CORRESPONDENCE

Duodenal Infusion of Feces for Recurrent *Clostridium difficile*

TO THE EDITOR: Van Nood et al. (Jan. 31 issue)[1] found fecal microbiota therapy to be superior to vancomycin for the treatment of recurrent *Clostridium difficile* infection, but the results of their study should be interpreted with caution. Small, index trials such as this one are vulnerable to exaggerated treatment effects, and subsequent trials typically show decreased effects.[2] Even though the trial was randomized, the results may have been influenced by inequalities among the three treatment groups in terms of either the number of pretreatment recurrences of *C. difficile* infection or post-treatment exposure to an antimicrobial agent or proton-pump inhibitor (both of which are well-defined risks for recurrence).[3] The cure rate in the control group treated with vancomycin was half of that reported in two randomized trials,[4,5] a finding that biased the results of Van Nood et al. toward the efficacy of fecal microbiota therapy, according to the power calculation of the study. This unexpectedly low cure rate in the control group produced a P value that triggered a trial-stopping rule that led to the trial's early termination; this in turn led to an inappropriate inflation of the efficacy of fecal microbiota therapy because of an alpha error.[2] In exploratory trials of novel therapies such as this one, in which mortality was neither part of the primary outcome nor a factor in the interim analysis, the continuation of the study to its originally powered end point would have provided more rigorous and informative results.

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TO THE EDITOR: Several potential biases reduce the validity of the results reported by van Nood et al., in which they conclude that donor feces infusion is superior to vancomycin in resolving recurrent diarrhea caused by infection with *C. difficile*.[1] Group awareness of assigned treatment can result in ascertainment bias and in this instance may have led to early trial stoppage when the data could have favored fecal infusion on the basis of chance.[1] The interim analysis was unplanned and occurred when investigators purportedly "became aware" of data favoring fecal infusion. There is less ethical imperative to stop a trial early on

the basis of symptomatic outcomes.[2] P values serve to evaluate random error, but bias can explain large treatment effects.[3] The cause-specific end point driven by the surrogate end point of *C. difficile* toxin testing hindered the evaluation of the net benefits and harms of donor infusion. The investigators should provide the outcomes for diarrhea from any cause for each group. Finally, the small sample size means that serious adverse events still could occur in approximately one in six patients, leaving the evaluation of harms and benefits unfinished.[4] Future well-designed clinical trials will be needed before it can be concluded that this intervention is safe and effective.

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TO THE EDITOR: We have used colonoscopic fecal transplantation to treat some patients with *C. difficile* colitis. To date, all patients have been cured and no side effects have been observed. Is it possible to prevent the risk of infection from donor feces? Which hazardous pathogens could be transferred through donor feces to the recipient? Why didn't van Nood et al. and other authors[1] screen donors for tuberculosis? Primary enteric infections caused by tuberculosis have been described.[2] If tuberculosis should develop in a recipient, serious consequences may arise. On the other hand, are all the laboratory tests performed by van Nood et al. necessary? For some of these pathogens, at least to date, there does not appear to be an association with enteral infection.

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

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TO THE EDITOR: The use of feces in medical practice predates the 1958 report by Eiseman et al.[1] by a considerable number of years. Christian Franz Paullini, a German physician, in his 1697 book, *Heilsame Dreck-Apotheke*, provided a comprehensive collection of "recipes" for the internal and external medical use of human and animal feces.[2,3]

Paullini was born in Eisenach, February 25, 1643. He studied medicine and theology, received a master's degree in Wittenberg, and his medical degree in Leiden. He served as physician to the Bishop of Münster and the Court of Braunschweig, and as *Herzoglichen Stadtphysikus* (ducal state physician) in Eisenach, where he died, June 10, 1712. Paullini was a polymath, who corresponded with, among others, mathematician Gottfried Wilhelm Leibniz and the Jesuit scholar Athanasius Kircher.

In *Heilsame Dreck-Apotheke*, Paullini cited numerous authorities of ancient and modern medicine as well as the folk medical practices of peasants, sailors, and poor people. He focused on the therapeutic effect of feces in encyclopedic breadth, including all possible applications from head to foot, and his book went through many editions and reprints.

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

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THE AUTHORS REPLY: The randomized trials mentioned by Van Schooneveld et al. reporting higher cure rates for vancomycin included patients with a first infection or first recurrence of *C. difficile* infection.[1,2] Most of the patients in our study had their fourth episode before study inclusion, which explains the low vancomycin cure rates. To our knowledge, there are no trials reporting an outcome for patients with multiple recurrences, but estimated cure rates are in accordance with our results.[3] The study groups in our trial were similar to those in other trials with regard to the number of recurrences and risk factors for recurrence.

It is true that our study was unblinded, and we agree that it was imperfect, as also mentioned by Hataye et al. However, to prevent ascertainment bias, we had an independent adjudication committee (whose members were unaware of study-group assignment) decide which patients were cured. The conservative Haybittle–Peto rule was applied during the interim analysis to minimize the effect of chance, but not before more than 33% of patients in the anticipated sample size had reached the primary end point.[4] Short but self-limiting episodes of diarrhea or loose stools occurred in our study population, in which many patients had coexisting conditions. Therefore, the use of all-cause diarrhea as an outcome measure could be misleading. Alternatively, the outcome measure of diarrhea with clinical suspicion for recurrence[1] was met by only one patient with a negative stool test for *C. difficile* during follow-up. Treating this event as a recurrence would have created the impression of a more pronounced difference between treatment groups.

We agree with Ramsauer that the selection criteria for the laboratory tests used to screen donors are debatable and may have been affected by geographic location and the likelihood of donor exposure to *Mycobacterium tuberculosis*. The risk of enteric tuberculosis was considered extremely low in our donor population on the basis of screening. Potential donors were excluded if they had diarrhea, showed signs of systemic illness, or had a history of tuberculosis. Screening was performed to prevent both enteric infection and possible enteric transmission of nonprimary enteric pathogens. Although reports of enteric transmission after donor-feces infusion are lacking, infusion should always be performed with caution.

In addition to the informative historical note by Lehrer, an earlier report of donor-feces infusions apparently appeared 1700 years ago in China. Zhang et al. reported "allocoprophagy" in a Chinese handbook of emergency medicine, *Zhou Hou Bei Ji Fang* (or *Handy Therapy for Emergencies*), written during the Dong-jin dynasty in the 4th century in China by Ge Hong.[5]

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Effect of Freezing on Oxytocin Ampules

TO THE EDITOR: Postpartum hemorrhage is a major cause of maternal death worldwide, particularly in developing countries.[1] Oxytocin ampules are included on the World Health Organization list of essential medicines used in the active management of the third stage of labor to prevent postpartum hemorrhage. Refrigerated storage minimizes the degradation of oxytocin,[2] but the ampules are also labeled with instructions against freezing during storage. Although data are lacking on the effects of freezing, there has been concern that oxytocin, a peptide, may be unsta-