THE PATHOLOGICAL MICROBIOTA

Microbiota and enteral nutrition

Nutrition entérale et microbiote

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Summary

Enteral nutrition is a nutritional therapy that is used in up to 10% of hospitalized patients. It involves a dramatic change in the provision of nutrients to the intestine and this, along with metabolic stress and drugs used, is responsible for a marked dysbiosis. Even though there is a huge level of between-subject variability, this dysbiosis is characterized by a decrease in the dominant flora, an increase in potentially pathogenic microorganisms and a reduction in the number of individual strains. The main characteristic of these changes in the microbiota is diarrhea, which has many consequences in these patients. Saccharomyces boulardii is able to prevent enteral nutrition-associated diarrhea, probably through an increase in short-chain fatty acid production. Alongside its role in the onset and prevention of diarrhea, the microbiota may be involved in energy harvesting and changes in the nutritional status. Manipulations of the microbiota may therefore be a novel way to increase feeding efficiency in tube-fed patients.

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Résumé

La nutrition entérale est une thérapeutique nutritionnelle utilisée chez les patients hospitalisés, jusque chez 10 % d’entre eux. Elle représente un changement considérable dans l’apport des nutriments à l’intestin, ce qui, de concours avec le stress métabolique et les médicaments utilisés, est responsable d’une dysbiose marquée. Même s’il existe une large variabilité entre sujets, la dysbiose est caractérisée par une diminution de la flore intestinale dominante, une augmentation des micro-organismes potentiellement pathogènes et une réduction du nombre de souches bactériennes individuelles. La caractéristique principale de ces modifications du microbiote est une diarrhée, avec ses multiples conséquences chez ces patients. Saccharomyces boulardii est capable de prévenir la diarrhée associée à la nutrition entérale, probablement via une augmentation de la production des acides gras à chaîne courte. En parallèle à son rôle sur l’apparition et la prévention de la diarrhée, le microbiote peut être impliqué dans l’homéostasie (stoc-
**Enteral nutrition: no longer a niche**

Enteral nutrition (EN) is a nutritional treatment based on the direct provision of nutrients to the digestive tract, whether the stomach or the jejunum, through a feeding tube. It can be either total, when the patient receives nutrients only with EN, or complementary, when the patient is still able to eat as well. The 2009 reports from the nutritionDay Worldwide hospitals survey show that in Europe and Japan about 10% of hospitalized patients receive EN, complementary in one-third of them, total in the other two-thirds (Fig. 1). These figures are steadily increasing due to the fact that 1) undernutrition is increasingly recognized and treated, and 2) compared to parenteral nutrition, EN is the preferable route for feeding patients when the oral route no longer suffices [1].

**Enteral nutrition: a model for dysbiosis**

The relationship between diet and the intestinal microbiota is still a much-debated issue. While daily changes in a normal Western diet are associated with only slight modifications in the fecal microbiota [2], these modifications can be more significant when there are extreme changes in the diet, such as fasting or switching to a fiber-free elemental diet. This has been described in animals, especially in rats studied for possible bacterial translocation from the gut [3-5]. Human studies have been conducted on healthy volunteers fed with a chemically defined diet. In addition to a reduction in fecal volume, reported modifications include a decrease in the number of enterococci [6-8] and an increase in the number of enterobacteria [6, 8]. Hydrogen production in the gut is increased in cases of small intestine bacterial overgrowth. Pimentel et al. have shown that the transition from a normal to an elementary diet was able to achieve normalization of the hydrogen breath test in such patients [9]. Total artificial nutrition, especially when used exclusively, can thus be expected to induce changes in the intestinal microbiota.

Many other conditions exist that may also disrupt the normal microbiota in tube-fed patients. First, most hospitalized patients receiving EN suffer from metabolic stress. Because of the acute phase reaction, a significant reduction of the commensal flora occurs early in the disease process [10]. In experimental pancreatitis, anaerobic bacteria and lactobacilli are significantly reduced within 6 to 12 hours after induction, both in the distal small bowel and in the colon.

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**Figure 1** Sources of nutrition in 11,296 hospitalized patients: the 2009 nutritionDay Worldwide hospital survey (http://www.nutritionday.org).

EN: enteral nutrition, P/E supplements: protein-energy supplements, PN: parenteral nutrition
These changes are almost instantly followed by significant overgrowth with potentially pathogenic microorganisms such as *E. coli*; there is also a dramatic increase in mucosal barrier permeability (lumen to blood) and endothelial permeability (blood to tissue) [11], associated with increased microbial translocation and bacteremia [12]. Fasting, antibiotic treatment, colon preparation and the usual use of fiber-free EN formulas are other causes of microbiota disruptions in these patients.

**Characteristics of the intestinal microbiota in tube-fed patients**

In patients on long-term total EN, there is indeed dysbiosis featuring a major imbalance (namely a drop in the number of fecal anaerobic bacteria and an increase in the number of aerobic bacteria), with a marked reduction in the number of cultured strains [13] (Fig. 2). The modifications of the intestinal microbiota induced by a fiber-free polymeric enteral diet can be compared to those induced by broad-spectrum antibiotics such as ceftriaxone and ciprofloxacin [14, 15]. These effects may be synergistic [16] and explain why antibiotics are a risk factor for enteral nutrition-induced diarrhea [17, 18] and why enteral nutrition is a risk factor for antibiotic-induced diarrhea [19] and *Clostridium difficile* infection [20]. These results were however obtained with identification and culture techniques that are no longer considered optimal for describing the microbiota. New molecular biology techniques have since emerged and have largely replaced the old ones. In a recent study, Whelan et al. analyzed the fecal microbiota in 20 total EN-fed patients using fluorescent *in situ* hybridization. They reported the absence of within-subject changes in the concentration or proportion of any of the bacterial groups measured between the start, middle, and end of the 14 days of enteral feeding [21]. However, far from being stable, data from individual patients indicated that some had large reductions of microbiota, some had large increases and some had very stable populations. This huge variability in the microbiota may suggest the role of factors other than age or antibiotics which were not associated with measurable changes in the microbiota of this study [21].

**Consequences of dysbiosis in tube-fed patients: enteral-nutrition-associated diarrhea**

Short-chain fatty acids (SCFA), one of the most important byproducts of anaerobes in the colon, are the main fuel for the colonocyte, and they are involved in water and electrolyte absorption by the colonic mucosa. They have been shown to reverse fluid secretion in the ascending colon during enteral feeding [22], and may be the link between diarrhea and the intestinal microbiota during EN. Indeed, diarrhea is the most frequent complication of enteral tube feeding, with an incidence as high as 63% [23]. Its consequences range from discomfort to life-threatening acidosis, increased morbidity and mortality, pressure sores and withholding of EN feeding and also include higher financial costs for health providers [24]. There seems to be a particular impairment of the microbiota in those tube-fed patients who develop diarrhea: in Whelan’s study [21], there were significantly higher concentrations and proportions of clostridia and higher proportions of bacteroides in patients who developed diarrhea.

**Interventions on the intestinal microbiota in tube-fed patients**

Three randomized controlled studies have reported the efficacy of the probiotic yeast *Saccharomyces boulardii* (2 g/ day) in the prevention of diarrhea in total EN patients from intensive care units, with a 25 to 83% reduction in the number of patient-days with diarrhea [25-27]. However, these studies did not address the mechanisms of action of the probiotic. We therefore designed a prospective study to assess the effects of *Saccharomyces boulardii* on fecal SCFA and intestinal microbiota in total EN patients [28]. At the end of a six-day supplementation with the yeast, there was a significant increase in total SCFA levels and in fecal bacteria.
butyrate levels, with no changes observed in the microbiota (identification and culture). Increased SCFA concentrations might explain the reported prevention of EN-induced diarrhea by *Saccharomyces boulardii* through increased water and electrolyte absorption and a reduction in colonic pH. In another randomized controlled study, a viable mixed culture of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (1 g t.i.d.) failed to prevent diarrhea in hospital inpatients receiving EN [29]. Unlike *Saccharomyces boulardii*, orally-administered lactobacilli do not increase SCFA fecal levels [30, 31], which could be a possible explanation for these negative results.

Prebiotics can also influence the fecal microbiota and increase SCFA levels in the colon. Studies of supplementation of enteral feeds with fructooligosaccharides in healthy subjects versus controls on a low-residue enteral feed have shown increases in bifidobacteria [32]. In another study, a two-week administration of a soluble dietary fiber (galactomannans) in 20 elderly inpatients receiving EN was shown to decrease the water content of the feces and the frequency of daily bowel movements [33]. These results were associated with an increase of fecal SCFA levels, and were significant for total SCFA, acetic and propionic acids. We also showed that in patients undergoing long-term total EN, the use of a polymeric formula enriched with a mixture of six fibers increased fecal SCFA levels, especially butyrate.

**Perspectives: enhancing the efficiency of enteral nutrition**

The influence of the dominant flora on energy balance and therefore nutritional status is a new and exciting domain in the continual discovery of intestinal microbiota [34]. There are several potential mechanisms involved: first, the gut microbiota may increase the capability of an individual to harvest energy from the diet through SCFA production; second, the gut microbiota may control triacylglycerol fate through the fasting-induced adipose factor; and last, the modulation of gut microbiota may influence plasma lipoplysaccharide levels, which trigger the inflammatory tone and the metabolic consequences of inflammation [35]. While this is a hot topic for researchers involved with type 2 diabetes and obesity, it is also a promising field of research in the treatment of undernutrition.

In an animal study, rats underwent fasting for three days and were then refed for three days with either one of two isonitrogenous and isenergetic diets, one of the diets being supplemented with two bacteria: *Bifidobacterium lactis* BL and *Streptococcus thermophilus*. Compared with both the sham group and the group without probiotics, the group refed with probiotics had a 57% greater feeding efficiency (ratio of weight gained to food eaten) [36]. To our knowledge, only one such study has been performed in humans [37]. Twenty-four elderly inpatients with dementia were refed with total EN for twelve weeks. One group was randomized to receive a fermented milk containing *Lactobacillus johnsonii* La1 (10⁶ colony-forming units) and *Streptococcus thermophilus* (10⁶ colony-forming units) each day [37]. Both diets were isonitrogenous and isenergetic. At the end of the study, no differences were observed in the microbiota; in the probiotic group compared with the control group, there was a higher increase of serum albumin levels (34.3 ± 3.2 to 35.8 ± 2.5 vs. 33.9 ± 3.6 to 35.0 ± 3.2 g/L, P < 0.01) and a reduction of the percentage of days with infections. There was no change in body weight, but total EN probably did not provide enough protein and energy (900 kcal/d) to produce such an observation.

**Conclusions**

Total EN is a model of dysbiosis, with diarrhea as a major consequence. The preventive effects of *Saccharomyces boulardii* in this condition may be due to its ability to increase fecal SCFA levels. The next frontier in the manipulation of the intestinal microbiota is certainly achieving greater feeding efficiency through the use of probiotics.

**Conflicts of interests**

The author received an honorarium from Biocodex to give the lecture based on this article. The company reviewed neither the lecture nor the article. Biocodex has funded one of the studies published by the author [28].

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