REVIEW ARTICLE

Fecal microbiota transplantation in gastrointestinal diseases

What practicing physicians should know

Thomas J. Borody[1], Nathan Connelly[2], Scott W. Mitchell[1]

1 Department of Research and Innovation, Centre for Digestive Diseases, Five Dock, Australia
2 Department of Research and Development, Moonee Valley Specialist Centre, Moonee Ponds, Australia

KEY WORDS

Clostridium difficile infection, fecal microbiota transplantation, full spectrum microbiota

ABSTRACT

Clostridium difficile infection (CDI) is one of the most commonly reported nosocomial pathogens in the United States and Europe, with recent CDI-associated mortality in the United States approaching 30 000 deaths annually. Antibiotics remain the preferred treatment for CDI; however, a minority of patients experience numerous relapses and are treated with restoration of the bowel microbiota, termed fecal microbiota transplantation (FMT).

FMT involves the introduction of a fecal suspension from a healthy donor into the gut of the infected patient to cure the CDI and replace depleted components of the gut microbiota. FMT is particularly effective and safe in curing CDI, using a colonoscope or enema to deliver 1 to 2 infusions. Given that 6425 CDIs were reported in Poland in 2014, practicing physicians should understand the benefits and limitations of FMT in CDI as this novel therapy has rapidly advanced to the level of the "standard-of-care" status in Australia, the United States, and many parts of Europe. FMT has been administered either as a suspension in saline, a highly refined liquid product which can be frozen, as lyophilized powder in capsules, and as an encapsulated spore preparation. The ultimate products to reach the market will be shaped by the indications approved by regulatory bodies. At present, the fecal suspension in saline remains the treatment of choice to terminate relapsing and severe CDI, which we will review here.

The use of FMT for non-CDI indications, such as inflammatory bowel disease and irritable bowel syndrome, is likely to increase. At present, these indications remain in the domain of research institutions.

Correspondence to:
Scott Mitchell, BBiomedSc Bsc(Hons), Department of Research and Innovation, Centre for Digestive Diseases, Level 1/229, Great North Rd, Five Dock NSW 2046, Australia, phone: +61 2 9713 4011, fax: +61 2 9712 1675, e-mail: scott.mitchell@cdd.com.au
Received: September 13, 2015.
Accepted: September 13, 2015.
Published online: September 23, 2015.
Conflict of interest: see page 856.
Pol Arch Med Wewn. 2015; 125 (11): 852-858

Introduction

General background In susceptible individuals, *Clostridium difficile* induces the activity of 2 exotoxins (TcdA and TcdB), leading to colonocyte death, neutrophilic colitis, and loss of intestinal barrier function. The infection is transmitted by spores that can withstand heat, acid, and antibiotics, and that are present in high concentrations in health care facilities, thereby leading to nosocomial infection. Colonization resistance is weakened by antibiotics but susceptibility is also increased with advancing age, cancer chemotherapy, and accompanying severe diseases. A new virulent strain emerged in North America in the early 2000s, accompanied by a marked increase in the reports of severe CDI cases. The ribotype 027 was identified, having high fluoroquinolone resistance, efficient sporulation, and high toxin production, leading to a mortality rate 3 times higher than less virulent strains, such as 001 or 004.[1] It has now achieved global dissemination, and epidemic strains can be found in numerous hospitals.[2] Hence, CDI has become a growing clinical challenge and one that needs to be treated promptly as the epidemic strains have a high level of morbidity with a mortality rate of 5% in severe cases, translating to approximately 29 000 deaths annually in the United States.[1]

Most cases of CDI are treated with either metronidazole, vancomycin, or fidaxomicin. Recurrence ranges from 20% after the initial episode to 60% after multiple treatments. In this group of patients in whom further antibiotic therapy is

ineffective, the composition of the gut microbiome is known to be abnormal with deficiencies in Firmicutes and Bacteroidetes.[3] Such patients respond well to fecal microbiota transplantation (FMT), achieving cure in more than 90% of cases with a single infusion, which also results in the restoration of microbiota abnormalities.[3] The rapid uptake of FMT in Australia, then the United States, and now Europe has provided the clinician with an inexpensive, rapid, and highly efficacious cure of relapsing CDI. Doctors and clinics performing FMT can even be found listed on the Internet, for example, thepowerofpoop.com.[4]

The epidemic of CDI has accelerated the broader use of FMT, the success of which has led to research in the non-CDI indications such as inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS), among others. This review attempts to acquaint the reader with the current state-of-the-art uses of FMT and emerging FMT products and looks into the future evolution of this field.

Focusing on Poland To demonstrate a local context, figures from Europe indicate that mortality from CDI reaches approximately 40 000 cases annually, indicating that the situation is similar to that in the United States and that the rapid rise in the incidence of CDI in Poland has now reached approximately 11 500 hospitalized cases in 2013.[5] Further publications confirm the gravity of this infection. An abstract analyzing 12 randomly selected hospitals and microbial laboratories throughout Poland determined the mean incidence of CDI in Polish hospitals to be 3.6 per 100 000 in 2011 and 7.1 per 100 000 in 2012.[6] Pituch et al,[7] who utilized data from 13 participating centers, determined the rate of incidence for CDI to be 3668 per 10 000 patients admitted to the hospital in 2011 (TABLE 1).

More robust figures relating to CDIs occurring in Poland before 2013 are difficult to assess because the Polish National Institute of Public Health only began to publish CDI-specific figures in 2013. Before this, they would have fallen under the published title of "other bacterial intestinal infections" as "total", "specified", or "unspecified", making the role of CDI in said incidences impossible to determine. Obtainable data report an incidence of 12.3 and 16.7 per 100 000 citizens in Poland in 2013 and 2014, respectively (with 4738 and 6425 corresponding cases, respectively).[8,9] Indices relating to any CDI analysis are most likely underreported, considering that individuals suffering mild CDI may not seek treatment.

A study performed by utilizing data from the Polish University Hospital in Krakow between 2008 and 2014 analyzed 1009 individuals, with 78% of patients suffering CDI once and 22% of patients suffering CDI more than once; 2.4% of the patients died within 14 days of CDI confirmation, and mortality rates were 12.9% in medical wards, 5.6% in surgical wards, and 27.7% in intensive care units. From 2008 to 2012, a 6.5-fold increase in the incidence of CDI occurred, and approximately two-thirds of patients that suffered CDI did so during hospitalization despite being admitted for other reasons.[10]

Financial cost There are scant data on the financial cost of CDI in Poland; however, the potential cost of *Clostridium difficile*-associated diarrhea in Europe was estimated at €3000 million per year in 2008 and predicted to double over the next 40 years.[11] In 2010, Ghantoji et al[12] demonstrated that non-United States-based studies indicated a cost ranging from $5243 to $8570 for each case of primary CDI, and $13 655 for each case of recurrent CDI (rCDI).[12]

In 2015, Kwon et al[13] reported a relatively low mortality rate associated with CDI previously compared with current statistics and an annual cost for acute care alone within the United States attributable to CDI ranging from $1.2 to $5.9 billion. Comparatively, in a review of literature published in 2012, McGlone et al[14] determined a median cost of $31 421 to account for hospital, societal, and third-party payer costs related to CDI.

Current treatment of *Clostridium difficile* infection Several factors influence the treatment of CDI, although mild cases are generally treated with metronidazole, and severe cases—with vancomycin (and more recently, with fidaxomicin).[15] While these antibiotics may resolve the first infection in 70% to 78% of the cases, given the known mortality, a good case can be made for patients to have earlier access to FMT after even a single recurrence of CDI.[16,17] Although alternative antimicrobial treatment options targeting CDI have been used, it is logical to avoid the drugs that originally contributed to the CDI problem and repair the gut microflora deficiency with healthy microbiota.[16]

The use of FMT for CDI is well documented although such variables as donor recruitment, formulation of fecal suspension, delivery route, and infusion frequency vary.[18-21] A recent randomized clinical trial compared the efficacy of vancomycin against FMT via colonoscopy using homogenized stool in saline. The trial was halted at the 1-year interim analysis.[22] In 90% of the patients receiving FMT, diarrhea symptoms resolved compared with only 26% of the patients receiving vancomycin.[22] Innovative in this trial was the recurrent use of FMT after the failure of the first infusion in 2 patients with pseudomembraneous colitis (PMC). The protocol was amended to 1 FMT every 3 days until colitis resolved. Recurrent PMC sufferers achieved a cure with multiple infusions.[22]

Similarly, in Poland, Grzesiowski et al[5] achieved a cure rate in 55 of 62 patients with rCDI (88.7%), with 76.5% cured after the first; 14.5%, after the second; and the remaining 9%, after the third nasogastric infusion.[5] It should be noted that in comparisons of administration routes of FMT for CDI, Gough et al[20] determined that for CDI treatment, "enema" or "rectal catheter" administration

TABLE 1 Incidence of *Clostridium difficile* infection in Poland

Year	Incidence per 100 000 citizens	Reference
2011	3.6	6
2012	7.1	6
2013	12.3	8
2014	16.7	9

of FMT was superior to "gastroscope and nasojejunal tube" with the respective values of 95.4%, 95.6%, and 76.4%. Additionally, Postigo and Kim compared colonoscopic and nasogastric administration for CDI from 12 published studies and reported a cure rate of 85.3% for nasogastric and 93.2% for colonoscopic infusion.[23]

The findings of Grzesiowski et al[5] are particularly important as they teach us to design CDI treatments to be multiple rather than single infusions seen in most CDI trials, in order to build an expectation of cure approaching 100%.

Moving away from infused fecal suspensions, a preliminary study demonstrated the effectiveness of frozen encapsulated FMT against refractory CDI. Despite utilizing a sample size of only 20 patients, 90% were cured of diarrhea. No significant adverse events occurred attributed to FMT capsules.[24]

The outcome and long-term follow-up of patients has also shown FMT to be not only highly effective but also surprisingly free of significant adverse events and long-term complications.[25] Apart from the upsurge of nosocomial CDI, this infection has increasingly become contracted outside hospitals with the need for novel CDI treatments becoming immediate.[25] The use of a single FMT infusion for rCDI was well documented. It soon became clear that in a minority of patients, especially those with severe CDI, multiple FMT treatments are required.[5,19,21,24,26]

Fecal microbiota transplantation benefits and evolution of *Clostridium difficile* treatment FMT began with a crude liquid stool suspension, progressed to a filtered and frozen format, to frozen filtered capsules, and is now being produced as lyophilized powder within delayed-release capsules and encapsulated spore-specific combinations.[4,27,28] However, the danger of contamination or strain mutation and altered genotype expression is a constant risk for culture-derived product. An understated boon relating to FMT treatment is the availability of the source material. For patients suffering from CDI who are lacking ready access to FMT treatment, a number of sources offer information on home, "do-it-yourself" FMT instructions.[4] While these options are "low-cost", they do not provide the standardized protocols such as those offered by accredited health care facilities, extensive testing of donor stool, patient support and care, and access to professionals that administer both treatment and knowledge on FMT use. Hence, it is important that a product be developed that can obtain the high cure rates associated with standard FMT treatments, be easily transportable, and generally palatable to the recipient. The Boston-based company, OpenBiome, is a not-for-profit organization that distributes throughout the United States frozen fecal suspension for FMT at low cost, yet it ensures the highest donor stool quality. Their product is used by gastroenterologists in numerous clinics and hospitals.

For these reasons, we believe the future of CDI treatment will utilize donor stool that has been filtered to remove all but the microbiota and a substantial amount of water content via lyophilization (freeze-drying) with the resulting component (largely fecal microbiota) being a powder containing the full spectrum microbiota (FSM). This would be encapsulated and could be immediately administered as an oral medication or could be stored for protracted periods and remain viable without refrigeration far longer than fresh or frozen FMT. The authors at the Centre for Digestive Diseases (CDD) are currently analyzing FSM capsules to determine optimal long-term storage conditions.[28] Such an optimized product would do away with transport issues, the discomfort associated with fecal enema infusions, and minimize the 'Ick' factor of handling human stool.[29] Even without encapsulated FSM, product acceptance of FMT has grown.[29] Jiang et al[30] sent questionnaires to gastroenterologists and infectious disease specialists, and of the 89 responses, the majority of both cohorts were supportive of a local fecal transplant (FT) clinic (64% and 69%, respectively), and a large majority indicated they would refer patients to a newly developed local FT center (89% and 81%, respectively).[30] As FMT progresses to using a prescribed medication avoiding the need for enema administrations, the need for specialized FT clinics and hospital departments could become a thing of the past.

Anecdotally, the 'Ick' factor associated with FMT has been less of an issue when referring to patients desperate for treatment.[29] Even though this is likely the case with the vast majority of patients who do not respond to initial antibiotic treatments, offering patients a short course of tasteless/odorless pills for the treatment of CDI rather than an enema is a major improvement on FMT therapeutics.

Data surrounding lyophilized FSM are scant, although our group at the CDD has presented an abstract showing the indices comparing whole cell count and viable cell count of FSM in the form of frozen FMT and lyophilized FMT.[31] Additionally, Jiang et al[32] have recently completed an analysis in which fresh, frozen, and lyophilized FMT were delivered colonoscopically into patients suffering from rCDI, with resulting responses considered successful and each format of FMT considered equally effective. Jiang et al[32] also indicated the value of expanding testing to lyophilized encapsulated FMT.

TABLE 2 Alternative gut disorder indication trials identified on ClinicalTrials.gov, utilizing fecal microbiota transplantation

Indication	Clinical Trials.gov identifier	Number of trials for indication
ileal pouchitis	NCT02428361	2
	NCT02049502	
constipation	NCT02301221	2
	NCT02291354	
Crohn disease	NCT02417974	10
	NCT02330211	
	NCT02199561	
	NCT01793831	
	NCT01847170	
	NCT02335281	
	NCT02108821	
	NCT02391012	
	NCT02033408	
	NCT02016469	
irritable bowel syndrome	NCT02328547	4
	NCT02299973	
	NCT02154867	
	NCT02092402	

Indications for fecal microbiota transplantation beyond *Clostridium difficile* infection FMT has been suggested as a therapy for other non-CDI gastrointestinal conditions as well as many nongastrointestinal conditions. Some of these have already been reviewed.[21,28,33]

Fecal microbiota transplantation and ulcerative colitis Apart from CDI, there is a high level of interest in FMT use as a potential therapy targeting IBD. It has been postulated that an aberrant mucosal reaction to gastrointestinal microbiota contributes to the pathogenesis of IBD although an alternative view is that an abnormal gut microbiota, or a dysbiosis, initiates the inflammatory process.

The first patient to receive FMT at our facility was in 1988, and she had indeterminate colitis without CDI. Her colitis completely disappeared and has not recurred over the past 27 years of follow-up.[34] We then reported further sporadic cases of ulcerative colitis (UC) responding to FMT.[35] FMT has been investigated in a number of cohort studies with variable results. Unlike CDI, the use of FMT in UC can result in transient improvement but only very occasionally—in a cure. A recent controlled study randomized 50 patients with mild-to-moderate UC of variable duration and used FMT via a nasoduodenal tube infusing either donor stools or autologous stool at 0 and 3 weeks.[36] Per-protocol "response rates" (clinical remission and ≥1 point decrease in the Mayo score) were 41.2% and 25%, respectively (P = 0.29). Moayyedi et al[37] reported a significant induction of remission in 75 patients receiving either 50 ml of FMT via enema (n = 38) or 50 ml of water enema (n = 37) once weekly for 6 weeks. By week 7, 9 of 38 patients on FMT (24%) and 2 of 37 patients on placebo (5%) were in remission (P <0.03).

A small study including 4 children with moderate-to-severe UC treated with 8 FMT infusions of 50 ml over 14 days found only transient improvement of symptoms, with poor long-term remission.[38] We can already see from these early results that FMT methods applied to the treatment of CDI do not work for IBD and the endpoints are different. In CDI, the endpoint is abolition of diarrhea and eradication of *Clostridium difficile*. Since there is no recognizable pathogen to eradicate in UC, the treatment endpoints can include response or remission (or both). Furthermore, 1 or 2 FMT treatments can cure most patients with relapsing CDI, whereas repeated infusions of FMT are required to achieve remission in UC, and even then other factors appear to be operating, such as donor differences.[37] Therefore, research on FMT in IBD will need to address the different pathophysiology in UC versus that in CDI.

Fecal microbiota transplantation and other gut disorders There is some provocative evidence for the use of FMT in other gut disorders, albeit the data are scant and generally confined to small cohort studies and case reports addressing such conditions as constipation, irritable bowel disease, IBS, pouchitis, and Crohn disease.[34,39-43] There are multiple trials currently underway to examine the potential benefits of FMT in such conditions and these are listed on ClinicalTrials.gov at the time of writing (**TABLE 2**).

Fecal microbiota transplantation and nongastrointestinal diseases There has been considerable interest in FMT for nongastrointestinal disorders in neurobehavioral disorders, which entail the connection between the gut and brain (gut–brain axis) and, more recently, the fecal microbiota and the brain.[44,45]

Most studies encompassing FMT and nongastrointestinal disease have focused on autism spectrum disorder (ASD). Patients with ASD commonly have gastrointestinal system disorders, and a correlation between the severity of ASD symptoms and gastrointestinal symptoms has been demonstrated.[46,47] Patients with ASD have been shown to have alterations in the fecal microbiome, compared with patients without ASD. The presence of aberrant Clostridia species has been the most reported.[48] Restoration of the normal microbiome has been attempted with prebiotics, probiotics, and antibiotics with varying success, while treatment with nonabsorbable vancomycin provides a short-term improvement, suggesting the microbiome activates bioactive molecules that may be reaching the brain to cause ASD behavior.[49] Evidence for the use of FMT for ASD is emerging, and a small cohort study has been reported as an abstract.[50] Other neurological

conditions of note that show the potential for treatment with FMT include the Parkinson disease and multiple sclerosis.[51,52]

It has also been suggested that the gastrointestinal microbiome plays a role in the pathogenesis of metabolic conditions. Changes in the gut microbiome have been reported in type 2 diabetes, and FMT has been demonstrated to improve insulin sensitivity in male patients with metabolic syndrome.[53,54]

Alterations in the microbiome have also been demonstrated in inflammatory conditions such as rheumatoid arthritis, in autoimmune disease, neurodevelopmental disorders, psychiatric diseases, and skin conditions.[45,55-58]

Conclusions Currently, the practicing physician should be aware that FMT for relapsing CDI has evolved from being an experimental treatment to an accepted life-saving therapy. In many countries, leading hospitals are developing FMT capability in the subspecialty of gastroenterology and infectious diseases. It needs to be stressed that the higher mortality epidemic strains such as 027 may drive the patient rapidly towards hypotension and renal failure, and an early referral to an FMT center is advisable. There is an active development of FMT products by biotech companies, and encapsulated treatment for CDI is likely to become available, permitting earlier and simpler therapy and obviating the need for the use of fecal suspension.

The use of FMT in conditions other than CDI is at present experimental but early reports point to potentially exciting changes in the way we will treat IBD, IBS, and possibly a number of other conditions. Research in such conditions is encouraged.

Conflict of interest TB has a financial interest in the Centre for Digestive Diseases, where FMT is offered. He also has filed patent applications in this field and is a consultant for CIPAC Limited, a start-up company developing microbiomebased therapeutics. NC accepts patients in the field of FMT and offers this treatment at Moonee Valley Specialist Centre, Australia. SM is an employee of the Centre for Digestive Diseases, Australia, where FMT is offered as a treatment.

REFERENCES

1 Leffler DA, Lamont T. Clostridium difficile infection. N Engl J Med. 2015; 372: 1539-1548.

2 He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemioca healthcare-associated Clostridium difficile. Nat Genet. 2013; 45: 109-113.

3 Khoruts A, Dicksved J, Jansson JK, et al. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. J Clin Gastroenterol. 2010; 44: 354-360.

4 The power of poop. http://thepowerofpoop.com/resources/innovation/. 2013. Accessed August 8, 2015.

5 Grzesiowski P, Hermann A, Dubaniewicz A, et al. Effectiveness of FMT in recurrent Clostridium difficile infection. 3rd International Conference on Prevention and Infection Control (ICPIC 2015); 2015 Jun 16-19; Geneva, Switzerland. Warsaw, Poland: Preventative Medicine and Rehabilitation Center, Infection Prevention Institute. 2015; 4 (Suppl 1): P27.

6 Pituch H, Lachowicz D, Obuch-Woszczatynski P, et al. Polish surveillance programme of clostridium difficile infections reveals persistently high prevalence of Clostridium difficile type 027. Paper presented at: 24th European Conference of Clinical Microbiology and Infectious Diseases. 2014; Barcelona, Spain: P0759.

7 Pituch H, Obuch-Woszczatynski P, Lachowicz D, et al. First results of a Polish surveillance programme of Clostridium difficile infections: high prevalence of Clostridium difficile polymerase chain reaction (PCR) ribotype 027. 23rd European Conference of Clinical Microbiology and Infectious Diseases. 2013; Berlin, Germany: P2495.

8 Czarkowski MP, Cielebak E, Kondej B, et al. Infectious diseases and poisonings in Poland in 2013. Warsaw, Poland: National Institute of Public Health; 2013: 1643-8655.

9 National Institute of Public Health, Government Institute of Hygiene and Epidemiology. Infectious diseases and poisonings in Poland in 2014- Basic working tables, preliminary data. Warsaw, Poland: National Institute of Public Health; 2014: 9.

10 Czepiel J, Dzierska JKE, Biesiada G, et al. Epidemiology of Clostridium difficile infection: results of a hospital-based study in Krakow, Poland. Epidemiol Infect. 2015: 1-9.

11 Kuijper EJ, Coignard B, Tüll P; ESCMID Study Group for Clostridium difficile; EU Member States; European Centre for Disease Prevention and Control. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006: Suppl 6: 2-18.

12 Ghantoji SS, Sail K, Lairson DR, et al. Economic healthcare costs of Clostridium difficile infection: a systematic review. J Hosp Infect. 2010; 74: 309-318.

13 Kwon JH, Olsen MA, Dubberke ER. The morbidity, mortality and costs associated with Clostridium difficile infection. Infect Dis Clin North Am. 2015; 29: 123-134.

14 McGlone SM, Bailey RR, Zimmer SM, et al. The economic burden of Clostridium difficile. Clin Microbiol Infect. 2012; 18: 282-289.

15 Pepin J. Vancomycin for the treatment of Clostridium difficile infection: for whom is this expensive bullet really magic? Clin Infect Dis. 2008; 46: 1493-1498.

16 Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile--associated disease: old therapies and new strategies. Lancet Infect Dis. 2005; 5: 549-557.

17 Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol. 2012; 107: 1079-1087.

18 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: 500-508.

19 Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis. 2014; 58: 1515-1522.

20 Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011; 53: 994-1002.

21 Brandt LJ. American journal of gastroenterology lecture: Intestinal microbiota and the tole of fecal microbiota transplant (FMT) in treatment of C. difficile infection. Am J Gastroenterol. 2013; 108: 177-185.

22 Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. cancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015; 4: 835-843.

23 Postigo R, Kim JH. Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: a review and pooled analysis. Infection. 2012; 40: 643-648.

24 Youngster I, Russell GH, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA. 2014; 312: 1772-1778.

25 Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol. 2009; 7: 526-536.

26 Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. Eur J Clin Microbiol Infect Dis. 2014; 33: 1425-1428.

27 Khanna S, Pardi DS, Kelly C, et al. Clinical evaluation of ser-109, a rationally designed , oral microbiome-based therapeutic for the treatment of recurrent Clostridium difficile. American Gastroenterological Association Freston Conference (AGAFC 2014). 2014; Chicago, United States: 26-27.

28 Borody TJ, Peattie D, Mitchell SW. Fecal microbiota transplantation: Expanding horizons for Clostridium difficile infections and beyond. Antibiotics. 2015; 4: 254-266.

29 Stone J. Comments on: "When s**t hits the fan". 2013 May 20. In: Scientific American. Molecules to Medicine. Scientific American. http://blogs.scientificamerican.com/molecules-to-medicine/the-st-hits-the-fan-fda-inds-and-fecal-microbiota-transplants/. Accessed August 9, 2015.

30 Jiang ZD, Hoang LN, Lasco TM, et al. Physician attitudes towards the use of fecal transplantation for recurrent Clostridium difficile infection in a metropolitan area. Clin Infect Dis. 2013; 56: 1059-1060.

31 Lin E, Jaworski A, Furnari V, et al. Twelve week storage trial of microbial viability in lyophilized and frozen fecal microbiota preparations. Paper presented at: Digestive Diseases Week. 2015; Washington DC, United States.

32 Jiang ZH, Ajami NJ, Lasco T, et al. Fresh, Frozen, or Lyophilized Fecal Microbiota Transplantation (FMT) for multiple recurrent C. difficile infection (CDI). Paper presented at: American College of Gastroenterology. 2014; Philadelphia, United States.

33 Borody TJ, Campbell J. Fecal microbiota transplantation techniques, applications, and issues. Gastroenterol Clin North Am. 2012; 41: 781-803.

34 Borody TJ, George L, Andrews P, et al. Bowel-flora alteration: a potential cure for inflammatory bowel disease and irritable bowel syndrome? Med J Aust. 1989; 150: 604.

35 Borody TJ, Warren FW, Leis S, et al. Treatment of ulcerative colitis using faecal bacteriotherapy. J Clin Gastroenterol. 2003; 37: 42-47.

36 Rossen NG, Fuentes S, van der Speck MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015; 149: 110-118.

37 Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology. 2015; 149: 102-109.

38 Karolewska-Bochenek K, Lazowska-Przeorek I, Grzsiowski P, et al. Fecal microbiota transplantation in refractory pediatric UC – preliminary data. ECCO 2015. 10th Congress of European Crohn's and Colitis organisation (ECCO); 2015. Barcelona, Spain: P427.

39 Borody TJ, Leis S, McGrath K, et al. treatment of chronic constipation and colitis using human probiotic infusions. 2001. Proceedings of Prebiotics and Probiotics and the New Foods Conference. 2001; Rome, Italy: P. 228.

40 Andrews PJ, Barnes P, Borody TJ. Chronic constipation reversed by restoration of bowel flora. A case and a hypothesis. Eur J Gastroenterol Hepatol. 1992; 4: 245-247.

41 Pinn DM, Aroniadis OC, Brandt LJ. Is fecal transplantation the answer for irritable bowel syndrome? A single center experience. Am J Gastroenterol. 2014; 109: 1831-1832.

42 Patel LN, Schairer J, Shen B. Fecal transplantation therapy for Clostridium difficile-associated pouchitis. 2014 Fecal transplantation therapy for clostridium difficile associated pouchitis. Int J Colorectal Dis. 2014; 29: 263-264.

43 Suskind DL, Brittnacher MJ, Wahbeh G, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiomed in active Crohn's disease. Inflamm Bowel Dis. 2015; 21: 556-563.

44 Lyte M. Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behaviour. PLoS Pathog. 2013; 9: e1003726.

45 Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013; 155: 1451-1463.

46 Buie T, Campbell DB, Fuchs GJ III, et al. Evaluation, diagnosis and treatment of gastrointestinal disorders in individuals with ASDS: A consensus report. Pediatrics. 2010; 125 Suppl 1: S1-S18.

47 Tomova A, Husarova V, Lakatosova S, et al. Gastrointestinal microbiota in children with autism in Slovakia. Physiol Behav. 2015 Jan; 138: 179-189.

48 Song Y, Liu C, Finegold SM. Real-time PCR quantitation of clostridia in feces of autistic children. Appl Environ Microbiol. 2004; 70: 6459-6465.

49 Sandler RH, Finegold Sm, Bolte ER, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol. 2000; 15: 429-435.

50 Hudy L, Manichanh C, Santiago A, et al. Phase I trial of FMT in autistic children. IHMC 2015. 5th International Human Microbiome Congress (IHMC); 2015 31; Luxembourg. 326.

51 Guseo A. The Parkinson puzzle. Orv Hetil. 2012 30; 153: 2060-2069.

52 Borody TJ, Leis S, Campbell J, et al. Fecal microbiota transplantation (FMT) in multiple sclerosis (MS)s. Am J Gastroenterol. 2011; 106:S352.

53 Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012; 490: 55-60.

54 Vrieze A, Van Nooe E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2013; 144: 250.

55 Scher JU, Sczesnak A, Longman RS, et al. Expansion of Prevotella copri correlates with enhances susceptibility to arthritis. Elife. 2013; 2: e01202.

56 Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. Nat Rev Gastroenterol Hepatol. 2011; 9: 88-96.

57 Forsythe P, Sudo N, Dinan T, et al. Mood and gut feelings. Brain Behav Immun. 2010; 24: 9-16.

58 Bowe W, Patel NB, Logan AC. Acne vulgaris, probiotics and the gut-brain-skin axis: from anecdote to translational medicine. Benef Microbes. 2014; 5: 185-199.

ARTYKUŁ POGLĄDOWY

Przeszczepianie mikrobioty jelitowej w chorobach przewodu pokarmowego

Co powinni wiedzieć lekarze praktycy

Thomas J. Borody[1], Nathan Connelly[2], Scott W. Mitchell[1]

1 Department of Research and Innovation, Centre for Digestive Diseases, Five Dock, Australia
2 Department of Research and Development, Moonee Valley Specialist Centre, Moonee Ponds, Australia

SŁOWA KLUCZOWE

pełne spektrum mikrobioty, przeszczepianie mikrobioty jelitowej, zakażenie *Clostridium difficile*

STRESZCZENIE

Zakażenie *Clostridium difficile* (*C. difficile infection* – CDI) należy do najczęstszych zakażeń szpitalnych w Stanach Zjednoczonych i w Europie. W Stanach Zjednoczonych liczba zgonów związanych z CDI sięga ostatnio 30 000 rocznie. Podstawowym sposobem leczenia CDI pozostaje antybiotykoterapia, ale niestety część chorych doświadcza wielokrotnych nawrotów; leczy się ich poprzez odtworzenie prawidłowej flory bakteryjnej jelit, co się określa jako przeszczepienie mikrobioty jelitowej (*fecal microbiota transplantation* – FMT). FMT polega na podaniu zawiesiny kału od zdrowego dawcy do jelita chorego, aby wyleczyć CDI i odtworzyć brakujące elementy składowe mikrobioty jelitowej.

FMT skutecznie i bezpiecznie leczy CDI; efekt uzyskuje się po podaniu 1–2 dawek za pomocą kolonoskopu lub wlewu doodbytniczego. W Polsce w 2014 roku zgłoszono 6425 przypadków CDI, dlatego lekarze powinni znać zalety i ograniczenia FMT w leczeniu CDI. Ta nowa metoda szybko zyskuje status standardu postępowania w Australii, Stanach Zjednoczonych i w wielu krajach Europy. FMT stosowano już w różnych postaciach: zawiesiny w roztworze chlorku sodu, wysoce oczyszczonego, nadającego się do zamrażania płynnego produktu, liofilizowanego proszku w kapsułkach czy też kapsułkowanego preparatu zawierającego przetrwalniki. To, jakie produkty ostatecznie znajdą się na rynku, będzie zależeć od wskazań zarejestrowanych przez odpowiednie urzędy. Obecnie w leczeniu nawrotowego i ciężkiego CDI metodą z wyboru pozostaje podanie zawiesiny kału w roztworze chlorku sodu, co omówiono w niniejszym artykule. Prawdopodobnie wzrośnie również wykorzystanie FMT w innych wskazaniach, takich jak nieswoiste zapalenia jelit i zespół jelita drażliwego, co obecnie pozostaje domeną badań naukowych.

Adres do korespondencji:
Scott Mitchell, BBiomedSc Bsc(Hons), Department of Research and Innovation, Centre for Digestive Diseases, Level 1/229, Great North Rd, Five Dock NSW 2046, Australia, tel.: +61 2 9713 4011, fax: +61 2 9712 1675, e-mail: scott.mitchell@cdd.com.au
Praca wpłynęła: 13.09.2015.
Przyjęta do druku: 13.09.2015.
Publikacja *online*: 23.09.2015.
Zgłoszono sprzeczność interesów: patrz str. 856.
Pol Arch Med Wewn. 2015; 125 (11): 852-858
Tłumaczył lek. Łukasz Strzeszyński