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GUT IN FOCUS: EXTENDED ABSTRACT

Anaerobically cultivated human intestinal microbiota as first-line treatment for *Clostridium difficile* infection

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Clostridium difficile infection (CDI), most often resulting from an antibiotic-induced disturbance of the healthy intestinal microbiota, is an increasing health problem (1–3). Antibiotics such as metronidazole or vancomycin are well-established and effective treatment options for first occurrences of CDI (4, 5) (so-called primary), but up to one third of patients experience treatment failure or recurrent disease within a few weeks (6–8). Repeated courses of antibiotics may be effective, but multiple recurrences are common (9). Recurrent CDI may result from re-infection with the same or a different *C. difficile* strain. Up to 50% of recurrences may be re-infections with strains different from the primary infection reinforcing the notion that appropriate colonization is disturbed after antibiotic treatment (10).

Fecal microbiota transplant (FMT) has been shown to be effective and safe in recurrent CDI in multiple uncontrolled studies (11), and recently, a randomized controlled trial (RCT) showed FMT to be superior to high-dose vancomycin for recurrent CDI (12). Theoretically, FMT as first-line treatment can prevent the vicious cycle of both types of re-infections (same or different strain) by rapidly restoring a favorable colonic microbial environment, and thus leaving the patient less susceptible to either kind of CDI recurrence. Reduced need for resistance-driving antibiotics and reduced proliferation of other resistant pathogens are possible advantageous spin-off effects of FMT as the primary treatment of CDI.

This is a description of the design of an ongoing RCT to compare the effect of intestinal microbiota transplantation with the effect of standard metronidazole treatment in primary CDI.

Based on the high recurrence rate of CDI after treatment with antibiotics and the convincing results of FMT for recurrent CDI, we hypothesize that intestinal microbiota transplantation can be beneficial also in the treatment of primary CDI (13).

The aim of this study is to investigate whether an anaerobically cultivated human intestinal microbiota (ACHIM) is more effective than metronidazole in inducing a durable cure for primary CDI (ClinicalTrials.gov identifier NCT02301000).

Material and methods

A continuously re-cultivated human intestinal microbiota, obtained from a healthy donor more than 15 years ago, has been shown to be an effective cure for recurrent CDI (14). This ACHIM, which has been extensively analyzed for pathogenic elements, will be used in the current trial, obviating the need for donor screening.

The trial is designed as a multicenter, single-blinded RCT.

Hospitalized patients with a first episode of CDI will be recruited and randomized 1:1 to a rectal instillation of ACHIM or to a 10-day course of metronidazole 500 mg t.i.d.

A first episode of CDI is defined as diarrhea and a positive stool test for *C. difficile* toxin A or B without evidence of recent CDI.

Patients are asked to report the number of daily bowel movements for 4 days after the initiation of CDI treatment. The number of daily bowel movements will also be recorded on day 7, 14, 21, 35, and 70. The primary end point is resolution of diarrhea and no evidence of recurrent CDI within 70 days after treatment initiation. A blinded study investigator will assess the primary end point. A pilot study including 40 patients (20 in each study arm) will be analyzed to guide the final sample size.

Results

The trial started in November 2014, and no results are yet available.

Conclusion

The effect of intestinal microbiota therapy for primary CDI is currently unknown. The current trial aims to document the effect of an ACHIM in primary CDI.

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