

Alterations of the intestinal microbiota may be involved in the pathogenesis of a number of disorders, but there is still uncertainty as to how such conditions should be treated

Faeces transplantation – new wonder medicine?

The work of mapping the human microbiome has revitalised an ancient interest in the makeup of the intestinal contents. Through their metabolic activity, the intestinal microbiota can affect all substances ingested orally or involved in the enterohepatic circulation. Microbes help us to break down poorly digestible food, modify drugs and foreign substances and produce a large number of signal molecules which affect both intestinal and extra-intestinal functions. The «microbe organ» is of evident importance to health, and alteration of the intestinal microbiota, so-called dysbiosis, is claimed to be the cause of an increasing number of diseases. Research in this field is still in its infancy, but there are already many views on how dysbiosis should be treated. Transplantation of faeces is one of the more promising, but also among the most controversial proposals.

Coprophagia – «consumption of faeces» occurs naturally among some species of animals, and therapeutic use of faeces has a long tradition, not least in Chinese medicine (1). Faeces transplantation as treatment for *Clostridium difficile*-associated diarrhoea was first described in the Journal of the Norwegian Medical Association in 1998 (2), and caused a justified stir (3–6). A lot has happened in the years that have passed since this publication. The efficacy of faeces transplantation for treating recurring *C. difficile* infection has now been documented (7), and the procedure has also been tried with other conditions, such as inflammatory bowel disease, irritable bowel syndrome, type 2 diabetes mellitus, multiple sclerosis, chronic fatigue syndrome and immunological thrombocytopenia (8). As a research tool, the method has yielded encouraging results. For example, improvement of insulin resistance has been demonstrated in patients with metabolic syndrome (9). Animal experiments indicate that intestinal microbiota can programme the individual's biological stress response (10) and that certain behavioural traits can be transferred via faeces transplantation (11). Great optimism with regard to what this treatment may achieve in the future can be sensed in the professional literature, and on websites we find recipes for how to perform personal interventions with the aid of ordinary kitchen utensils. Is this the new wonder medicine?

Faeces transplantation is indisputably burdened with both aesthetic and ethical challenges, but also with problems of a more practical nature. We still have divergent answers to quite elementary questions: What should the indication be? How sick must the patient be? Should one intervene early or late in the course of the disease? Must the patient have prior treatment with antibiotics? Should fresh, frozen or cultivated faeces be used? From one or more donors? And how extensively should the donors be screened for disease? Should the faeces be administered from above or below? Must the treatment be repeated in order to be effective? And last, but not least: Who is to be responsible for treatment of the «microbe organ»?

As a treatment principle, manipulation of the intestinal microbiota has come to stay, also in modern medicine. Faeces transplantation must nonetheless be regarded as a temporary solution: There are not many doctors who will insist on using ordure as therapy if there are viable alternatives. The short-term aim must be to administer intestinal microbiota in a non-fluid form (12). The long-term aim must be to identify specific microbial dysfunctions and selectively restore these functions. This is contingent upon our learning far more about the form of government within the intestines – the

«microcracy». And lawlessness certainly does not prevail here; in contrast to our own lack of legislation concerning intestinal microbiota (13), the «microbe organ» itself has definite rules in place.

The development of so-called next-generation microbiota therapeutics (14) is already well under way, and for some conditions this kind of microbial medicine may be just around the corner. The well-known Irish gastroenterologist Eamonn Quigley stated recently: «If we are still doing fecal transplants in five years' time, we have failed» (15).

Jørgen Valeur
jorgen.valeur@lds.no
Tore Midtvedt

Jørgen Valeur (born 1979) PhD, junior registrar and researcher at the Department of Medicine and at the Unger-Vetlesen Institute at Lovisenberg Diakonale Hospital.

The author has completed the ICMJE form and reports the following conflicts of interest: He has received consultancy fees from Shire and Almirall and heads a research project that has received financial support from Genetic Analysis.

Tore Midtvedt (born 1934) Specialist in medical microbiology and professor emeritus at the Karolinska Institute in Stockholm.

The author has completed the ICMJE form and reports no conflicts of interest.

References

1. Zhang F, Luo W, Shi Y et al. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol* 2012; 107: 1755–6, author reply 1755–6.
2. Lund-Tønnesen S, Berstad A, Schreiner A et al. *Clostridium difficile*-assosiert diaré behandlet med homolog feces. *Tidsskr Nor Lægeforen* 1998; 118: 1027–30.
3. Bjørnklekk A. Om å reparere et økosystem. *Tidsskr Nor Lægeforen* 1998; 118: 1026.
4. Waldum HL. Behandling med homolog feces. *Tidsskr Nor Lægeforen* 1998; 118: 1604–5.
5. Aavitsland P. Risikofylt behandling uten effekt? *Tidsskr Nor Lægeforen* 1998; 118: 1604–5.
6. Midtvedt K. *Clostridium difficile*-assosiert diaré behandlet med homolog feces. *Tidsskr Nor Lægeforen* 1998; 118: 1758.
7. van Nood E, Vrieze A, Nieuwdorp M et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368: 407–15.
8. Smits LP, Bouter KE, de Vos WM et al. Therapeutic potential of fecal microbiota transplantation. *Gastroenterology* 2013; 145: 946–53.
9. Vrieze A, Van Nood E, Holleman F et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology* 2012; 143: 913–6.e7.
10. Sudo N, Chida Y, Aiba Y et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* 2004; 558: 263–75.
11. Bercik P, Denou E, Collins J et al. The intestinal microbiota affect central levels of brain-derived neurotrophic factor and behavior in mice. *Gastroenterology* 2011; 141: 599–609.
12. Youngster I, Russell GH, Pindar C et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014; 312: 1772–8.
13. Holst-Jensen A, Rogne S. Lovløse tilstander i tarmen. *Dagbladet* 16.5.2014. www.dagbladet.no/2014/05/16/kultur/kronikk/meninger/bioteknologiloven/33329135/ [24.10.2014].
14. Petrof EO, Khoruts A. From stool transplants to next-generation microbiota therapeutics. *Gastroenterology* 2014; 146: 1573–82.
15. Critical views in gastroenterology & hepatology: Fecal microbiota transplantation: where is it leading? *Gastroenterol Hepatol (N Y)* 2014; 10: 307–9.