Fecal Biotherapy: Can Human Waste Cure a Disease?

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THE STUDY: *N ENGL J MED. 2013 Jan 16. [Epub ahead of print]*
Els van Nood, Anne Vrieze, Max Nieuwdorp, Susana Fuentes, Erwin G. Zoetendal, Willem M. de Vos, Caroline E. Visser, Ed J. Kuijper, Joep F.W.M. Bartelsman, Jan G.P. Tijssen, Peter Speelman, Marcel G.W. Dijkgraaf, and Josbert J. Keller. Duodenal infusion of donor feces for recurrent Clostridium difficile.

BACKGROUND

Clostridium difficile infection (CDI) is the leading cause of diarrhea in the healthcare setting and is becoming increasing prevalent in the community. A recent report by the Centers for Disease Control (CDC) reported that CDI prevalence broke all past records; the infection rate doubled to 336,600 and deaths soared to 14,000 each year [1]. The treatment of choice for CDI is antibiotics metronidazole or vancomycin; however, during the past decade their efficacy against this pathogen has decreased. The estimated efficacy of antibiotic therapy for a first recurrence is 60%, a proportion that further declines in patients with multiple recurrences [2, 3]. The resistant spores of Clostridium difficile, with the rise of susceptible host population, and use and misuse of antibiotics, all predispose to CDI [4].

WHY WAS THE STUDY CONDUCTED?

Fecal biotherapy or intestinal microbiota transplantation (IMT) is the technique of transfusing donor feces to a recipient. Surprisingly, it is not a new concept; its history dates back to four cases that were treated successfully and case reports were published in the Journal of Surgery in 1958 [5]. Over the past few decades, many case series and reports have tested this method. A recent comprehensive systematic review by Gough, Shaikh and Manges found a staggering 92% cure rate [6]; the only thing missing was a randomized controlled trial that could assess efficacy of IMT. Researchers from the Netherlands thus decided to fill in this gap.

THE STUDY

It was an open label randomized controlled trial conducted at the Academic Medical Centre in the Netherlands. Forty-three patients were enrolled in the study; all of them were suffering from a relapse of Clostridium difficile infection and had received the standard vancomycin and metronidazole regimen, which had failed to induce remission. Three treatment regimens for recurrent Clostridium difficile infection were compared;

- The first group (16 patients) - donor feces infusion preceded by an abbreviated course of vancomycin and a standard bowel lavage
- The second group (13 patients) - standard vancomycin therapy only
- The third group (13 patients) - standard vancomycin therapy and bowel lavage.

Donor Feces Infusion:
Donors <60 years of age volunteered; they were screened twice for recent or past illnesses with questionnaires and their stool samples were screened for various pathogenic microorganisms. The samples were diluted with 500 ml of 0.9% normal saline, stirred and supernatant separated into a sterile bottle, which was then fed via a nasoduodenal tube at 2-3 minutes per 50 ml to the patient who was monitored for adverse effects. An analysis of the fecal microbiota was carried out by DNA extractions from the patient and donor sample before and after the infusions.

WHAT DID THE STUDY FIND?

Patients underwent randomization from January 2008 to April 2010.

- 94% of the patients in the infusion only group achieved complete cure (13/16)
- 18 patients who had a relapse after initial antibiotic treatment received off-protocol donor-feces infusions; of these patients, 15 (83%) were cured; 11 with the first infusion and 4 with the second
- 31% patients of the vancomycin only group were cured (4/13)

- 23% patients of the vancomycin-bowel lavage group were cured (3/13).

The overall cure rate ratio of donor feces infusion was 3.05 as compared with vancomycin alone (99.9% confidence interval [CI], 1.08 to 290.05) and 4.05 as compared with vancomycin with bowel lavage (99.9% CI, 1.21 to 290.12); thus, donor feces infusion was superior (P value <0.001) to either of the two vancomycin regimens.

The Simpson's Reciprocal Index of diversity was used to assess the fecal microbiota before and after the infusions; after 2 weeks, the diversity levels of the recipients matched that of the donors as their symptoms resolved.

- Recipient level: Before the donor feces infusions, mean 57±26
- Recipient level: Two weeks after the donor feces infusions, 179±42 (P<0.001 for baseline vs. IMT)
- The diversity level of the donors was mean 172±54.

Quantitative changes were observed in relevant groups of intestinal bacteria (P<0.05). These changes included increased numbers of Bacteroidetes species and Clostridium clusters IV and XIVa (by a factor of 2 to 4 for both groups) and decreased numbers of Proteobacteria (by a factor of up to 100).

No serious adverse effects, except a benign diarrhea, were noted.

LEARNING POINTS FROM THE STUDY

First, it confirms the observation from case series that donor feces infusion is superior to antibiotics for recurrent Clostridium difficile infections. Secondly, it opens a whole new research field to a new and potent therapeutic strategy. What should be the optimal protocol for the donor feces infusion? What amount of feces will be the safest and most potent? Are other routes other than nasoduodenal equal, more, or less effective? The thinking mind wanders off in multiple directions to search for these answers and this ground breaking study will surely be followed by numerous trials.

IS SOMETHING IN IT FOR A DEVELOPING COUNTRY?

An important cause of CDI is frequent and inappropriate antibiotic usage. In developing countries, no definite antibiotic prescription policies are in practice and there is limited antibiotic resistance surveillance. In addition, lack of good quality research data compounds the problem. Few studies show a high incidence of CDI in hospitalized patients. For example, Naqvi and Chaudhry recently found that 40% of patients who received antibiotics for various reasons in a public sector Pakistani hospital developed diarrhea; and 29% of them tested positive for Clostridium difficile [7]. The major antibiotics implicated were augmentin (amoxicillin/clavulanic acid) and amoxicillin which are used commonly and at times unnecessarily in healthcare.

LIMITATIONS

Three categories of patients were excluded from the study; immune-compromised patients, those admitted to the ICU and those receiving antibiotics for infections other then Clostridium difficile. All these patients are prone to developing Clostridium difficile infections while those in the ICU are particularly associated with high death rates; research has previously shown donor feces infusion to be beneficial for this group and therefore, this group of patients was not randomized. It is important to remember that patients included in this study had failed vancomycin therapy and therefore, were likely to fail vancomycin therapy again. This study establishes the superiority of IMT only in those patients who have failed therapy with vancomycin and did not explore comparative effectiveness in first CDI.

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