



# NUTRITION RESOURCE LINE

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### Strategies to Improve and Maintain Intestinal Flora Balance: The Role of Prebiotics and Probiotics

**Las Vegas** – Research into prebiotics and probiotics on human health continues and emerging evidence appears promising. Both are able to provide optimal balance in the vast ecology of intestinal microbes and both have been associated with significant clinical benefit in a variety of therapeutic areas. Among their many proven effects is an ability to reduce antibiotic-associated diarrhea, including diarrhea caused by *Clostridium difficile*, alleviation of pouchitis and symptoms of ulcerative colitis, enhancement of immune function, improvement of the body's ability to absorb calcium, and normalization of bowel function. With new advances in the field anticipated, clinicians have a potential tool by which to improve human health and alleviate significant discomfort.

“Typically, we think of a malnourished patient as someone who is thin and you would think that that would be an obvious diagnosis,” noted Annalynn Skipper, PhD, Annalynn Skipper and Associates, Oak Park, Illinois, in an interview. As she explained, there are situations in hospital in particular where patients can be obese—for example, they still weigh 200 lbs. and are only 5 ft. tall. “But if they weighed 300 lbs. six months ago, they are malnourished,” she said.

Inflammation can also complicate matters, she noted. Patients come to the hospital with an infection, or they develop inflammation in response to an injury. “We can feed these patients all we want but indicators of malnutrition won't change in response to the feeding,” she stated.

Traditional indicators of nutrition are also not reliable when making the diagnosis of malnutrition, she added. When health care professionals first started to diagnose malnutrition in the late 1970s, they would test patients for albumin and prealbumin levels. Both albumin and prealbumin levels are indicators of visceral protein status and illnesses commonly associated with protein-calorie malnutrition including cancer, chronic illnesses, liver disease, pancreatitis and burns to over 30% of the body. In reviewing the literature, however, Dr. Skipper found that there was no correlation between serum albumin levels and weight loss in patients with anorexia nervosa. Nor did she find any correlation between serum albumin and weight loss in non-

malabsorptive gastric partitioning bariatric surgery or with intentional weight loss from calorie-restricted diets. “In the four models of prolonged protein-energy restriction, there was no correlation between serum albumin and weight loss either,” Dr. Skipper observed.

Similarly, regarding studies of serum prealbumin, Dr. Skipper was again unable to identify any correlations between serum prealbumin and weight loss in anorexia, intentional weight loss or weight loss in starvation.

#### Nutrition Screening Tools

In order to test the reliability and validity of currently available nutrition screening tools, Dr. Skipper and colleagues in the Nutrition Screening Workgroup compared currently available nutrition screening tools for their sensitivity and specificity in helping identify patients with malnutrition (Table 1). “We decided that the most important criteria were weight change over time—that is, patient's weight declining over time—as well as nutrient intake,” she observed.

These criteria help distinguish between malnutrition related to a disease and malnutrition related to not having enough nutrients. It is important to make these distinctions, as Dr. Skipper noted; if malnutrition is related to a disease, “patients will not get better no matter how much you feed them

<b>Tool</b>	<b>Grade</b>	<b>Reference standard</b>	<b>Patients (N)</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Reliability</b>
MNA-SF	II	MNA	408	100%	70%	
MNA-SF		MNA	904	98%	100%	
MUST	II	SGA	50			
MUST		SGA	995	61%	76%	
Simple Two-Part Tool	II	SGA	2211	63%	97%	
MST	II	SGA	408	93%	93%	k=0.84-0.93
MST		SGA	2211	74%	76%	
MST		SGA	106	100%	81%	
MST		PG-SGA	50	100%	92%	k=0.83-0.88
NRS-2002	I	SGA	995	62%	93%	
NRS-2002		MNA	80	39%	83%	
NRS-2002		SGA	120	70%	85%	

NRS=Nutritional Risk Screening; MST=Malnutrition Screening Tool; MUST=Malnutrition Universal Screening Tool MNA-SF=Mini Nutritional Assessment-Short Form; NRS=Nutritional Risk Score SGA=Subjective Global Assessment.

until you control the disease.” The distinction also has to be made between patients who are still eating and yet not doing well vs. patients who are not doing well because they are not eating.

“It depends on the status of the patients as to whether they are candidates for an oral nutritional supplement (ONS) or not,” Dr. Skipper told delegates. Candidates for an ONS such as Ensure are those who need to recover lost weight and maintain a healthy body weight through an improvement in their overall nutritional status. Cancer patients who are experiencing chemotherapy-induced nausea may also benefit from ONS.

## **The Role of Prebiotics**

As discussed by Gail Cresci, PhD, Director, Surgical Nutrition Service, Medical College of Georgia, Augusta, the intestinal tract plays host to a vast ecology of microbes, some of which confer healthful benefits and others harm. “Bacteria will survive no matter what the host feeds them, but they survive not necessarily in a manner that is beneficial to the host,” Dr. Cresci noted in an interview.

For example, studies in obese animals indicate that they have a different blend of gastrointestinal flora than lean animals. “These studies have been done in mice,” she added, “but when researchers switched their diet to a low-fat, low-carbohydrate, high-fibre diet, not only did obese animals lose weight but their bacteria blend went back to what the same blend as lean animals have.”

Both prebiotics and probiotics beneficially influence the gut flora in specific ways. “Prebiotics” as defined by Dr. Cresci are non-digestible food ingredients that beneficially affect

host health by selectively stimulating the growth and activity of a limited number of bacterial species in the colon, usually bifidobacteria and lactobacilli.

One example of a prebiotic is fructo oligosaccharides (FOS). FOS occur naturally in plants such as onion, garlic, asparagus, banana and artichoke but in supplemental forms, Ensure Prebiotics contains 3 g of NutraFlora sc FOS prebiotics per 235-mL bottle. The major fermentation products of prebiotic metabolism in the large bowel are short-chain fatty acids (SCFAs), which have varying effects on colon morphology and function. FOS also selectively stimulates the proliferation of bifidobacteria in the colon, while dietary fibre provides a substrate for fermentation and SCFA production. “A prebiotic is the food source for the probiotic,” Dr. Cresci confirmed, stimulating the growth of probiotic strains.

Some prebiotics have also shown activity against pathogens, and can block their adhesion to specific receptors of mucosal cells, thereby inhibiting the first step of the pathogen colonization process. In addition, up to 80% of the body’s immune system cells are located in the gut, the preferred food source which comes from fermentation of prebiotics by beneficial bacteria. Prebiotics therefore support the immune system by maintaining a balanced gut flora.

Fermentation of prebiotics also creates an acidic environment which is required to help free calcium molecules from dietary complexes such as the phytates: thus, ingestion of either natural or supplemental prebiotics helps individuals absorb dietary calcium, which is necessary to maintain bone mineral density.

This effect was supported by a study carried out by Japanese investigators who found that a drink containing FOS at a

**Table 2. Guidelines for Probiotic Use**

Clinical condition	Clinical effectiveness*	Organism**
Adult and childhood diarrhea		<i>Lactobacillus reuteri</i>
Prevention	B	<i>Lactobacillus GG, L. casei, L. acidophilus, S. boulardii</i>
Treatment	A	Bifidobacteria
Antibiotic-associated diarrhea	A	<i>S. boulardii, Lactobacillus GG</i>
Radiation	C	VSL no. 3
Vaginosis	C	<i>L. acidophilus</i>
Helicobacter pylori	C	<i>L. johnsonii</i>
Ulcerative colitis	C	Escherichia coli, Bifidobacteria and Lactobacillus, VSL no. 3
Crohn's disease	C	<i>E. coli, S. boulardii, Lactobacillus GG</i> (variable)
Pouchitis	A	VSL no. 3
Irritable bowel syndrome	C	<i>L. plantarum, VSL no. 3, Bifidobacterium infantis</i>
Prevention of cardiovascular disease	C	Lactobacillus in milk and yogurt
To improve immune response	B	<i>L. acidophilus, L. plantarum, B. lactis, Lactobacillus GG, L. johnsonii</i>

\*A=indicates strong evidence; B=suggestive evidence; C=inadequate studies to be certain  
 \*\*Exact dosage used is in appropriate reference  
 VSL no. 3 indicates *L. casei, L. plantarum, L. acidophilus, L. delbreueckii, B. longum, B. breve, B. infantis* and *Streptococcus salivarius*.

Adapted from Koch et al. *J Clin Gastroenterol* 2006;40:275-8.

dose of 3 g/100 mL improved calcium bioavailability with no side effects. For the study, investigators had healthy university students drink both a FOS-containing malt followed by a control drink with no FOS. Six to 12 hours after drinking the FOS malt, they found that the cumulative amount of total urinary calcium was significantly greater than total urinary calcium levels after the control drink. The FOS-containing drink was subsequently given to subjects between the ages of 2 and 40 years for 13 weeks and was well tolerated by all subjects.

### Therapeutic Benefit

Consumed in adequate numbers, SCFAs, prebiotics and probiotics can confer health benefits and have shown to be of therapeutic benefit in a variety of clinical settings. As cited by Patz et al. (*Am J Gastroenterol* 1996;91(4):731-4), five out of 10 patients with distal ulcerative colitis who had failed to respond to either rectal or oral 5-aminosalicylic acid and corticosteroids had decreased bleeding, tenesmus and endoscopic improvement when treated with SCFA enemas twice a day for six weeks.

A number of other studies in ulcerative colitis similarly demonstrated that overall, the majority of small groups of patients treated with some form of SCFA enema improved both clinically and endoscopically after two to six weeks of therapy.

Regarding prebiotics, Whelan et al. randomly assigned subjects to a formula containing FOS and fibre as their sole nutrition source for 14 days after which they were assigned to a standard enteral formula after a six-week washout phase (*J Nutr* 2005;135:1896-902). During both formula phases,

investigators noted significant reductions in total fecal bacteria. However, concentrations of total fecal bacteria were significantly higher when subjects were fed the FOS/fibre formula compared with the standard formula. Researchers also noted that the FOS/fibre formula significantly increased bifidobacteria and significantly reduced clostridia compared with the standard formula. Compared with the standard formula, the FOS/fibre formula also resulted in higher concentrations of SCFAs.

As the authors observed, these alterations may diminish colonization resistance and reduce water absorption in the colonic lumen, both of which are involved in the pathogenesis of diarrhea in patients requiring enteral tube feeding and which may be partially prevented by fortification of an enteral preparation with FOS and fibre. In addition, sc FOS fermentation produces SCFAs, which actually increase water absorption in the colon, which in turn decrease the volume of water inside the colon.

It is important to note that both fibre and prebiotics are usually non-digestible and both are fermented by gut bacteria. However, only a small number of beneficial bacteria optimally should ferment a prebiotic, which is not the case with fibre. Added to both food products and infant formulas, investigators have shown that prebiotics stimulate the growth of non-pathogenic intestinal microflora and, at a dose of between 4 and 15 g/day, reduce constipation (*J Physiol Biochem* 2009.65(3):315-28).

Other investigators (*Nahrung* 1987;31:427-36) found that fecal microflora improved in 23 subjects fed a FOS-containing drink at a dose of 8 g/day for two weeks. Specifically, the population of bifidobacteria in feces increased by approximately

10 times compared to pre-test levels while the average pH was 0.3 lower than pre-study levels. These findings indicate that ONS containing FOS may induce an intestinal environment that is hostile to pathogenic microflora.

It has subsequently been shown that the best dose of sc FOS to increase fecal bifidobacteria is 10 g/day.

## Probiotics and Intestinal Microflora

Probiotics are microorganisms that favourably affect intestinal microflora as well, among them *Lactobacillus* and *Bifidobacterium*. “A lot of pathogenic bacteria adhere to intestinal epithelial cells where they may either invade the cell or secrete toxins into the cell,” Dr. Cresci explained, “and it is thought that probiotics limit the number of pathogenic bacteria that can adhere to the epithelium through competitive inhibition.” Probiotics may also secrete antimicrobial proteins into the intestinal lumen and alter the luminal pH which makes the lumen a less favourable host for pathogenic bacteria.

In a number of clinical trial settings, probiotics have been proven therapeutically beneficial. As many investigators have observed, antibiotics alter the microbial balance within the gastrointestinal tract, subsequently leading to antibiotic-associated diarrhea (AAD). Johnston et al. (*Evidence-based Child Health—A Cochrane Review Journal*. 2008;392:280-315), for example, found that based on their per-protocol analysis, nine out of 10 studies assessing a variety of probiotics showed the incidence of AAD was reduced by at least 50% in pediatric recipients who were given concomitant probiotics along with the antibiotic compared with controls. Based on this review, the most promising evidence was for probiotic strains of *Lactobacillus GG*, *L. sporogenes* and *Saccharomyces boulardii* at 5 to 40 billion colony-forming units per day.

In a randomized, double-blind, placebo-controlled trial, Hickson et al. (*BMJ* 2007;335(7610):80-3) reported that only 12% of elderly patients who consumed a drink containing *L. casei*, *L. bulgaricus* and *Streptococcus thermophilus* during one week after their antibiotic course developed AAD compared with 34% of placebo controls. In the same study, none of the

patients in the probiotic group developed diarrhea caused by *C. difficile* compared with 17% of placebo patients. The authors suggested that consumption of a probiotic drink containing *L. casei*, *L. bulgaricus* and *S. thermophilus* had the potential to decrease morbidity, health care costs and mortality if routinely used in patients over the age of 50 who were being treated with antibiotics.

Manley et al. in turn (*MJA* 2007;186(9):454-7) randomly treated 27 renal patients colonized with vancomycin-resistant enterococci (VRE) with either yogurt containing *L. rhamnosus GG* (LGG) or standard yogurt for four weeks. Patients on the standard yogurt drink who failed to clear VRE after four weeks were switched to the LGG-containing yogurt at the four-week time point, and remained on it for an additional four weeks.

All patients in the LGG treatment group who completed the study cleared VRE, as the authors reported. In contrast, only one patient out of 12 who received the standard yogurt drink cleared VRE at study end point and all eight patients who crossed over to the LGG-containing drink at four weeks had cleared VRE by study end point.

## Disease State

As Dr. Cresci discussed, clinicians must first identify the disease state where prebiotics and probiotics have been shown to be therapeutically beneficial. They must also be aware that different strains of the same genus or species are not necessarily the same and they need to know exactly what strain was used in which clinical setting and in which patient population before recommending treatment for their own patients. Patients should also realize that they may need to consume the same product following acute treatment for continued benefits, albeit at decreased frequency, perhaps three to four times per week.

There is a growing interest in the field of prebiotics and probiotics and what is not yet known is likely to be explored in the coming years. Armed with new information, clinicians may soon be able to recommend a host of strategies that will improve and maintain a balanced gut flora and preserve health in a wide range of patients. □

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