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# FAECAL MICROBIOTA TRANSPLANT BEYOND THE GUIDELINES?

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***Abstract:*** *Clostridioides difficile infection (CDI) represents the most common cause of diarrheic disease associated to public health services, an important public health problem due to the potential risk of complications, severe forms of pseudomembranous colitis and death. Although the great majority of CDI patients have a favourable response to specific antibiotic drug therapy, a significant percentage will present one or several relapses and the risk of relapse increases with the increase in numbers of infectious episodes, reaching 50-60% after the third CDI episode. Faecal microbiota transplant (FMT) is a proven effective treatment method with high rates of curability in recurrent and refractory CDI. However, can we use FMT earlier than the current recommendations of the treatment guidelines? The evidence is beginning to pile up.*

CDI represent a current public health issue in both Romania and the whole world due to the increase of its occurrence and severity. Clostridioides difficile (CD) is an anaerobic, spore-forming, Gram-positive bacteria, the major etiological factor of antibiotic-associated colitis(1); it represents the most common cause of diarrheic disease associated to public health services, and accounts for 15-25% of postantibiotherapy diarrhea cases(2), 75% of the cases of postantibiotherapy colitis cases, of which 90-100% are pseudomembranous colitis(3), with an important morbidity and mortality.

At least two prerequisites are necessary for the occurrence of CDI: alteration of normal intestinal flora determining a decrease in resistance against colonization with CD and, acquisition of the organism from an exogenous source. Other factors are represented by the host's susceptibility, virulence of the strains, or nature and period of exposure to antibiotics.(4)

By far, the most important risk factor is the use of antibiotics in the period foregoing onset, even in the form of a single prophylactic dose, almost any antibiotic can lead to the occurrence of the infection.(5) If, certain risk factors cannot be intervened upon (age), there are attempts to implement guides for the well-balanced use of antibiotic therapy and specific epidemiology measures for infected patients who are hospitalized(6,7) nevertheless, the number of infections has not decreased. Other risk factors are also incriminated: anti-secretory medication, co-morbidities, immunosuppressed status.

CDI should be suspected in all patients with nosocomial diarrhea, patients with unexplainable diarrhea and new onset of ≥ 3 poorly formed stools/24 hours (types 5-7 on the Bristol scale), post antibiotic diarrhea with community origin, elderly patients, those who were administered antibiotics, immunosuppressors or gastric antisecretory medication, those who do not belong to an acute diarrhea focal group within the community are the ones representing the target population to be tested.(8)

CDI becomes manifest only in the case of toxins' production as non-toxin generating forms will not lead to diarrheic disease therefore, diagnosis relies on identifying toxins from either faeces, or from cultures of CD.

Recommendations for CDI treatments have evolved and developed throughout time. Pending an update of the ESCMID guide, in 2018 the American Society of Infectious Diseases and the American Society of Epidemiology-IDSA/SHEA published an updated version to the previous guide with a number of changes, vancomicin or fidaxomicin are the first line treatment for 10 days.(9) Concurrently with specific treatment methods, other additional treatment methods include: interruption of useless antimicrobial treatments, correction of hydroelectric balances, avoidance of motility inhibiting medication, and revision of proton pump inhibitors medication.

Although the great majority of CDI patients have a favourable response to specific antibiotic drug therapy, a significant percentage will present one or several relapses and the risk of relapse increases with the increase in numbers of infectious episodes. After a first CDI episode, 11-25% patients will relapse within the first 30 days since the completion of therapy.(10-12) After the first relapse episode, up to 46.2% of patients will have a second episode of relapse.(13) Moreover, the risk of recurrence continues to rise, reaching 50–60% at the third episode.(14)

These recurrences generate additional costs for the medical system, morbidity and risk of fatalities.

Despite having been empirically used for several centuries for the treatment of certain forms of diarrhea, the first documented use of a human faecal microbiota suspension for the treatment of severe forms of diarrhea dates back to 4th century China(15), the first reporting dates back to 1958, belonging to Eiseman et al., via enemas (16), FMT stands out as an extremely effective treatment method, a higher than 90% cure rate, for

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patients with multiple recurrences(17) or with severe forms of CDI.(18) Multiple randomized controlled trials, systematic reviews and meta-analyses have confirmed the very high cure rate, ranging between 85% and 92%.(19-22)

FMT is the instillation of fecal material from a healthy donor to a patient gastrointestinal tract to treat a condition associated with alteration of the intestinal microbiota - intestinal dysbiosis. The mechanism of action is that of restoring a new intestinal microbiota to restore normal intestinal functioning. In addition to the clearly proven role in CDI recurrences, data are gathered on the beneficial role of TMF in other conditions such as: inflammatory bowel diseases, irritable bowel syndrome, autoimmune diseases, allergic conditions, metabolic diseases such as obesity.

Currently, the FMT is included in the European treatment guidelines of CDI, for multiple recurrences(8), mild or severe recurrent CDI and refractory CDI(23), while in the American treatment guideline of CDI, after the second or subsequent recurrent CDI.(9)

Currently, there are no recommendations in the treatment guidelines that FMT should be used for primary, nonrecurrent CDI forms, there are insufficient data to make this recommendation(23), but data about FMT usefulness in primary CDI is starting to pile up. Initial studies included only patients with severe or complicated forms, Zainah included 6 patients with severe primary CDI of which 3 relapsed after a first FMT.(24)

Other subsequent studies included patients with severe primary CDI (25,26), but reported only an overall success rate, which also included patients with recurrent CDI. Roshan et al. reported a 98% success rate of FMT for primary CDI, including 44 patients, who had a negative test for CDI 4-8 weeks after TMF, including both patients with severe and non-severe primary CDI.(27)

In another study published in 2021, which included 25 patients with primary CDI, the success rate was 92% after a first TMF.(28) Another argument for TMF in patients with primary CDI comes from Langier et al. study who found a 5-fold decrease in mortality in the early FMT versus conventional-therapy group, but these patients were infected with the hypervirulent ribotype 027 Clostridoides difficile, during an outbreak in Marseille.(29)

The relapse rates after a first CDI episode treated only with antibiotics are between 11 and 25%(10-12), and the relapse rates after FMT for a primary CDI were between 2-8 % (27,28) which would make sense to use FMT from the first CDI episode, theoretically reducing treatment costs, hospitalizations and also the risk of death of these patients.There still are questions about FMT long-term safety profile, but severe immediate complications have been seldom reported.(30)

Data from prospective and controlled studies are necessary to establish FMT role in primary CDI, but meanwhile we should remember that FMT it may be the proper instrument for primary CDI.

## REFERENCES


1. Bartlett JG, Chang TW, Gurwith M, et al. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med. 1978;298:531–534.
2. DePestel DD, Aronoff DM. Epidemiology of Clostridium difficile infection. J Pharm Pract. 2013;26(5):464-75.
3. Pepin JV, 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.
4. Tonna I, Welsby P. Pathogenesis and treatment of Clostridium difficile infection. Postgrad Med J. 2005;81:367–369.
5. Bouza E, Munoz P, Alonso R, et al. Clinical manifestations, treatment and control of infections caused by Clostridium difficile. Clin Microbiol Infect. 2005;11(4):57–64.
6. Valiquette L, Cossette B, Garant MP, et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of Clostridium difficile-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis. 2007;45(Suppl 2):S112-121.
7. Public Health Agency of Canada. (2013, 01 11). Clostridium Difficile Infection - Infection Prevention and Control Guidance for Management in Acute Care Settings. Retrieved September 08, 2019, from https://www.canada.ca/en/public-health/services/infectious-diseases/nosocomial-occupational-infections/clostridium-difficile-infection-prevention-control-guidance-management-acute-care-settings.html.
8. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20 Suppl 2:1-26.
9. McDonald LC, Gerding DN, Johnson EJ, 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 for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):987-994.
10. Olsen MA, Stwalley D, Demont C, et al. Increasing Age Has Limited Impact on Risk of Clostridium difficile Infection in an Elderly Population. Open Forum Infect Dis. 2018;5(7):ofy160.
11. Noren Akerlund T, Back E, et al. Molecular epidemiology of hospital associated and community-acquired Clostridium difficile infection in a Swedish county. J Clin Microbiol. 2004;42:3635–3643.
12. Bemer PT, Eckert C, et al. Clostridium difficile infections: analysis of recurrence in an area with low prevalence of 027 strain. J Hosp Infect. 2016;93:109-112.
13. Pepin J, Routhier S, Gagnon S, et al. Management and outcomes of a first recurrence of Clostridium difficile associated disease in Quebec, Canada. Clin Infect Dis. 2006;42:758-764.
14. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent Clostridium difficile disease: Epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999;20:43–50.
15. Zhang F, Lou W, Shi Y, et al. Should we standardize the 1,700-year-old fecal microbiota transplantation? Am J Gastroenterol. 2012;107:1755-1756.
16. Eiseman B, Silen W, Bascom S, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery,1958; 44:854–85.
17. van Nood E, Vrieza A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368:407–415.
18. Weingarden AR. Microbiota transplantation restores normal fecal bile acid composition in recurrent Clostridium difficile infection. Am. J. Physiol. Gastrointest. Liver Physiol. 2014;306:310-319.
19. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015;41:835–43.
20. Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for Clostridium difficile infection:

systematic review and meta-analysis. Am J Gastroenterol. 2013;108:500–8.
21. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent Clostridium difficile infection: a randomized clinical trial. JAMA. 2016;315:142–149.
22. Kelly CR, Khouruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. Ann Intern Med. 2016;165:609–616.
23. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66:569-580.
24. Zainah H, Hassan M, Shiekh-Sroujieh L, et al. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory clostridium difficile infection. Dig Dis Sci. 2015;60:181–185.
25. Fischer M, Sipe BW, Rogers NA, et al. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated clostridium difficile infection: description of a protocol with high success rate. Aliment Pharmacol Ther. 2015;42:470–476.
26. Kelly C, Yen EF, Grinspan AM, et al. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. Gastroenterology. 2021;160:183-192.
27. Roshan N, Clancy, AK, Borody TJ. Faecal Microbiota Transplantation is Effective for the Initial Treatment of Clostridium difficile Infection: A Retrospective Clinical Review. Infect Dis Ther. 2021;9:935-942.
28. Popa D, Neamtu B, Mihalache M, et al. Fecal Microbiota Transplant in Severe and Non-Severe Clostridioides difficile Infection. Is There a Role of FMT in Primary Severe CDI?. J Clin Med. 2021;10(24):5822.
29. Lagier JC, Delord M, Million M, et al. Dramatic reduction in Clostridium difficile ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. Eur J Clin Microbiol Infect Dis. 2015;34:1597-1601.
30. Wang S, Xu M, Wang W, et al. Systematic Review: Adverse events of Fecal Microbiota Transplantation PLoS One. 2016;11(8):e0161174.