytotoxin).

The pathogenic effect involves several steps. Before toxin production, which is essential for gut damage and diarrhea occurrence, the germination of C. Difficile spores is required. The survival in spore formula provides resistance to antibiotics and is responsible for recurrent disease following the eradication treatment (12-14).

The lumen of the colon is anoxic, thus creating the perfect environment for anaerobic bacteria such as Clostridium Difficile to survive and moreover, to proliferate and produce toxins. The bacterial spores resist against oxygen, heat, and common ethanol-based disinfectants, which favor proliferation (15).

Many efforts have been made throughout the years to understand Clostridium Difficile sporulation, but understanding is still currently limited. Commonly, C. Difficile acts like a nosocomial pathogen, the source of infection being contaminated by humans or healthcare facilities. Spores are resistant to gastric acidity and germinate into the vegetative form in the intestine. Hospitalized patients may acquire CDI by the ingestion of spores or vegetative bacteria from the environment or the hands of healthcare personnel (16).

Liver cirrhosis is a progressive disease, evolving from an asymptomatic, compensated stage to a complicated, decompensated one, usually associated with poor prognosis. Any type of infection can decompensate a compensated liver cirrhosis and lead to complications of cirrhosis such as upper digestive bleeding, ascites, hepatorenal or hepatopulmonary syndrome, or hepatic encephalopathy, all of which have high mortality rates. Regardless of its etiology, cirrhosis, as the end stage of chronic liver disease, commonly evolves to a syndrome called cirrhosis-associated immune dysfunction syndrome (CAIDS). Abnormalities of the immune function in patients with liver cirrhosis are caused by the immunodeficiency and systemic inflammation that occur in cirrhosis. The syndrome of decreased immunity is a combination of different immunological mechanisms and

reactions which result from an advanced stage of the liver disease (17, 18). The local impaired immune response is responsible for not recognizing antigens; in this way, the effector mechanisms are improper (19). An imbalance between the pro-inflammatory and anti-inflammatory mechanisms occurs and the activation of the immune system is inefficient (20, 21).

Clinical entities such as pneumonia, spontaneous peritonitis, skin inflammatory diseases, infections of the urinary system, fungal infections, and C. Difficile diarrhea should be promptly recognized and treated (22-24). By adopting this approach, the risk of complications decreases and both prognosis and outcome can be improved (25, 26).

Risk factors

Cirrhotic patients represent a particular category of patients, their disease carrying many potential risk factors for the development of CDI, especially in decompensated stages of the illness (27, 28). Clostridium Difficile infection has an increased prevalence as a second infection in cirrhotic patients.

Many studies confirm the idea that intercurrent infections in patients with liver cirrhosis, especially in advanced stages (Child Pugh B or C), increase mortality by 4 times. One third of patients die within the first month after the infection and another third die within the first 12 months. This category of patient is at increased risk of developing Clostridium Difficile colitis for many reasons, most of which can be explained briefly as follows.

The use of antibiotics remains the most widely recognized risk factor for the development of C. Difficile infection. Cirrhotic patients often require prophylactic or curative antibiotic therapy, for example Norfloxacin, which is commonly used in the outpatient prophylaxis of spontaneous bacterial peritonitis (SBP), and quinolones or third-generation cephalosporins used in case of upper digestive bleeding. Also, these patients are more frequently cared for in an intensive care unit (ICU) and antibiotics are prescribed during their hospitalization (5).

Almost all antibiotics can disrupt the normal gut microbiota, allowing Clostridium Difficile to spread and produce toxins. The risk of infection is increased directly proportional to the duration and quantity of antibiotics administered, but cases of infection have been reported even after a single dose administration (29).

Rifaximin is a routine medication in the prevention of hepatic encephalopathy, as well as Lactulose. Rifaximin has a broad antimicrobial spectrum, including aerobes and anaerobes, Gram-positive and Gram-negative bacteria. According to literature data, when administered orally, 400 mg twice per day, 10 days a month, it seems to be useful in C. Difficile infection as well, because it is virtually non-absorbed and its activity occurs mostly within the intestinal lumen (30). Recent studies have revealed that both Rifaximin and Lactulose are associated with a reduced risk of developing CDI in hospitalized patients, whether or not they received other antibiotics. This phenomenon could be possible due to the fact that Lactulose reduces the production of short chain fatty acids and Rifaximin suppresses the enteral ammonia, with those effects having a protective effect by reducing the suitable conditions for Clostridium Difficile proliferation (31). However, resistance was noted. There are few studies regarding the risk of developing CDI in cirrhotic patients receiving Rifaximin, so clinicians should also be aware of this risk.

Other potential risk factors in cirrhotic patients could be frequent and prolonged hospitalization periods which place the patient in a suitable environment for high exposure to CDI, proton pump inhibitors (PPI) utilization for peptic ulcers, ligation-induced ulcers or gastroesophageal reflux, advanced age associated with a multitude of comorbidities, malnutrition, cancer, antiviral treatments, and the overall immunocompromised state. As an observation, C. Difficile infections were more frequently detected in patients with alcoholic liver cirrhosis (32, 33).

C. Difficile infections in patients with liver cirrhosis worsen the disease outcome; however, the overall mortality is not affected if appropriate diagnosis is made and suitable treatments are applied (34). Severe hypoalbuminemia and intensive care admission are predictors of increased mortality in cirrhotic patients with C. Difficile infection (11, 13).

Treatment

The diagnosis of C. Difficile infection takes into account clinical manifestations such as diarrhea - Bristol stool chart types 5–7, meaning more than three stools within 24 hours, accompanied by abdominal pain and systemic signs and symptoms such as fever, hypotension, or shock, but also a positive result of C. Difficile and/or its toxins in laboratory testing. Antibiotic therapy is the first choice for CDI, and specific guideline recommendations are based on the severity of the disease.

The latest guideline treatment recommendation for an initial episode of mild to moderate Clostridium Difficile infection has changed, recent data suggesting an overall superiority of vancomycin over metronidazole. The oral formula of vancomycin in dosages of 125 mg four times per 24 hours for 10–14 days is preferred. In case of

recurrence, fidaxomicin 200 mg twice a day for ten days is preferred, but this medication is not available in Romania (28).

For severe or fulminant cases, metronidazole 500 mg intravenously three times a day for 10–14 days combined with vancomycin 125 mg orally four times a day for 10–14 days is recommended.

The first recurrence requires the same treatment as the initial episode, but for the second or further recurrences, vancomycin in a pulsed regimen and fecal microbiota transplantation (FMB) are recommended (21).

Fecal microbiota transplantation for an initial episode has not yet been sufficiently studied, but it is considered to be the most effective, inexpensive, and quickest solution for a recurrent infection. Despite ongoing studies, donor selection and screening, along with timing and route of transplantation remain important issues regarding FMB (35).

A unified standard to screen donors is not available at the moment. Summarized donor criteria include being able to give written consent, being over 18 years or parental consent and child assent in the case of minors. The exclusion criteria are: drug use, history of incarceration, history of chronic gastrointestinal disease, autoimmune, atopic diseases, chronic neurologic disorders, obesity or severe malnutrition, malignancy or ongoing immunosuppressive therapy/chemotherapy, and strong family history of colorectal neoplasia; in the past 12 months: blood transfusions, unprotected intercourse, and known interaction with HBV, HCV, HIV; in the past 6 months: tattoos, piercings, and international tropical travels; in the past 3 months: antibiotic use and smallpox vaccine; and in the past month: diarrhea, emesis, and fever or family members showing signs of gastrointestinal infection. There are both mandatory and optional blood tests in the guidelines. The required ones are HBV surface antigen, HCV antibody, HAV IgM, HIV 1+2, syphilis tests; and optionally, patients could be tested for HTLV 1+2, BK virus, Epstein-Barr virus, HBV core antibody, and HBV surface antibody. Blood tests such as complete blood counts, liver and kidney tests could be useful, but are not compulsory. Mandatory stool testing includes Clostridium Difficile, and then bacterial culture for Salmonella, Yersinia, Shigella, Campylobacter and E. Coli; parasite and ovum examination, and additional tests depending on the case such as Giardia, Rotavirus, Listeria spp, Vibrio spp, Isospora, Cyclospora, Helicobacter Pylori, Entamoeba histolytica (36, 37).

When choosing the treatment for the C. Difficile infection associated with liver cirrhosis, severe illness, cachexia related to impaired protein balance, and complications limit the treatment options and efficacy (31).

Conclusions

C. difficile is a Gram-positive bacterium living in many resistant forms, overwhelming harsh environments and conventional sterilization options. It is a nosocomial pathogen, the source of infection is infected by humans and contaminated hospital or medical devices.

Cirrhotic patients are more frequently cared for in an intensive care unit (ICU) and they are prescribed antibiotics during their hospitalization; spontaneous bacterial peritonitis (SBP), prophylactic or curative antibiotic use; the administration of antibiotics in variceal upper digestive bleeding, all of these being particular CDI development risk factors in patients with liver cirrhosis.

The Clostridium Difficile infection is becoming an increasingly incident disease, with the highest risk of infection occurring in hospitalized patients and with unusually high mortality in immunosuppressed patients. C. Difficile infections in patients with liver cirrhosis are associated with a significant increase of a 30-day mortality, but not overall mortality. Liver failure producing severe hypoalbuminemia and ICU admissions worsen the mortality rates and prognosis in cirrhotic patients infected with C. Difficile. However, it is difficult to fix the mortality rates attributable to C. Difficile infection in a group of patients with severe comorbidities, such as the liver cirrhosis group.

During the past decade, understanding the pathogenesis of Clostridium Difficile infection has substantially increased, thus leading to new therapeutic approaches. Fecal microbiota transplantation is considered a giant step forward, because it is indisputably effective as a curative treatment. We thus predict that CDI could be the first infection efficiently treated with bacteriotherapy.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010; 31(5): 431–455.
2. Ott E, Saathoff S, Graf K, Schwab F, Chaberny IF. The prevalence of nosocomial and community acquired infections in a university hospital: an observational study. *Dtsch Arztebl Int*. 2013; 110(31-32): 533–540.
3. Alasmari F, Seiler SM, Hink T, Burnham CA, Dubberke ER. Prevalence and risk factors for asymptomatic Clostridium difficile carriage. *Clin Infect Dis*. 2014; 59(2): 216–222.
4. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013; 108(4): 478–498.
5. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, Zadvornova Y, Dye A, McGinley EL, Saeian K, Heuman D, Sanyal AJ, Hoffmann RG. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. *Am J Gastroenterol*. 2010; 105(1): 106–113.
6. Sherlock S, Dooley J, editors. Diseases of the Liver and Biliary System. 11th Edition Blackwell Science; Oxford, UK; Malden, MA: 2002
7. Suceveanu AI, Mazilu L, Tomescu D, Ciufu N, Parepa IR, Suceveanu AP. Screening of Hepatopulmonary Syndrome (HPS) with CEUS and Pulse-Oximetry in Liver Cirrhosis Patients Eligible for Liver Transplant *Chirurgia* 2013; 108(5): 684-688.
8. Gheorghe L, Csiki IV, Icob S, Gheorghe C, Trifan A, Grigorescu M, Motoc A, Suceveanu, AI, Curascu M, Caruntu F, Sporea I, Brisc C, Rogoveanu I, Cerban R, Tugui L, Alexandrescu A. Hepatitis Delta Virus Infection in Romania: Prevalence and Risk Factors. *J Gastrointestin Liver Dis*. 2015; 24(4): 413-421.
9. Leblebicioglu H, Arama V, Causse X, Marcellin P, Ozaras R, Postawa-Klozinska B, Simon K, Suceveanu AI, Wiese M, Zeuzem S, Klauck I, Morais E, Bjork S, Lescrauwaet B, Kamar D and Zarski JP for the AI463-121 European Longitudinal Chronic Hepatitis B Study Group. Predictors associated with treatment initiation and switch in a real-world chronic hepatitis B population from five European countries. *J Viral Hepat*. 2014; 21(9): 662-70.
10. Dudukgian H, Sie E, Gonzalez-Ruiz C, et al. C. difficile colitis--predictors of fatal outcome. *J Gastrointest Surg*. 2010; 14(2): 315–22.
11. Vonberg RP, Reichardt C, Behnke M, Schwab F, Zindler S, Gastmeier P. Costs of nosocomial Clostridium difficile-associated diarrhoea. *J Hosp Infect*. 2008; 70(1): 15–20.
12. Radulescu A, Madan V, Aungurenci A, Bratu O, Farcas C, Dinu M, Mischianu D. Antibiotic resistant urinary tract infections in a urology ward. *Rom J Mil Med*. 2015; 118(3): 20-22.
13. Spinu D, Bratu O, Popescu R, Marcu D, Radulescu A, Mischianu D. Clostridium difficile-an emerging plague. *Rom J Mil Med*. 2015; 118(3): 12-15.
14. Zaha DC, Bungau S, Aleya S, Tit DM, Vesa CM, Popa AR, Carmen P, Maghiar OA, Bratu OG, Furau C, Moleriu RD, Petre I, Aleya L. What antibiotics for what pathogens? The sensitivity spectrum of isolated strains in anintensive care unit. *Science of the Total Environment*. 2019; 687: 118-127.
15. Pereira FC, et al. The spore differentiation pathway in the enteric pathogen Clostridium difficile. *PLoS Genet*. 2013; 9(10): e1003782.
16. Gerding DN, Johnson S, Rupnik M, Aktories K. Binary toxin CDT: Mechanism, epidemiology, and potential clinical importance. *Gut Microbes*. 2014; 5(1): 15–27.
17. Diaconu C, Balaceanu A, Costache C. Prevalence of hypoxic hepatitis in heart failure patients. *Journal of Hepatology*. 2014; 60(Supplement 1): S515-S515.
18. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2011; 9(9): 727–738.
19. Gao B, Jeong WI, Tian Z. Liver: An organ with predominant innate immunity. *Hepatology*. 2008; 47(2): 729–736. DOI: 10.1002/hep.22034
20. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014; 61(6): 1385–1396.
21. Garcia-Tsao G, Wiest R. Gut microflora in the pathogenesis of the complications of cirrhosis. *Best Pract Res Clin Gastroenterol*. 2004; 18(2): 353–372.
22. Bălălău C, Voiculescu S, Motofei I, Scăunasu RV, Negrei C. Low dose Tamoxifen as treatment of benign breast proliferative lesions. *Farmacia*. 2015, 63(3): 371- 375.
23. Hung YP, Lee JC, Lin HJ, et al. Clinical impact of Clostridium difficile colonization. *J Microbiol Immunol Infect*. 2015; 48(3): 241–248.

24. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013; 108(4): 478–498.
25. Trifan A, Stoica O, Stanciu C, Cojocariu C, Singeap AM, Girleanu I, Miftode E. Clostridium difficile infection in patients with liver disease: a review. *Eur J Clin Microbiol Infect Dis*. 2015; 34(12): 2313–2324.
26. Popoiag RE, Pantea-Stoian A, Suceveanu AP, Suceveanu AI, Mazilu L, Parepa IR, Serban LM, Paunica M, Motofei C, Braticevici CF. The relationship between gut microbiota and spontaneous bacterial peritonitis in patients with liver cirrhosis - a literature review. *J Mind Med Sci*. 2019; 69(1): 26-30. DOI: 10.22543/7674.61.P2630
27. McDonald LC, Dale NG, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Ciaran K, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018; 66(7): 987-994.
28. Balaceanu A, Diaconu C, Aron G. Budd-Chiari syndrome as an initial presentation of hepatocellular carcinoma – a case report. *Medical Ultrasonography* 2014; 16(2): 172-174.
29. Suceveanu AI, Pantea Stoian A, Mazilu L, et al. Interferon-free therapy is not a trigger for hepatocellular carcinoma in patients with chronic infection with hepatitis C virus. *Farmacia* 2018; 66(5): 904-908.
30. Collins CE, Ayturk MD, Flahive JM, Emhoff TA, Anderson FA, Santry HP. Epidemiology and outcomes of community-acquired Clostridium difficile infections in Medicare beneficiaries. *J Am Coll Surg*. 2014; 218(6): 1141-1147.
31. Bass NM. Review article: the current pharmacological therapies for hepatic encephalopathy. *Aliment Pharmacol Ther*. 2006; 25 (suppl 1): 23-31. DOI: 10.1111/j.1746-6342.2006.03218
32. Musa S, Moran C, Rahman T. Clostridium difficile infection and liver disease. *J Gastrointestin Liver Dis*. 2010; 19(3): 303-310.
33. Ciuhu AN, Pantea-Stoian AM, Nitipir C, et al. Assessment of cachexia in cancer patients with advanced disease. Conference: 3rd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications (INTERDIAB) Location: Bucharest, ROMANIA Date: MAR 02-04, 2017.Sponsor(s): Assoc Renal Metab & Nutrit Studies; AstraZeneca Diabetes; MSD Diabetes; novo nordisk; SANOFI INTERDIAB 2017: DIABETES MELLITUS IN INTERNAL MEDICINE Book Series: International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications. 2017: 139-147.
34. Balaceanu A, Diaconu C, Mateescu D, Stanica A. Hepatocellular carcinoma with hepatic and pulmonary metastasis, inferior vena cava and left pulmonary artery thrombosis in a patient with asymptomatic hepatitis C. Case report. *Medical Ultrasonography*. 2010; 12(4): 345-348.
35. Ciocarlan M, Draghia L, Manuc D, et al. Nutritional status of patients with digestive cancers, Conference: 3rd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications (INTERDIAB) Location: Bucharest, ROMANIA Date: MAR 02-04, 2017Sponsor(s): Assoc Renal Metab & Nutrit Studies; AstraZeneca Diabetes; MSD Diabetes; novo nordisk; SANOFI INTERDIAB 2017: DIABETES MELLITUS IN INTERNAL MEDICINE Book Series: International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications. 2017: 132-138.
36. Weingarden AR, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent Clostridium difficile infection. *Am J Physiol Gastrointest Liver Physiol*. 2014; 306(4): G310–G319.
37. Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, Yan F, Cao H, Wang B. Systematic review: Adverse events of fecal microbiota transplantation. *PLoS One* 2016; 11: e0161174. DOI: 10.1371/journal.pone.0161174