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GUT IN FOCUS: EXTENDED ABSTRACT

Experience with cultivated microbiota transplant: ongoing treatment of *Clostridium difficile* patients in Sweden

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Bacteria should no longer be seen as pure enemies. Nowadays, there are enough evidences to place microorganisms as key elements in human homeostasis. It is known that a balanced human intestinal microbiota constitutes an important protection against the establishment and overgrowth of pathogenic microorganisms, e.g. *Clostridium difficile* (CD) causing intestinal disorder in the host. The intestinal microbiota has a pivotal role in the maintenance of health of the human beings, especially in the defence against pathogenic microorganisms.

The degree of diarrhoea defines the choice of therapy – most often different antibiotics. However, the risk for recurrent infections is about 35%, which sometimes occur several months after the termination of therapy. These patients are recommended a new antibiotic treatment. After the first recurrence is the risk for a new recurrence up to 65%. The chance of a cure is reduced with the number of recurrent infections.

Faecal microbiota transplantation (FMT), also known as stool transplantation, is a procedure aimed at restoring an altered intestinal microbiota balance by administration of stool microorganisms from a single healthy donor – often from a close relative, or alternatively several donors donating faeces to a 'faeces bank'. The donor(s) and the faeces must undergo a rigorous screening process to determine that no pathogens are transmitted (1). These tests are both time consuming and very expensive. Despite initial scepticism, FMT is today regarded as an alternative for patients with recurrent CD infection in several countries. Regulatory authorities in the EU and the USA have, however, not given formal approval for FMT. But due to high efficacy against CD infections, FMT is more or less accepted on a temporary basis as an experimental treatment. There is a worldwide growing interest for using FMT as a treatment of other diseases as well, including *Clostridium difficile* infection (CDI), inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS). Today, there are groups worldwide who are introducing FMT as a treatment regime, faeces obtained from healthy donor(s) into diseased individuals using different approaches, both for selection of donors and treatment mode either administered by naso-duodenal sond or as an enema.

In our group, we have established an anaerobically cultivated human intestinal microbiota approximately 20 years ago (2–4). The cultured microbiota originates from one faecal sample from one single healthy donor on a Western diet (2). The microbiota has regularly been recultivated on a rich bacteriological medium under anaerobe conditions and carefully checked for the absence of pathogen organisms as *Salmonella, Shigella, Yersinia*, *Clostridium difficile*, *Cryptosporidium, Cyclospora, Isospora*, cysts and worm eggs, HIV, hepatitis A, B and C, and *Treponema pallidum*. This ready-to-use anaerobe culture is kept frozen in tubes at -80°C until use.

In some previous studies, the anaerobic cultured microbiota has been installed into a number of CDI patients during the years – cultured microbiota transplant (CMT) – with very good results (2–4). Now there is an ongoing clinical study, where a group of antibiotic-associated diarrhoea (AAD) patients, both male and female at different ages, are included. Inclusion criteria are one or several metronidazole treatments followed by vancomycin 125 mg four times daily during at least 10 days without recovery. These patients are randomised to either CMT or continuation on vancomycin 125 mg four times daily for at least 10 days, followed by periods of 7, 30 and 90 days control – the responsible scientist phones the patients. In the CMT group, 6 out of 11 patients recovered after one CMT treatment, three patients recovered after two CMT treatments, and one patient after three CMT treatments. One patient was withdrawn for personal reasons. In the

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vancomycin group, two patients out of 10 recovered after the vancomycin treatment, but four patients did not and two patients were withdrawn for personal reasons. Of these four patients, one patient recovered after one CMT treatment and two patients after two CMT treatments, and the last patient, so far, has recovered after two CMT treatments, but the follow-up at day 90 still remains. In this study, there are also possibilities to compare cost effective issue between CMT and antibiotic and hospitalisation treatments.

Despite the increasing number of studies where an unbalanced microbiota is suggested to cause intestinal disturbances, there are no standard protocols. Alterations in the microbiota composition and function are obviously involved in the pathogenesis of a variety of Western world diseases/disturbances, and CDI is one of the most common health care-associated infections in the world. However, CDI, IBD and IBS, obesity, and diabetes are also discussed when research regarding intestinal microbiota ecological balance is actual. Based on the assumption that a disturbed microbiota might cause intestinal disturbances/diarrhoea, it seems logical that a CMT treatment should prove to be both health promoting and cost effective, and in line with this, this current study supports the role of transplanting a balanced anaerobic gut ecosystem into patients with intestinal disturbances – a resetting of the intestinal ecosystem.

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