

ENTERAL NUTRITION AS A TOOL FOR IMMUNOMODULATION IN CRITICALLY ILL

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My personal interest has focussed on the use of combinations of lactic acid bacteria (LAB) and plant fibres (synbiotics) as tools for immunomodulation. I have during the last fifteen years dealt with clinical studies with two synbiotic products:

Up to the year 1999: A *single strain/single-fibre synbiotic*: *Lactobacillus plantarum* 299 or 299V + oat fibre. When based on a strain called 299V it is often called PRO VIVA™. The composition was constructed after extensive studies of human lactobacillus strains.¹ It is produced and marketed by AB Probi, Lund, Sweden. The composition contains 10 g of oat fibre and 10^9 e.g. 1 billion of *lactobacillus plantarum* 299. A common dose is one or two billion LAB per day, occasionally 5 billion LAB per day has been tried.

From the year 2000: A *multi-strain/multi-fibre synbiotic*: Synbiotic 2000™. It consists in a mixture of four LAB, one from each of the four main genera of lactobacillus; 10^{10} of *Pediococcus pentosaceus* 5-33:3, 10^{10} of *Leuconostoc mesenteroides* 32-77:1, 10^{10} of *Lactobacillus paracasei* subsp *paracasei* 19 and 10^{10} of *Lactobacillus plantarum* 2362, e.g. 40 billion LAB per dose, plus a mixture of four well studied bioactive plant fibres: 2.5 g betaglucan, 2.5 g inulin, 2.5 g pectin and 2.5 g resistant starch, totally 10 g plant fibres. The composition is constructed after extensive studies of > 350 human and >180 plant strains by Lund university microbiologists Åsa Ljungh and Torkel Wadström.^{2,3} They choose the LAB to be used in the composition based on the ability of the various LAB to produce bioactive proteins, transcribe NF- κ B, produce pro- and anti-inflammatory cytokines, produce antioxidants, and to functionally complement each other. The four LAB function individually differently, but show synergistic effects when supplemented together. Synbiotic 2000 is produced and marketed by Medipharm, Kågeröd Sweden and Des Moines, Iowa, USA. Since a few months there also exists a Synbiotic 2000 FORTE and a Probiotic 2000 FORTE (no fibre added), based on 10^{11} of each of the four LAB, e.g. 400 billion LAB per dose or if supplemented twice or three times daily 800-1200 billion LAB per day and 20 to 30 g fibres.

Acute pancreatitis Microbial infection of the pancreatic tissue in patients with severe acute pancreatitis increases considerably the morbidity and mortality. Colonization of the lower gastrointestinal tract and oropharynx with Gram-negative, but sometimes also Gram-positive, bacteria precedes contamination of the pancreas. Patients with acute pancreatitis were randomized into two double-blind groups.⁴ The treatment group received a freeze-dried preparation containing live *L. plantarum* 299 in a dose of 10^9 organisms, together with 10 g oat fibre, administered by nasojejunal tube during one week. The control group received a similar preparation but the *Lactobacillus* was inactivated by heating. A total of 45 patients completed the study; twenty-two patients treated with live and 23 with heat-killed *L. plantarum* 299. Infected pancreatic necrosis and abscesses occurred in one of 22 patients (4.5 %) in the treatment group, compared with seven of 23 in the control group (30 %, $P = 0.02$). The only patient in the live LAB group, who developed infection, had signs of urinary infection on the 15th day e.g. at a time when he had not received symbiotic treatment during the last eight days. Positive growth was observed in pancreatic tissue in 1 vs 7, in pancreatic necroses 1 vs 4, and in blood cultures in 1 vs 3. Re-operations were performed on 1 vs 7. No significant differences in numbers of chest infections, SIRS, MOFs or mortality were observed. The length of stay was considerably shorter in the live LAB group (13.7 days vs. 21.4 days), but the limited size of the material did not allow statistical significance to be reached. In a yet unpublished study in 62 patients the multi-strain synbiotic (Synbiotic 2000) was supplemented in a much larger dose of LAB (2x40 billion per day), and double dose of fibres (20 g) per day. A significant reduction ($p < 0.05$) was observed in combined SIRS+MOF, as 8/33 treated (24 %) developed the syndromes compared to 14/29 (48%) control patients (Olah A, personal communication).”

Abdominal surgery Early enteral nutrition with probiotics and fiber has in experimental studies proven effective to prevent bacterial translocation and subsequent infection. In a prospective randomized trial in 172 patients undergoing major abdominal surgery or liver transplantation, the incidence of bacterial infections was compared in patients receiving either conventional parenteral or enteral nutrition, enteral nutrition with *lactobacillus plantarum* 299 and fiber or enteral nutrition with heat-inactivated lactobacilli and fibre (control).⁵ Routine laboratory parameters, nutritional parameters and the cellular immune status

were measured preoperatively and on postoperative days 1, 5 and 10. The incidence of bacterial infections after liver, gastric or pancreas resection was 31 % in the conventionally treated group compared to only 4 % in the synbiotic-treated group b) and 13 % in the control group. Cholangitis and pneumonia were the most frequent infections and *enterococci* the most frequently isolated bacteria. The beneficial effects of synbiotic treatment seemed to be most pronounced the largest operations (gastric and pancreatic resections) with a sepsis rate of 7% with live LAB, 17 % with heat-inactivated LAB and 50 % with standard enteral nutrition. The live LAB-treated patients received significantly less antibiotics ($p=0.04$); the mean length of antibiotic treatment was 4 ± 3.7 days with live LAB, 7 ± 5.2 days with heat-killed LAB and 8 ± 6.5 days with only standard enteral nutrition. The incidence of non-infectious complications were: enteral nutrition 30 % (9/30), heat-inactivated LAB 17 % (5/30) and live LAB 13 % (4/30). A recent not yet published study in abdominal cancer surgery patients reports postoperative infections in 6.7 % with Synbiotic 2000, 20 % with only the fibres in the composition and 47 % in the control group receiving standard enteral nutrition (Han Chun Mao et al, personal communication). Significant improvements in prealbumin, C-reactive protein, serum cholesterol, serum endotoxin, white cell blood count are also reported

Liver transplantation. Liver transplant patients are extremely susceptible to infections and infection rates of 50 to 85% have recently been reported. It is generally agreed that microbial overgrowth in the intestine is a major source of infection, but efforts to reduce the infection rate by aggressive antibiotic policies have generally failed. In a prospective, randomized placebo-controlled trial consisting of 95 patients, the incidence of postoperative infections and other complications after liver transplantation was studied in three groups of patients, all supplied with early enteral nutrition with a standard formula: selective digestive tract decontamination (SDD), live *Lactobacillus plantarum* 299 and fibre (LLP), and heat-killed *Lactobacillus plantarum* 299 and fiber (HLP).⁶ The patients who received living lactobacilli plus fibre developed significantly fewer bacterial infections (13%) than the patients with SDD (48%). The incidence of infections in the group with inactivated lactobacilli and fibre (HLP) was 34 %. The most dominating infections were cholangitis, occurring in SDD 10, HLP 8 and LLP 2 patients respectively, and pneumonia, in SDD 6, in HLP 4 and LLP 1 patient respectively. The most often isolated microbes were *Enterococci*: SDD 8, HLP 8 and LLP 1 patients, and *Staphylococci*: SDD 6, HLP 3, and LLP 1 patient respectively. No *E. coli* or *Klebsiella* infections were seen in the LLP group. The numbers of patients requiring hemodialysis were SDD 8, HLP 4 and LLP 2 and the number of reoperations SDD 6 HLP 2 and LLP 4 respectively. The same investigators did continue their efforts and try to further reduce the morbidity in connection with liver transplantation using the combination of four LAB and four fibres in a 40 times larger dose of LAB. A prospective randomised double-blind trial was undertaken in 66 liver transplantation patients, 33 patients were supplied Synbiotic 2000™ and 33 patients received the four fibres only.⁷ All patients received enteral nutrition beginning immediately after the operation. The incidence of postoperative bacterial infections was significantly reduced; being 48% with only fibres and 3% with live LAB and fibres. No statistically significant difference was observed in length of hospital stay, but the duration of antibiotic therapy was significantly shorter in the group receiving live lactic acid bacteria (LAB) and fibres.

Critically ill. ITU patients suffer a 5-10 fold increased risk of contracting infection when compared to patients elsewhere in the hospital. A smaller study compared treatment with live *Lactobacillus plantarum* 299 plus oat fibre with heat-killed *Lactobacillus plantarum* 299 and oat fibre as control.⁸ There were 19 patients in each group and mortality was 26% in the active synbiotic group versus 42% in the controls. The investigator regarded the material to be too small to allow statistical significance, but the same unit is currently undertaking a large scale trial in a clinical material in excess of 300 patients (Gomersall Ch. pers.communication)

A recent, not yet published, study in trauma patients reports dramatic decrease in number of both total infections and chest infections with supply of Synbiotic 2000™ in comparison to Only fibre, peptide or glutamine respectively (Kompan L, personal communication. Of these treatments did only glutamine and Synbiotic 2000 down-regulate Il-6 but none Il-8 and TNF α . The total number of infections were with Synbiotic 2000™; 2/14 patients - 14 %, with Only fibre; 16/28 patients - 57 %, with Peptide; 11/21 patients - 52 %, and with glutamine; 19/37 patients - 51 %). Similarly the numbers of chest infections

were with Synbiotic 2000™; 1/14 patients - 7 %, with Only fibre; 11/28 patients - 39 %, with Peptide; 10/21 patients - 48 %, and with glutamine: 12/37 patients - 32 %).

Not all synbiotics are effective; A standard commercial product (TREVIS® , Ch Hansen, Denmark) containing *Lactobacillus acidophilus* LA5, *Bifidobacterium lactis* BP12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* was mixed with 7.5 g oligofructose and supplied in to 45 critically ill patients⁹ and 45 controls, and to 72 elective abdominal surgery patients and 65 controls.¹⁰ No clinical benefits were reported from any of the studies. The study in ICU patients reported significant reductions in number of potentially pathogenic organisms (PPMs) in the stomach of the treated patients, but no influence on intestinal permeability or clinical benefits.. The peri-operative study reported no differences in bacterial translocation, gastric colonization, or systemic inflammation, or septic complications. See also my commentary to the ICU study.¹¹

Not all lactic acid bacteria ferment semi-resistant fibres. Only a small minority of LAB can ferment semi-resistant prebiotics such as oligofructans: inulin and phleins. When the ability of 712 different LAB to ferment oligofructans was studied only 16/712 were able to ferment the phleins and as little as 8/712 the inulin type fibre. Only four LAB species fermented these fibres: *Lactobacillus plantarum* (several strains), *Lactobacillus paracasei* subsp. *paracasei*, *Lactobacillus brevis* and *Pediococcus pentosaceus*.¹²

Not all lactic acid bacteria control infections. The ability to control various pathogens is strain-specific and often limited to a few strains. When the ability of fifty different LAB to control 23 different pathogenic *Clostridium difficile* strains was tested, only 5 proved effective against all, 8 were antagonistic to some, but 27 were totally ineffective.¹³ The five most effective strains were *Lb paracasei* subsp. *paracasei* (2 strains) and *Lb plantarum* (3 strains). Clearly information like this is important for choice of probiotics for clinical use.

Not all lactic acid bacteria enhances the innate immune system and increase resistance to disease . It is often suggested that yoghurt consumption enhances the immune functions, a statement that is generally unproven. Although in vitro studies with yoghurt suggest such an effect, it is clearly not substantiated in vivo.¹⁴ The observed differences might be explained by a recent observation that consumption of milk counteracts attachment of LAB to mucosal surfaces.¹⁵

Not all lactic acid bacteria survive the passage through the GI tract. The survival and ability to induce cytokine production after passage through the stomach and small intestine of four different LAB species: *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus* and *Bifidobacter animalis* was studied.¹⁶ From an originally administered 10^8 cells ml remained after the passage in the intestinal content between 10^7 (*Lactobacillus plantarum*) and 10^2 (*Lactobacillus rhamnosus*) bacterial cells. Most of the strains showed, at this level, a significantly reduced and weak (especially *Lactobacillus rhamnosus*) ability to induce cytokines such as TNF- α and IL-6. Interestingly, *Lactobacillus plantarum*, in sharp contrast to the other LAB tested, demonstrated after the passage through the stomach and small intestine an despite reduction in numbers increased capacity to induce IL-6.

New tube-feeding tools: Most experience support that enteral nutrition, when the patient cannot eat, is provided via nasojejunal tube. I have developed for the purpose a special auto-positioning, regurgitation-resistant tube with ability to absorb GI motility for placement where intended, and this without assistance of radiology or endoscopy (Bengmark Flo-Care tube, Royal Numico-Nutricia group, Amsterdam, The Netherlands). When used in a study consisting in 56 patients with cerebrovascular lesions, 22 with acute pancreatitis and another 15 critically ill patients did 92.5% of the tubes pass pylorus, and 89% reach the first jejunal loop. The tip of the tube reached its final position within a mean period of 5.2 hours, 8% instantly and all within 24 hours.¹⁷ A recent study obtained successful placement in patients with normal gastric emptying within 24 hrs in 78% compared to 14% with a standard straight tubes ($P=0.04$), and in patients with impaired gastric emptying (as most SAP patients) a successful within 24 hour placement in 57% compared to 0% with standard tubes ($P=0.07$).¹⁸ Another recent study reports successful insertion in 12/16 (75 %) acute pancreatitis patients with the tube reaching the Treitz ligament with a median of 12 hours.¹⁹

References:

1. Johansson ML, Molin G, Jeppsson B et al. Administration of different lactobacillus strains in fermented oatmeal soup: in vivo colonization of human intestinal mucosa and effect on the indigenous flora. *Applied Environmental Microbiology* 1993;59:15-20
2. Kruszevska K, Lan J, Lorca G et al.. Selection of lactic acid bacteria as probiotic strains by in vitro tests. *Microecology and Therapy* 2002; 29: 37-51. The proceedings of the XVI International Congress on Microbial Ecology and Disease held Noordwijkerhout, The Netherlands., Oct 2001
3. Ljungh Å, Lan J-G, Yamagisawa N. Isolation, selection and characteristics of *Lactobacillus paracasei* ssp *paracasei* isolate F19. *Microbial Ecology in Health and Disease* 2002; Suppl 3:4-6
4. Oláh A, Belágyi T, Issekutz Á, Gamal ME, Bengmark S. Early Enteral Nutrition with Specific Lactobacillus and Fibre reduces Sepsis in Severe Acute Pancreatitis. *Br. J. Surg* 2002;89:1103-1107
5. Rayes N, Hansen S, Boucsein K, et al. Early enteral supply of fibre and lactobacilli vs parenteral nutrition - a controlled trial in major abdominal surgery patients. *Nutrition* 2002;18:609-615
6. Rayes N, Hansen S, Seehofer D et al. Early enteral supply of Lactobacillus and fibre vs selective bowel decontamination (SBD) - a controlled trial in liver transplant recipients. *Transplantation* 2002;74:123-127
7. Rayes N, Seehofer D, Theruvath T. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation - a randomised, double-blind trial. *Am J Transplant* 2005;5:125-130.
8. Gomersall CM. Does the administration of lactobacillus to critically ill patients decrease the severity of multi-organ dysfunction and failure? A pilot study. Roehampton Institute, School of Life Sciences. London 1998
9. Jain PK, McNaught CE, Anderson ADG, MacFie J, Mitchell CJ. Influence of synbiotic containing *Lactobacillus acidophilus* LA5, *Bifidobacterium lactis* BP12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose on gut barrier function and sepsis in critically ill patients: a randomized controlled trial. *Clinical Nutrition* 2004;23:467-475.
10. Woodcock NP, McNaught CE, Morgan DR, Gregg KL, MacFie J. An investigation into the effect of a probiotic on gut immune function in surgical patients. *Clin Nutr.* 2004;23:1069-1073.
11. Bengmark S Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients. *Clinical Nutrition.* 2004;23:441-445.
12. Müller M, Lier D. Fermentation of fructans by epiphytic lactic acid bacteria. *J Appl Bact* 1994;76:406-411.
13. Naaber P Smidt I, Stsepetova J, Brilene T, Annuk H, Mikelsaar M. Inhibition of *Clostridium difficile* strains by intestinal Lactobacillus species. et al. *Med Microbiol* 2004;53:551-554.
14. Campbell CG, Chew BP et al. Yogurt consumption does not enhance immune functions in healthy premenopausal woman- *Nutrition and Cancer* 2000;37:27-35
15. Kankanpää PE, Salminen SJ, Isolauri E, Lee YK. The influence of polyunsaturated fatty acids on probiotic growth and adhesion. *FEMS Microbiology Letters* 2001;194:149-153
16. Miettinen M, Alander M, von Wright A et al. The survival of and cytokine induction by lactic acid bacteria after passage through a gastrointestinal model. *Microbial Ecology in Health and Disease* 1998;10:141-147.
17. Mangiante G, Marini P, Fratucello GB et al. The Bengmark tube in surgical practice and in the critically ill patient. *Chir Ital* 2000;52:573-578. In Italian
18. Lai CWY, Barlow R, Barnes M, Hawthorne AB Bedside placement of nasojejunal tubes: a randomized-controlled trial pf spirale- vs straight-ended tubes tubes. *Clin Nutrion.* 2003;22:267-270.
19. Karsenti D, Viguier J, Bourlier P et al. Enteral nutrition during acute pancreatitis. Feasibility study of a self-propelling spirale distal end jejunal tube. *Gastroenterol Clin Biol* 2003;27:614-617.