



# TECHNICAL BULLETIN

## REMOVE, REPLACE, REINOCULATE, REPAIR: THE 4R™ GASTROINTESTINAL SUPPORT PROGRAM

The goal of a 4R gastrointestinal therapeutic program is to support the improvement or normalization of the various GI functions through appropriate evaluation, indicated therapy, and nutritional, digestive enzyme, pre- and probiotics support. While the overall concept defines a basic approach, its use is individualized to the needs of each person based on his or her own unique combination of functional and dysfunctional GI factors. The precision with which a 4R program can be tailored is related to the extent to which an individual's functional profile can be defined. We will consider the evaluation of each of these areas of function as we discuss each of the four "Rs" individually.

### REMOVE

Remove refers to the elimination of any pathogenic microflora and/or parasites that may be present. Pathogens may be identified with standardized stool evaluation techniques. Culture and parasitic stool analysis provide information on the pathogens that are present, as well as the relative proportions of these pathogens compared to "normal" microflora. A list of therapeutic agents to which the pathogenic organisms are sensitive and resistant may also be provided. (While the "stool for culture, ova, and parasites" is common, a more comprehensive assessment, such as the CDSA, provides valuable additional information of the functional gastrointestinal milieu.)

If a pathogen is present and is causing inflammation or other pathological processes within the gastrointestinal tract, simply adding probiotics, nutrients, or digestive enzymes will not usually be enough to counterbalance and support the immune or other GI defensive mechanisms in

eliminating the pathogen. Pathogens and parasites must first be eliminated, then efforts to support GI mucosal repair and restoration of normal function are more likely to be successful.

In addition, Remove also stands for the removal of foods from the diet to which an individual is allergic, sensitive, or otherwise intolerant. Ultimately, each individual may have a somewhat different set of foods that must be avoided. Distinguishing this list of foods is likely to involve some trial removal and rechallenges over time. Therefore, oligoantigenic diets provide a basis from which to individualize specific therapeutic diet plans.

An oligoantigenic diet is one that contains only foods to which there is a very low overall prevalence or likelihood of allergic or antigenic reactivity for a given population. The most common food groups possessing allergenic activity are dairy and gluten-containing grain and cereal foods. For this reason, rice (a non-gluten-containing grain) that has been enriched or fortified with additional amounts of its two most limiting amino acids (L-lysine and L-threonine) is often used as a basic protein source around which an oligoantigenic diet is constructed. Other protein-containing foods may also be used as the basis of an oligoantigenic diet. The choice is ultimately made based on the unique allergenic profile of the individual. Examples of protein that may be considered for use in some individuals include soy, hydrolyzed lactalbumin, or whey protein isolates.

Milk immunoglobulin concentrates may also be helpful in cases of dysbiosis and other conditions of undesirable microbe overgrowth within the GI tract. These are concentrates of SIgA (secretory IgA) derived from the whey portion of cow's milk. These concentrates function by combining with antigens (antigenic protein or other molecular sequences). By this attachment, the ability of pathogenic microorganisms or food antigens to be absorbed or to adhere to the GI mucosal surfaces is diminished. It should be noted that some dairy-sensitive individuals may not be able to tolerate this product.

## REPLACE

Replace refers to the replacement of digestive factors and/or enzymes whose intrinsic, functional secretion may be limited or inadequate. Substances in this category facilitate the breakdown of

foods to the basic molecular composition units and/or their preparation for absorption. This process of digestion or molecular disassembly also eliminates antigenic properties that are innate to larger, more complex substances, particularly protein/polypeptides and more complex polysaccharides. These factors, excluding regulatory GI hormones, include:

1. Hydrochloric acid (HCl)
2. Intrinsic factor
3. Gastric lipase (tributyrase), amylase, gelatinase, pepsinogen/pepsin
4. Pancreatic enzymes: trypsin, chymotrypsin, carboxypolypeptidases, ribonuclease and deoxyribonuclease, amylase, lipase, cholesterol esterase, proelastase/elastase, and phospholipase
5. Bile (fat emulsification)
6. Intestinal enzymes: dipeptidases and amino-peptidases, disaccharidases (e.g., lactase)

An individual may have one or any combination of such insufficiencies or deficits. The presence, sufficiency, or lack of each of these factors can be determined by taking a symptom history and, if possible, using selected laboratory testing techniques. More common symptoms of enzyme insufficiency can include a prolonged feeling of fullness following meals, dyspepsia or indigestion, abdominal bloating and gas, belching, undigested food particles in the stools, and loose or diarrheal stools. Once determined, replacement therapy is individualized according to assessment and therapeutic response results. Replacement products include:

1. HCl salts with or without intrinsic factor
2. Plant-derived digestive enzymes (proteases, amylases, lipases, cellulases)
3. Animal-derived enzymes (proteases, amylases, lipases, elastases)
4. Microbe-derived digestive enzymes
5. Lactase enzyme supplements
6. Bile salts

From a slightly different perspective, fiber (soluble and/or insoluble) may also be considered a replacement product. If an individual's overall diet does not provide adequate fiber to support

optimal elimination or provide the raw material from which desirable or “friendly” intestinal microflora manufacture the beneficial short-chain fatty acids (e.g., acetate, propionate, and butyrate), then replacement of fiber may also be a therapeutically valuable factor. Furthermore, if the removal of antigens is an issue for an individual, then use of an oligoantigenic fiber source may be necessary to meet an individual’s Remove and Replace requirements.

## REINOCULATE

Reinoculate refers to the reintroduction of desirable GI microflora, also called “friendly bacteria” or “probiotics,” to obtain a more desirable balance of microflora. The two commonly used and well-researched genera of microflora are:

1. Lactobacillus (acidophilus is the most common species, but also bulgaricus and thermophilus species)
2. Bifidobacteria (bifidus is the most common species, but also longum, infantis, breve species, etc.)

Both of these genera of microflora predominate in young, healthy individuals and are known to proportionately decrease with advancing age and in conditions of dysbiosis following courses of some antibiotics. Other causes of dysbiosis include decreased immune status, maldigestion, decreased gut motility, intestinal infection, presence of xenobiotics, and increased intestinal pH.

These bacteria produce numerous factors that aid in the maintenance of normal microflora populations and the production of short-chain fatty acids, which have been shown to have beneficial/protective effects on the colonic mucosa.

The need to rebalance or reinoculate may be established on the basis of symptoms or with the help of a microbial stool sample. Once the need for reinoculation has been determined, the choice of probiotics should be guided by quality control product standards that maintain consistency of adequate numbers of viable organisms.

Viable species of *Lactobacillus* and *Bifidobacteria* are available as oral supplements in the form of powders, tablets, and capsules. Because these are live culture products, attention to conditions of shipping and/or storage are important in maintaining their viability. They should be constantly kept at cool temperatures, and product lifetime dates should be considered. *Lactobacillus* and *Bifidobacteria* are also available in some cultured yogurt and other milk products.

The addition of fructooligosaccharides (FOS) or inulin to the diet has been shown to selectively support the growth and sustain the presence of these desirable microflora, especially *Bifidobacteria*.

## REPAIR

Repair refers to providing nutritional support for regeneration or healing of the gastrointestinal mucosa. The GI mucosal cells represent the largest mass of rapidly proliferating cells in the bodies of normal individuals. Repair is indicated whenever there has been a loss of integrity of the GI mucosal structure and/or function. This loss may be the result of chronic nutritional insufficiency, food allergen and xenobiotic exposure, dysbiosis, pathological intestinal infection, inflammatory bowel disease, or other less common GI diseases. Assessment of individual need may include a dietary history, nutritional analysis, and any other investigative techniques that reveal the presence of dysfunction, disease, or nutritional insufficiencies. The Lactulose/Mannitol Permeability Test may also be useful in this regard. This test assesses the functional capacities of absorption of larger and smaller molecules, and therefore the functional status or integrity of the GI mucosa.

Direct nutritional support in Repair of the intestinal mucosa involves the use of supplements containing nutrients known to be critical in intestinal wall structure and function. Included in this group of nutrients are many of the antioxidants, including vitamins C, E, and A/beta-carotene, the minerals zinc and manganese, the amino acids cysteine, N-acetylcysteine, glutamine, the tripeptide glutathione, and the carbohydrates inulin and/or FOS. Supplementation of other nutrients closely involved with collagen formation, including the vitamin pantothenic acid, is also practiced. Pre- and post-testing using lactulose/mannitol is typically conducted to evaluate and monitor the repair process.

When considered together, the four steps of the 4R™ gastrointestinal support program appropriately address, from a clinical standpoint, underlying dysfunction. In evaluating any individual's health and nutritional status, each of the above factors can contribute to increasing and self-generating pathophysiology.

## REFERENCES:

1. Schneeman B. Nutrition and gastrointestinal function. *Nutr Today*. 1993;28(1):20-24.
2. Mitsuoka T. Intestinal flora and aging. *Nutr Rev*. 1992;50(12):438-446.
3. Gardner MLG. Gastrointestinal absorption of intact proteins. *Ann Rev Nutr*. 1988;8:329-350.
4. McCallum RW, Weber FH. Clinical approaches to irritable bowel syndrome. *Lancet*. 1992;340:1447-1452.
5. Finch W. Arthritis and the gut. *Enteropathic Arthritis*. 1989;86(2):229-234.
6. Hoover DG. Bifidobacteria: activity and potential benefits. *Food Technology*. 1993;47(6):120-124.
7. Delzenne N, Gibson GR, Roberfroid M. The biochemistry of oligofructose, a nondigestible fiber: an approach to calculate its caloric value. *Nutr Rev*. 1993;51(5):137-146.
8. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. *NEJM*. 1993;328(25):1821-1827.
9. Bland JS, Barrager E, Reedy RGM, Bland K. A medical food-supplemented detoxification program in the management of chronic health problems. *Alternative Therapies*. 1995;1(5):62-71.
10. Macleod RJ, Bennett HP, Hamilton JR. Inhibition of intestinal secretion by rice. *Lancet*. 1995;346:90-92.
11. Darmaun D, Just B, Messing B, et al. Glutamine metabolism in healthy adult men: response to enteral and intravenous feeding. *Am J Clin Nutr*. 1994;59:1395-1402.
12. Engelhardt WV, Reckemmer G. Colonic transport of short-chain fatty acids and the importance of the microclimate. In: *Intestinal Absorption and Secretion*. E Skadhauge, K Heintze, eds. Hing Ham: MTP Press; 1983:93-101.