CORRESPONDENCE

Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection

TO THE EDITOR: *Clostridium difficile* infection is a major health problem.[1] Antibiotic treatment is associated with a considerable rate of recurrence of infection and is related to the emergence of antibiotic-resistant bacteria. Recently, fecal microbiota transplantation has been shown to be effective in the treatment of recurrent *C. difficile* infection.[2] We undertook a proof-of-concept trial (ClinicalTrials.gov number, NCT02301000) to evaluate the use of fecal microbiota transplantation as treatment for primary *C. difficile* infection.

The trial began on November 25, 2014, and the first patient underwent randomization on February 22, 2015. From February 2015 through November 2017, at six hospitals in Norway, we randomly assigned 21 adult patients with acute *C. difficile* infection (≥3 loose stools per day and a positive *C. difficile* stool test) who had not had previous *C. difficile* infection to recommended treatment in Norway[3] (oral metronidazole at a dose of 400 mg three times a day for 10 days) or fecal microbiota transplantation (one 60-ml enema of anaerobically cultivated human intestinal microbiota) (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).[4,5] Achim Biotherapeutics, which provided the fecal microbiota suspension free of charge to the investigators for the purpose of the trial, had no role in the design, conduct, or analyses of the trial. The protocol, available at NEJM.org, was approved by the institutional review board, and all patients provided written informed consent.

The primary end point was clinical cure (firm stool consistency or ≤3 bowel movements per day) with no evidence of recurrence of *C. difficile* infection when the patient was evaluated at day 70 by an assessor who was unaware of the treatment assignment. Secondary end points were evaluations 4 and 35 days after the initiation of treatment and adverse events. Patients in whom clinical cure was achieved after initial treatment and who had no recurrence of infection were defined as having a full primary response. Patients who received additional treatment to achieve clinical cure, but who did not have recurrence of infection during the follow-up period, were defined as having a full secondary response. Full details of the trial are provided in the protocol and the statistical analysis plan, available at NEJM.org.

One patient was excluded because of a norovirus infection that was diagnosed the day after randomization. Of 20 eligible patients, 9 were randomly assigned to fecal microbiota transplantation and 11 were assigned to metronidazole. A full primary response was observed in 5 patients (56%; 95% confidence interval [CI], 21 to 86) in the transplantation group and in 5 in the

THIS WEEK'S LETTERS

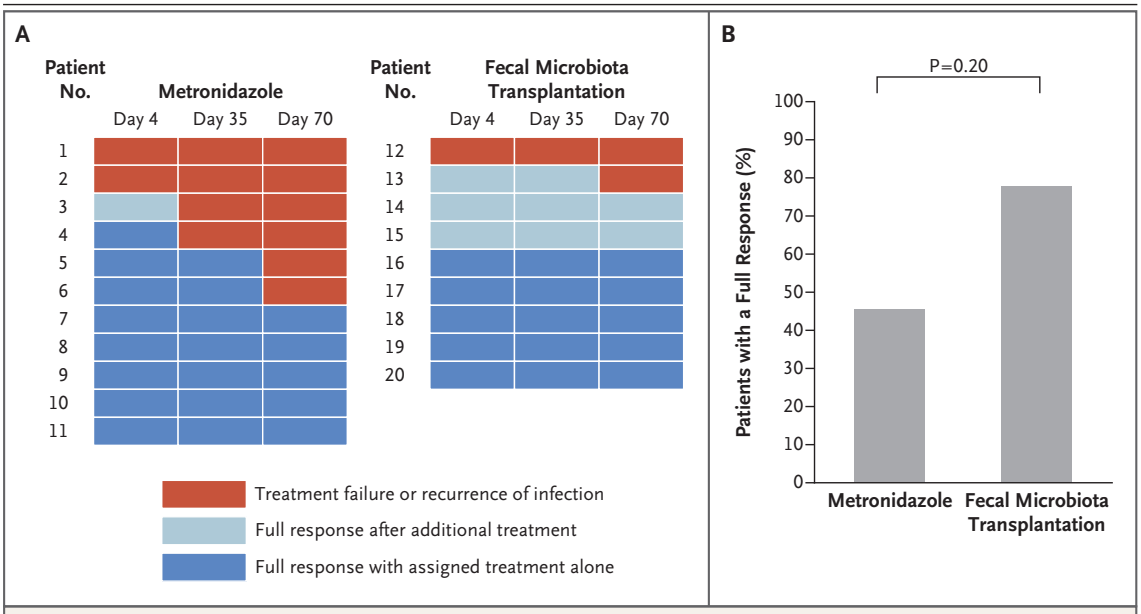

Figure 1. Results of Fecal Microbiota Transplantation versus Antibiotic Therapy with Metronidazole for Primary *Clostridium difficile* Infection.

Panel A shows the results at the evaluation of patients at 4, 35, and 70 days after the start of treatment. Panel B shows the overall response to treatment (full primary or secondary response after 70 days).

metronidazole group (45%; 95% CI, 17 to 77) (exact P=1.00) (Fig. 1A).

Three of the four remaining patients in the transplantation group received antibiotics by day 4 after the initiation of treatment; two of them had a full secondary response. In the metronidazole group, of the remaining six patients, none had a full secondary response, either because of refractory or recurrent infection. Thus, the overall response to treatment (full primary or secondary response) was achieved in seven patients in the transplantation group (78%; 95% CI, 40 to 97), as compared with five in the metronidazole group (45%; 95% CI, 17 to 77) (P=0.20) (Fig. 1B). No serious treatment-related adverse events were observed in either group. Details on the treatment course of individual patients are provided in the Supplementary Appendix.

This was a small trial, but the results suggest that fecal microbiota transplantation may be an alternative to antibiotic therapy in primary *C. difficile* infection. A phase 3 trial to assess fecal microbiota transplantation as primary treatment for *C. difficile* infection is under way.

Frederik E. Juul, M.D.
Kjetil Garborg, M.D., Ph.D.
Oslo University Hospital
Oslo, Norway

Michael Bretthauer, M.D., Ph.D.
University of Oslo
Oslo, Norway
michael.bretthauer@medisin.uio.no

Hilde Skudal, M.D.
Telemark Hospital
Skien, Norway

Mari N. Øines, M.D.
Rigshospitalet
Copenhagen, Denmark

Håvard Wiig, M.D.
Sørlandet Hospital
Kristiansand, Norway

Øystein Rose, M.D.
Vestre Viken Bærum Hospital
Gjettum, Norway

Birgitte Seip, M.D., Ph.D.
Vestfold Hospital
Tønsberg, Norway

J. Thomas Lamont, M.D.
Beth Israel Deaconess Medical Center
Boston, MA

Tore Midtvedt, M.D., Ph.D.
Karolinska Institutet
Stockholm, Sweden

Jørgen Valeur, M.D., Ph.D.
Lovisenberg Diaconal Hospital
Oslo, Norway

Mette Kalager, M.D., Ph.D.
Øyvind Holme, M.D., Ph.D.
University of Oslo
Oslo, Norway

Lise Helsingen, M.D.
Oslo University Hospital
Oslo, Norway

Magnus Løberg, M.D., Ph.D.
University of Oslo
Oslo, Norway

Hans-Olov Adami, M.D., Ph.D.
Oslo University Hospital
Oslo, Norway

A complete list of contributors is provided in the Supplementary Appendix.

Supported by the Toppforsk program of the Research Council of Norway, a network grant from the Southeastern Norway Regional Health Authority, and a Ph.D. scholarship grant (to Dr. Juul) from the Southeastern Norway Regional Health Authority.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on June 2, 2018, at NEJM.org.

1. 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 for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66(7):e1-e48.
2. Leffler DA, Lamont JT. *Clostridium difficile* infection. N Engl J Med 2015;372:1539-48.
3. National guidelines for antibiotic use in hospitals in Norway. Helsedirektoratet, 2013 (In Norwegian.) (https://helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/seksjon?Tittel=abdomen-2516#clostridium-difficile-infeksjon).
4. Jorup-Rönström C, Håkanson A, Sandell S, et al. Fecal transplant against relapsing Clostridium difficile-associated diarrhea in 32 patients. Scand J Gastroenterol 2012;47:548-52.
5. Gustafsson A, Berstad A, Lund-Tønnesen S, Midtvedt T, Norin E. The effect of faecal enema on five microflora-associated characteristics in patients with antibiotic-associated diarrhoea. Scand J Gastroenterol 1999;34:580-6.
DOI: 10.1056/NEJMc1803103

Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes

TO THE EDITOR: The study by Bjerregaard et al. (April 5 issue)[1] provides valuable insights about patterns of overweight from childhood to early adulthood and the risk of type 2 diabetes. However, the generalizability of the findings may be limited, given the low-risk population and the low rates of childhood obesity and type 2 diabetes at the time of the study.

As the obesity epidemic spreads, it has become apparent that the incidence of type 2 diabetes among young people has been increasing worldwide.[2,3] In fact, one study estimated that among high-risk ethnic groups, the incidence of type 2 diabetes may be surpassing that of type 1 diabetes by mid-to-late adolescence.[4] The timing of the obesity epidemic and the limited diversity of Denmark put the population in the study by Bjerregaard et al. at lower risk for type 2 diabetes at all ages than the risk in much of the world.[2,5]

The lower bound of 30 years for the age at the diagnosis of type 2 diabetes was appropriate for the population in the study. Yet, given the current global obesity epidemic, data are lacking from studies using diagnostic codes instead of age cutoff points to delineate the association between weight trajectories in childhood and the risk of type 2 diabetes among multiethnic and multiracial populations.

Joshua B. Cadwell, B.S.
Columbia University Institute of Human Nutrition
New York, NY
joc2089@med.cornell.edu

Alpana P. Shukla, M.D.
Weill Cornell Medicine
New York, NY

No potential conflict of interest relevant to this letter was reported.

1. Bjerregaard LG, Jensen BW, Ängquist L, Osler M, Sørensen TIA, Baker JL. Change in overweight from childhood to early adulthood and risk of type 2 diabetes. N Engl J Med 2018;378:1302-12.
2. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus — present and future perspectives. Nat Rev Endocrinol 2011;8:228-36.
3. Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. Pediatrics 2005;116:473-80.
4. Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. JAMA 2007;297:2716-24.
5. Central Intelligence Agency. The World Factbook: Denmark. May 2018 (www.cia.gov/library/publications/the-world-factbook/geos/da.html).
DOI: 10.1056/NEJMc1805984

TO THE EDITOR: The large-scale study by Bjerregaard et al. has given pastry lovers like us hope by showing that the effects of childhood obesity are reversible. However, data are lacking on the duration of obesity, owing to time gaps between the ages examined in the study. A longer duration of obesity may lead to a higher incidence of