

Clinical Substantiation Research Paper for Oral Hydrobiotic (re:iimmune®).

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Background

Hospital readmissions have been used as an outcome measure for assessing the performance of a healthcare system. Hospitals face penalties for readmitting recently discharged Medicare patients. Beginning in October of 2012 the Affordable Care Act required the Department of Health and Human Services to establish a program to reduce the revolving door of re-hospitalizations. The resulting program included a reduction in reimbursement of up to 3% in Medicare payments for potentially avoidable readmissions in some Medicare patients with heart conditions, pneumonia, chronic lung disease, and hip and knee replacements.

The Healthcare Cost and Utilization Project (H-CUP), statistical brief presented data on 30-day all cause readmissions in 2013. The average cost of hospital readmissions for Medicare patients was calculated at

\$ 13,800. All cause readmission rates for Medicare patients were 17.3 percent per 100.

Approximately 8 million Medicare patients were admitted to the hospital with a medical diagnosis.

According to this data approximately 1.3 million medical patients were readmitted within 30 days totaling close to 2 billion dollars in hospital charges. It is hypothesized that if the intervention in this study could decrease the readmission rate by just 1 percent (13,000), it could save the healthcare system \$179,400,000 (13,000 x \$13,800) in Medicare patients admitted with a medical diagnosis.

Steps to reduce hospital readmissions have included improved discharge planning, timely follow-up appointments with primary care providers, efforts to improve medication adherence, the use of telemedicine and virtual doctor visits, home health assessments, the appropriate use of skilled nursing care, and efforts to improve communication between the patient/caregiver and the healthcare system. All of these are significant to the improvement of care for patients recently discharged from the hospital. However, these interventions do not directly address the allostatic and physiological demands of the human response to recovering from an illness.

Illness Recovery

The concept of illness recovery encompasses both the allostatic and physical stressors that are experienced during an illness or injury. There are two bodies of evidence that support the belief

that hydration and intestinal immune support can be used as a safe and effective supplement that when used once daily for 10 days can help “fast-track” a person’s recovery experience.

In recent years, the use of postoperative recovery management protocols, such as the “enhanced recovery after surgery (ERAS[®]) protocol” and “fast track program”, is steadily spreading to clinical institutions across the country. ERAS is a multimodal perioperative care pathway designed to attenuate the stress response during the patients' journey through a surgical procedure, to facilitate the maintenance of preoperative bodily compositions and organ function, and thus achieve early recovery. The key factors that keep surgical patients in the hospital include the need for parenteral analgesia, intravenous fluids secondary to persistent gut dysfunction, and bed rest caused by lack of mobility. The elements of the ERAS pathways are aimed to address these issues and the interventions that facilitate early recovery cover all three phases of the perioperative period during the patient’s journey. This paradigm shift in the care of surgical patients challenges standard doctrine by implementing protocols that address the physiological responses to recovery. Prevention of nausea and vomiting, early onset of oral nutrition and the use of oral rehydration therapy to manage fluids and electrolytes as an alternative to IV fluids are components of ERAS protocols. The term “fast-track” is also relevant in that this term has been used in the literature to describe the process of enhancing recovery 91, 92, 128.

The second body of evidence supporting the general concept of illness recovery is grounded in the concept of post-hospital syndrome. The 30-Day readmission study by Krumholz et. al., evaluated Medicare patients who were recently hospitalized. The study reported that recently discharged Medicare patients are not only recovering from their acute illness; they also experience a period of generalized risk for a range of adverse health events. Thus, their condition may be better characterized as a post-hospital syndrome, an acquired, transient period of vulnerability. The researcher’s theory would suggest that the risks in the critical 30-day period after discharge might derive as much from the allostatic and physiological stress that patients experience in the hospital as they do from the lingering effects of the original acute illness. At the time of discharge, physiological systems are impaired, reserves are depleted, and the body cannot effectively defend against health threats. Hospitalized patients are not only enduring an acute illness, which can markedly perturb physiological systems, but are experiencing substantial stress. During hospitalization, patients are commonly deprived of sleep, experience disruption of normal circadian rhythms, are nourished poorly, have pain and discomfort, confront a baffling array of mentally challenging situations, receive medications that can alter cognition and physical function, and become deconditioned by bed rest or inactivity. Each of these perturbations can adversely affect health and contribute to substantial impairments during the early recovery period, an inability to fend off disease, and susceptibility to mental error 49. The relevance of this theory to our concept of illness recovery is the recognition that during illness recovery, regardless of the illness, there are common physiological stressors that if addressed could improve patient outcomes and enhance or “fast-track” the illness recovery process. This study did not directly recommend oral rehydration but it did highlight the need to address poor nutrition and factors that could perpetuate a decrease in cognitive functioning along with interventions that could enhance the body’s ability to fend

off disease. We hypothesize that balancing fluids and electrolytes, decreasing the incidence of nausea, and supporting the intestinal immune system can help fast-track illness recovery and decrease potentially avoidable hospital readmissions.

It has been documented that 1 in 5.8 Medicare patients will be readmitted to the hospital within 30 days of discharge. Several studies have indicated that 31% of the readmissions could have been prevented.

The researchers believe that the intervention being assessed here is not just effective in Medicare patients but in promoting wellness from a number of illnesses and injuries such as surgical interventions.

The researchers believe developing strategies for mitigating post-hospital syndrome and its accompanying risks by targeting stressors that can contribute to patient vulnerability after discharge is critical . The oral hydro-biotic being tested should be useful in reducing those stressors, and thus vulnerability to post-hospital syndrome as discussed below.

Dehydration

Water is essential for life. Body fluids move nutrients, gases and wastes throughout the body and are essential in in metabolizing food into energy as well as assisting in all bodily functions and this is particularly beneficial during times of stress and illness. Fluid balance is controlled by homeostatic mechanisms responding to the state of body water. This mechanism is precise and can be activated with deficits or excesses of water of only a few hundred milliliters. A water deficit produces an increase in extracellular ionic concentration resulting in intracellular cell shrinkage that activate brain receptors controlling drinking and excretion of urine. The brain receptor sends a message to the kidneys via the antidiuretic hormone vasopressin to produce smaller volume of more concentrated urine. When the body detects an excess of water the opposite occurs. The kidneys play a key role in regulating fluid balance. If the kidneys sense a water deficit (few hundred milliliters) they produce a more concentrated urine which results in increased energy needed by the kidneys and excessive wear on kidney tissue 7,8,9,16,40,47,88,.

Dehydration is a risk factor for poor outcomes and can impede the illness recovery process. Dehydration is a risk factor for delirium and confusion presenting as dementia in the elderly and the very ill 3,16,75, . Fluid intake and maintenance of water balance is complicated by factors such as disease, dementia, incontinence, renal insufficiency, restricted mobility and medication side effects. The National Institute of Health (NIH) has reported that water is quantitatively the most important nutrient 152. There is evidence that good hydration is associated with a reduction in urinary tract infections, hypertension, fatal coronary heart disease, venous thrombosis and stroke. Maintaining an optimal hydration state can help mitigate symptoms of dehydration (table 1) 96,97, 101, 172,.

Table 1. Signs and symptoms of dehydration

Mild - Moderate	Severe
Increased thirst	Severely decreased urine output or no urine output
Dry mouth	Dizziness or lightheadedness
Tired or sleepiness	Low blood pressure
Decreased urine output	Rapid heart beat
Headache	Fever
Dry skin	Poor skin elasticity
Dizziness	Lethargy
Impaired cognitive function	Confusion
Few or no tears	Shock/coma
	Seizure

To meet the goal of achieving stability and improving outcomes in patients admitted with a medical diagnosis, it is important to understand the physiological responses of dehydration. Older individuals are less responsive to thirst, and thus less inclined to replenish their water deficit even when they are dehydrated. Studies have demonstrated that even when older persons are offered a highly palatable selection of drinks they still fail to consume an adequate amount of fluid. Illness and limitations in activities of daily living also can result in a decreased fluid intake contributing to an increased risk of dehydration. Fluid management is a critical factor in illness recovery. Correcting dehydration improves pathogen removal, improves cognitive function, reduces risk factors for dementia, improves kidney function, helps maintain optimal blood pressure, reduces the risk for headache, and is associated with a reduction in urinary tract infections 3,8,40,47,63,84,115,126,.

Description of Hydrobiotic

Hydration is the addition of a water-based fluid in order to restore and maintain fluid balance in the human body. Dehydration is the excessive loss of water from the body or from an organ/body part, as part of an illness, fluid deprivation, or physical exertion. Dehydration is most often caused by excessive sweating, vomiting or diarrhea, excessive urine output, fever, loss of appetite due to illness, nausea, or sore throat and is usually accompanied by a deficiency in electrolytes as well. The body's initial response to dehydration is thirst, dry/sticky mouth, followed by lethargy or coma. Some of the symptoms also include low or no urine output or dark yellow urine as well as no tear formation and sunken eyes. Physical signs may also include low blood pressure, rapid heart rate, delayed capillary refill, poor skin elasticity, impairment of healing, decreased respiratory and cardiac function, increased risk of cardiovascular and gastrointestinal disorders, poorer physical function, shock, and even death. Maintaining proper fluid balance in the human body is thus of extreme importance for proper functioning and well-being of each person 8,34,35,40,68,84,88.

Clinical Oral Rehydration

Clinical rehydration is the process of normalizing the body's water/fluid balance and correcting dehydration. Fluids in the diet are absorbed in the proximal small intestines and the rate of absorption is determined by the rate of gastric emptying. The rate at which rehydration occurs is dependent on the rate of delivery of fluids to the intestinal mucosa.

Widespread use of oral rehydration began in the 1970's as an effective and inexpensive method of treating mild-moderate dehydration. Oral rehydration therapy is proven to be as effective as intravenous therapy in treating mild-moderate dehydration and is recommended as first line therapy by the World Health Organization 13,18,38,81,182.

The oral hydrobiotic supplement developed by Make People Better contains the optimal hydration formula of electrolytes, sodium, potassium, chloride, and citrate as well as other immune and gut supporting ingredients such as zinc, ginger root, inulin fiber, L-glutamine, and a probiotic blend. These ingredients have carefully been selected to support the body during rehydration and to support the gastrointestinal tract for proper nutrient absorption while maintaining an isotonic osmolality equal to the human body.

The current recommended ORS by the World Health Organization compared to: **re:iimmune®**

Reduced osmolarity ORS	mmol/liter	re:iimmune®	mmol/liter
Sodium	75	Sodium	75
Anhydrous Glucose	75	L-Glutamine	75
Chloride	65	Chloride	65
Potassium	20	Potassium	20
Citrate	10	Citrate	10
Total Osmolarity	245	Total Osmolarity	280

MECHANISMS OF ACTION

Water is essential for the human body to function properly. Our bodies are made up of 55-75% water depending on age/gender and the majority of water is found inside our cells (intracellular) and the rest can be found outside the cell wall (extracellular). The physiologic mechanism in which water enters and leaves the cells is critical. Cell membranes have high water permeability and do not have the ability to withstand significant hydrostatic pressure gradients. The cellular hydration state is also an important factor in determining cell function as is cell volume, which has shown to be influential in physiological roles such as cell function regulation 88. Electrolytes play a major role in ionic mechanism of cell volume regulation and are presented in Figure 1.

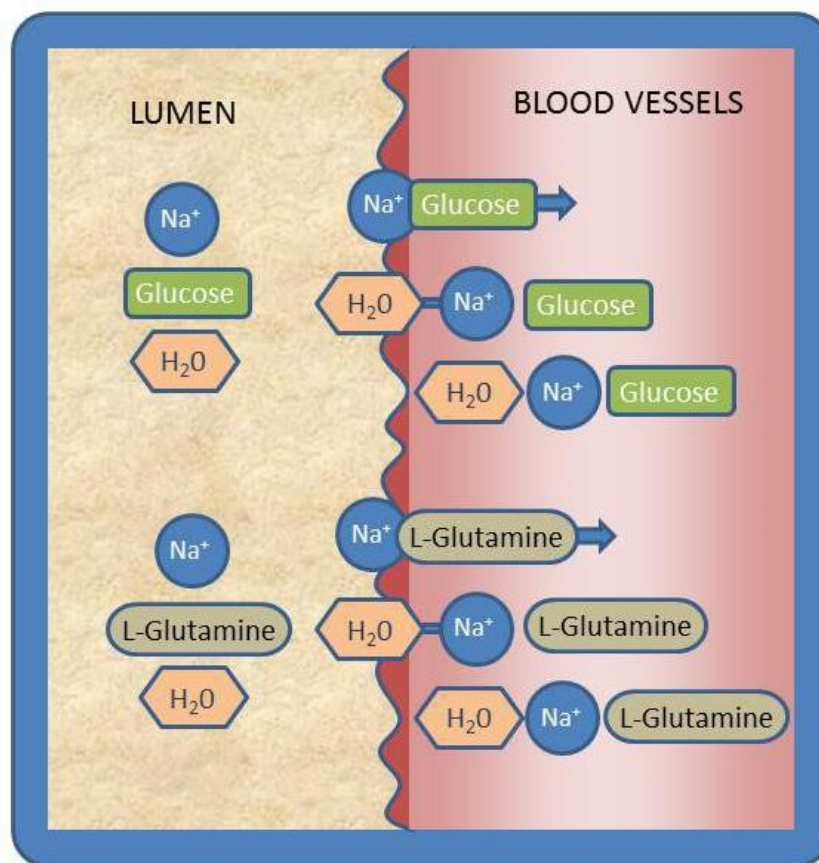


Figure 1. Transport of sodium across cell membrane.

Electrolytes

Electrolytes are substances which dissociate into cations and anions in aqueous solutions. Normal plasma concentration of sodium (Na^+) is 132-152 mmol/L, potassium (K^+) is 3.5-5.5 mmol/L, chloride (Cl^-) is 90-110 mmol/L, with a pH of 7.4. The intracellular concentrations are 10, 155, and 8 mmol/L respectively with a pH of 7.4 as well.

Total body sodium in a healthy adult is over 4 grams of which 40% are in the bones, 50% in the extracellular space and the rest in the intracellular and interstitial space. The total amount of chloride in an adult is in the range of 2.8-3 grams and it is the most abundant anion in the extracellular space. Sodium and chloride make up about 80% of the osmolality of the extracellular space and there is a linear relationship between serum concentration and serum osmolality. Potassium concentration in a normal healthy adult is about 3500 mmol and can decrease with age but it is the most important cation inside the cell. Both sodium and potassium are key circulating electrolytes that also function in the regulation of ATP-dependent channels. These channels are referred to as Na^+/K^+ -ATPases and their primary function is in the transmission of nerve impulses in the brain 104.

The concentration of sodium inside the plasma has to be held to within close limits (132-152 mmol/l) for proper functioning of the body and normally, this sodium concentration is controlled by the renal function (kidneys). However, in a state of dehydration, water is conserved by not urinating and the sodium regulation cannot work effectively. In a stressed state, such as dehydration, the cells of the intestine are impaired and sodium cannot be effectively absorbed. With too much sodium in the lumen increased water can be secreted, worsening the dehydration state with severe loose stool as a result.

If glucose is added to a saline solution a new mechanism comes into play. The glucose molecules are absorbed through the intestinal wall and in conjunction sodium is carried through by a co-transport coupling mechanism. This occurs in a 1:1 ratio; one molecule of glucose co-transporting one sodium ion (Na^+). Glucose does not transport the water alone. Glucose has to be paired with sodium that pulls the water through (Figure 1). However, too much glucose also has a negative effect. Several other molecules apart from glucose have a similar capacity to co-transport sodium including amino acids such as L-Glutamine 38, 43, 81. Additionally, research supports that an L-Glutamine, glucose free, oral rehydration solution is as effective as the World Health Organizations recommended oral rehydration solution containing glucose 81. The absorption of these molecules occur independently of each other and at different sites in the intestine and the effects can be additive. Plain water and high glucose sports drinks may not rehydrate and in some cases worsen the situation. Sosa Léon *et al.* (1995) showed that the influence of osmolalities on absorption in horses. Orally administered hypertonic fluids (628 mOsm/kg body weight) were less rapidly absorbed than isotonic (314 mOsm/kg bw) and hypotonic fluids. The inclusion of glucose also did not influence absorption rates 182.

Chloride is important to maintain the function of numerous cellular pumps. It is one of the components of the digestive juice and is used in the production of hydrochloric acid (HCl) in the stomach. Chloride is also responsible for maintaining acid/base balance, transmitting nerve impulses and regulate fluids in and out of cells. It is carefully regulated and controlled by the kidneys.

L-Glutamine

In addition to the ability of L-Glutamine to effectively transport sodium in the hydration process, L-Glutamine also plays a role in maintain the integrity of the gastrointestinal mucosa and immune response. The rate at which hydration occurs is directly related to the rate at which fluids reach and cross the intestinal mucosa. Maintaining the integrity of the GI mucosa is an important component of illness recovery not only because it can speed up the rate of water absorption in a dehydrated state but glutamine is an important fuel source for cells that rapidly turn over including the GI epithelia, lymphocytes, fibroblasts and reticulocytes. Human studies on L-Glutamine have been conducted using various doses of both parenteral and PO L-Glutamine 4,5,10,28,30,54,60,71,81,111.

Glutamine (Gln) is the most abundant naturally occurring amino acid in the body due to its high concentration in the blood and large storage of free glutamine in muscles. It is classified as a nonessential amino acid since it can be produced from glutamate/glutamic acid and ammonia with the help of the enzyme glutamine synthase and ATP primarily from stores in muscle tissue (Figure 2) but can also be synthesized in the liver, lung, and brain 1,26,27,138.. Glutamine is a unique amino acid because it contains two nitrogen atoms.

This amino acid may become conditionally essential under certain conditions, such as intense exercise, endurance exercise, stress, infections, surgery, gastrointestinal disorders, injuries, and other illnesses. Under these stress conditions the body's need for this amino acid can exceed the tissues ability to produce it and thus the term "conditionally essential" 1,4,5,10,27,31,46,60,70,71,118.. Glutamine is one of the most popular as well as profitable nutritional supplement due to the claims of boosting immune function and increase muscle mass and volume.

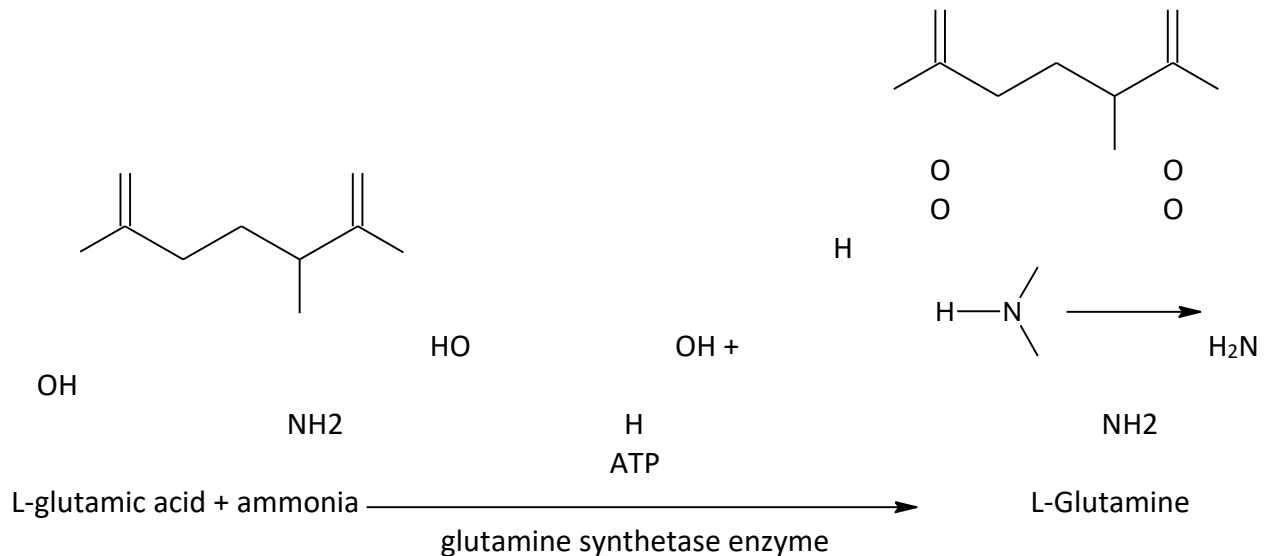


Figure 2. Synthesis of glutamine from glutamic acid/glutamate and ammonia with the help of the glutamine synthetase enzyme and ATP. In a solution of neutral pH both the amino and carboxylic acid groups of glutamine are charged.

Glutamine is formed directly from glutamate by the addition of ammonia with the help of ATP and the cytoplasmic enzyme glutamine synthetase. Glutamine is usually formed for its use in synthetic reactions, ammonia detoxification, or for export to other tissues. Aminotransferase enzymes easily convert glutamine back to glutamate, whereby the amide nitrogen is transferred to other molecules. Thus, glutamine becomes essential for the production of other amino acids, purine and pyrimidine bases (DNA bases), amino sugars, and many coenzymes 1, 27,201.

The normal plasma concentration of glutamine is fairly high and that of glutamate is fairly low and cells usually exhibit large glutamine import capacity, where it is readily converted to glutamate. In most tissue, except muscle tissue, the intracellular concentration of glutamine is lower than glutamate 1,39,90,190 and an increase in glutamine plasma concentrations down-regulates endogenous glutamine synthesis 26,149. Glutamine represents the primary source of intracellular glutamate and becomes a vital role in intracellular cell osmolarity and cell volume 45,90,139,186.

Glutamate produced from glutamine conversion, is involved in many reactions such as donating the amino nitrogen to ultimately produce aspartate, alanine, and citrulline 27. The glutamate anion serves as a precursor for the amino acid proline synthesis as well as to support the synthesis of glutathione, the cells major antioxidant 1, 165. Glutamate enters the TCA cycle and is oxidized to CO₂ and pyruvate to ultimately produce energy in the form of ATP 27,125,205.

Lungs, muscles, and adipose tissue are major pools of glutamine and during catabolic states increase glutamine production. In response to stress hormones, the gene expression for glutamine production is increased and glutamine is exported out of the cells. This mechanism is regulated by a feed-back inhibition mechanism that responds to the need for glutamine synthesis to maintain a balanced production of glutamine 2,39,87,113 .

Kidneys also utilize glutamine to control blood acidity, acidosis. This is accomplished by utilizing the ammonia obtained from glutamine which is an ideal candidate since it contains 2 ammonia equivalents 44. Ammonia then binds hydrogen ions to produce ammonium ions, which are ultimately eliminated through the urine together with acid anions. During severe stress on the human body metabolic acidosis can occur due to increased keto-acid concentration and loss of bicarbonate ions. To counteract these effects, the kidney greatly increases the use of glutamine and thus the production of systemic glutamine greatly increases 44,153,173. Glutamine metabolism in the kidney thus is an essential tool for acid-base buffering in the plasma. The rest of the glutamine skeleton is ultimately converted to glucose and provides about 25% of the circulating plasma glucose *in vivo* 44,78,138,184.

The addition of glutamine is necessary to support numerous cellular processes, especially for proliferating cell activity. In the adult human this is especially true during times of wound healing but also in the intestinal tract and immune system where there is a lot of cell turnover 1. Replacement of epithelial cells in the gastrointestinal tract is supported by glutamine.

Epithelia cell cultures are glutamine dependent and consume large concentrations of glutamine 57,58,59,106,159. The immune system also has a large cell turnover and is glutamine dependent for both activation and proliferation. Glutamine has also been referred to as an "apoptosis suppressor", since it inhibits apoptosis caused by cellular stressors 125,137.

Glutamine plays an important role in the catabolic state, which can occur from injury, stress, disease, intense exercise, etc 30. During the catabolic state stress hormones trigger an increase in muscle protein degradation as well as decrease muscle protein synthesis 87. Free amino acids are produced and the branched chain amino acids are the preferred substrate for oxidative energy production by the muscle and ultimately become waste nitrogen. The muscle tissue utilizes glutamine to eliminate this nitrogen waste and lean body mass is ultimately converted into energy 21,26,93. With increased protein turnover there will also be increased nitrogen waste, which needs to be eliminated via the kidneys 1,19,141. Increased immune activation and expansion might also happen which also causes an increase in glutamine demand. With a concurrent infection, the liver will also consume more glutamine to support acute phase protein synthesis 19. If any of these demands are continuing, the catabolic state can lead to lean body mass depletion and thus reduce muscle mass and its ability to produce glutamine, ultimately leading to poor wound healing, impaired immune function, etc 85. With persisting catabolic state, lean body mass is lost and thus the ability of muscle to produce glutamine and maintain inter-organ glutamine flux. Thus supplementation with glutamine is an excellent strategy to counteract the loss in concentration.

Total parenteral nutrition (TPN) is the intravenous feeding where oral nourishment is not tolerated. Since it was shown that glutamine is such an important amino acid for the intestines, it was finally included as a substrate to alleviate intestinal atrophy 22,28,109,110,171,197,200. Glutamine as well as glucose is required for an effective immune system and endogenous supplementation is required if there is a deficiency due to various factors described above 181. This amino acid can also be called an immuno nutrient. Concentrations of glutathione are at low concentrations in clinical patients suffering from some form of infection. As described above, glutamine is involved in the production of glutathione and thus glutamine is beneficial in reducing symptoms of the clinical conditions. However, both the amino acids cysteine and glycine need to be present to produce glutathione. It has also been shown that glutamine induces the expression of heat shock protein, which plays a role in tissue protection after injury and stress, and reduces the expression of inflammatory cytokines 203,204. Studies in patients admitted to the intensive care unit usually show low plasma glutamine concentrations and the addition of glutamine in nutritional formulas to these patients was shown to reduce infection and inflammation rate 77,140,142.

Oral supplementation may directly influence the proliferation and development of gut associated lymphoid tissue (GALT). Factors such as immunoglobulin antibodies, enzymes, saliva, bile, as well as this extensive immune system called the Gut-Associated Lymphoid Tissue (GALT) are all involved at keeping the gastrointestinal tract healthy and well balanced. The number of lymphocytes in the GALT can be about the same as in the spleen, depending on the area of the intestine. The GALT is made up of several lymphoid tissues that are important in storing T and B

lymphocytes, immune cells that help against pathogens as well as other white blood cells 120,196.

Zinc

Zinc is thought to be the most important micronutrient. It is essential to human growth and development and serves as a key co-factor of the immune system 102, 154,155,160. It is needed for proper T-cell and natural killer (NK) cell function as well as for proper lymphocyte activity 83,177. With its catalytic capabilities, zinc is essential in many enzyme systems. It interacts with a wide range of organic ligands 86, and thus plays a major role in the metabolism of RNA and DNA and gene expression 42, 83,132,175 as well as signal communication to other cells 89. About 10% of all 2800 human proteins potentially require and bind zinc for proper function as well as hundreds more that transport, and regulate zinc 41, 189. Most zinc is stored in the brain, muscle, bones, kidneys, liver, and especially the prostate where it is particularly rich and serves as key factor for healthy prostate gland function 20,86,135. Two of these zinc-containing enzymes are carbonic anhydrase and carboxypeptidase which are essential in the digestion of proteins and process of carbon dioxide back into bicarbonates 76,107,183,189.

Clinical studies have been done with zinc to investigate the outcome of zinc supplementation on health. In 2011 a Cochrane review showed that using zinc sulfate as a prophylactic for at least 5 months reduced the incidence of colds, absence from school and antibiotic use in children. In another review done by Science *et al.* in 2006, zinc treatment shortens the duration of symptoms of the common cold in adults 174.

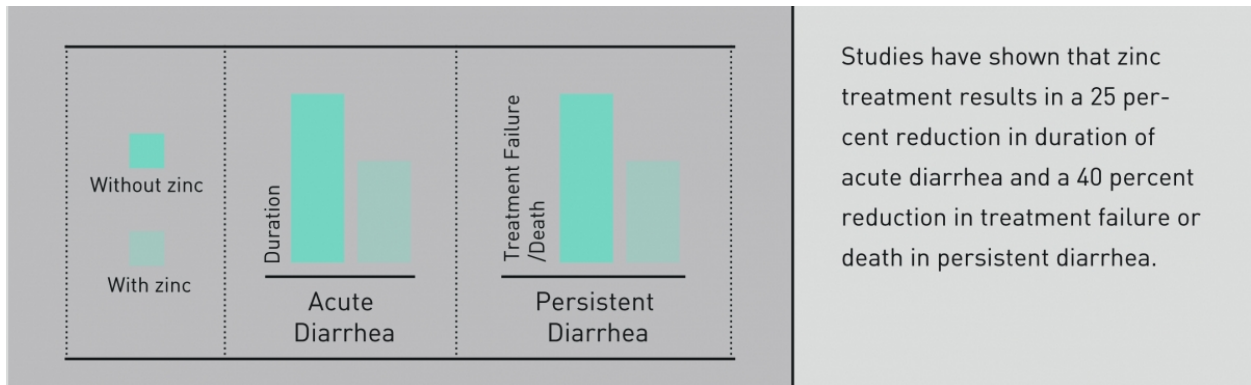
Zinc appears to work in two ways. First, zinc interferes with the ability of rhinoviruses, which are responsible for about 80% of all colds, to reproduce. Second, it appears to block their ability to dock on cell membranes and subsequently cause infection. In a study published in 2008 in the *Journal of Infectious Diseases*, researchers tested zinc lozenges against placebo in 50 study participants. Half got 13.3 milligrams of zinc every 3-4 hours in a zinc acetate lozenge; the other half got a dissolvable wafer with inactive ingredients that tasted the same. Researchers reported that "Usually it takes about eight days for a cold to disappear, but with zinc, it cuts down by about 50%"

A total of 13 trials pitted zinc against a placebo in people under age 65 suffering from early cold symptoms, including sore throats, headaches, coughs, fever, runny or stuffy noses, sneezing, hoarseness, and muscle aches. When taken within the first 24 hours of symptoms, results from six trials showed that using zinc lozenges or syrup appeared to shorten the duration of a cold by about a day. Results from five studies, representing more than 500 people, showed that those using zinc had less severe symptoms compared to those taking a placebo. An analysis of two combined studies, representing more than 1,500 people, found about 40% fewer colds in those who were taking zinc supplements to prevent colds compared to those taking a placebo 114,180.

There has been significant research in the use of zinc supplementation in the treatment of diarrhea and prevention of pneumonia in children. Cochrane Review published results in 2010 which concluded that zinc supplementation in children is associated with a reduction in the incidence of pneumonia. In 2013 the same Review published results which supported the use of zinc supplementation in the treatment of diarrheal disease in children 33,62,114,154,155,160.

In 2004, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) issued a joint statement regarding the clinical management of acute diarrhea. This statement recommended the use of zinc treatment 163.

The dose of zinc found in **re:iimmune**[®] correlates to the WHO recommended dose of 20mg per day when used twice a day.



Ginger

Ginger is an ancient Chinese medicinal root plant that has been used to treat a myriad of conditions.

Reducing nausea and vomiting can enhance the illness recovery process. Controlled trials have demonstrated that the use of ginger can reduce the incidence of nausea and vomiting in post-operative patients, pregnancy-induced nausea and vomiting and patients receiving chemotherapy 23,31,50,54,124,131,144,145,164,167,.

The dose of ginger root used in **re:iimmune**[®] hydrobiotic is equivalent to 275 mg of ginger root. This dose is comparable to the dosage used in the literature of 250 mg.

Prebiotic

The normal bacteria found throughout the intestine play a significant role in overall health. During an episode of acute illness, the protective mucous membrane lining the intestinal tract is disrupted causing a state of imbalance. Prebiotics differ from probiotics (good bacteria) in that they are not a live organism but are a non-digestible carbohydrate and thus food for the probiotics. Once ingested they almost completely bypass the upper digestive system and reach the intestine intact where they begin fermentation by the normal gut microbiota. The fermentation process stimulates and promotes the production of "good bacteria" such as *Bifidobacteria* and *Lactobacilli*. This process allows the recovery of a healthy microflora and improves overall immunity 12,74,94,98,147,162,193,195.

Probiotic Blend

The intestinal system is responsible for 70-80% of the human immune response. Bacteria are a normal part of the human gastrointestinal tract, where more than 400 species have been found 185. Colonization of the gut is essential and begins at time of birth and continuous throughout life 53,130,192. The ecology of the human gut is complex and generally includes a) indigenous beneficial bacteria that have established a symbiotic relationship with the host and b) potentially pathogenic bacteria. The health of the epithelial layer of the intestine is essential in acting as a barrier to bacterial invasion and thus essential for the health in humans 194. Therefore, an optimal balance between "good" and "evil" bacteria populations is associated with good health 56,69,129,176. For efficient and maximum absorption of nutrients in the intestines it is necessary and essential that the correct balance of microorganisms is maintained. This balance can often be disrupted during diseases, stress, antibiotic therapy, and other factors allowing harmful bacteria to overgrow the intestine and potentially over-stimulating your immune system. Certain microorganisms such as lactic acid bacteria are natural inhabitants of the gastrointestinal tract and can facilitate a favorable microbial profile composition in the intestines.

Thus, fortifying with healthy probiotics supports and promotes digestive health and supports a healthy immune system. The function of probiotics includes proteolysis (breakdown of protein), lipolysis (breakdown of fat), and the ultimate conversion of carbohydrates (including lactose) into lactic acid. As they travel into the gastrointestinal tract, probiotics produce metabolites beneficial in suppressing putrefactive microorganisms. These metabolites include end-products such as lactic acid and bacteriocins. The metabolic activity of these beneficial gut bacteria enzymes also help in the further digestion of food components, improve bioavailability of minerals and other nutrients, produce short-chain fatty acids, polyamines, vitamins (such as Vitamins B and K), antioxidants, etc 14,127,148,198.

Probiotics also modulate the immune system by stimulating various aspects of the immune system (phagocytosis of various immune cells), enhance immunoglobulin response, antibody, and reticuloendothelial system stimulation 73,95,120,191,192,194.

To be classified as a beneficial probiotic microorganism to humans the following criteria have to be met:14,69,170

- Survive the harsh acidic and bile environment of the stomach and small intestine
- Be metabolically active in the gastrointestinal tract
- Must be able to colonize and adhere to the intestinal wall of the gastrointestinal tract
- Must possess antimicrobial activity towards pathogens
- Must reduce colon pH by producing acid
- Non-pathogenic to humans

Re:iimmune Oral hydrobiotic contains a probiotic blend that contains multiple beneficial probiotic microorganisms such as a variety of Bifidobacteria, Lactobacilli, Saccharomyces, and Streptococcus (Table 2). Each of these species have unique benefits in the gut. Once the probiotics enter the digestive tract, they support the complex gastrointestinal microflora by improving the ecology through replenishing the quantity of desirable obligate microorganisms and antagonizing pathogens.

Table 2. Probiotic blend found in *re:iimmune*

Genus	Species
Lactobacillus	L. acidophilus, L. rhamnosus, L. reuteri, L. bulgaricus, L. plantarum, L. casei, L. salivarius
Bacillus	B. longum, B. infantis, B. bifidum, Lactospore
Saccharomyces	S. boulardii
Streptococcus	S. thermophilus

After oral supplementation, the probiotic mix arrives in the stomach, followed by entering the upper intestinal tract where the bacteria start to multiply rapidly. They move further down the intestinal tract to reach their final destination in the colon where they become active 17.

Probiotics may directly influence the proliferation and development of the Gut-Associated Lymphoid Tissue (GALT). The GALT as well as immunoglobulin antibodies, enzymes, saliva, bile, are all involved at keeping the gastrointestinal tract healthy and well balanced. The number of lymphocytes in the GALT can be about the same as in the spleen, depending on the area of the intestine 124,136. The GALT is made up of several lymphoid tissues that are important in storing T and B lymphocytes, immune cells that help against pathogens as well as other white blood cells 120,196.

Payer's Patch in the gastrointestinal tract is a secondary lymphoid tissue that is part of the surveillance system in detecting potential hazards and triggers an immune response within the mucosa.

Macrophages, dendritic cells, B- and T-lymphocytes are found in Payer's Patches which are also covered in microfold cells (M cells). These M-cells transport antigens directly from the gastrointestinal lumen (via phagocytosis or endocytosis) and deliver them to immune cells (T-

cells) which stimulate a mucosal immune response 108. When certain strains of pathogenic microorganisms such as Shigella, Salmonella, and Yersinia as well as some viruses get the upper hand, they can bind to these M cells and be transported across the protective epithelium cell barrier and cause infections 66,143,146.

L. reuteri has been used to study the recovery of children from rotavirus associated acute diarrhea. In a randomized placebo-controlled study by Shornikova *et al.* (1997) *L. reuteri* was investigated in 40 children hospitalized for acute diarrhea, age 6-36 months old. The children were treated daily for the length of the hospital stay or up to 5 days and at the end of the treatment period the results showed that the mean duration of watery diarrhea after treatment with *L. reuteri* was 1.7 days compared to the placebo group (2.9 days). Two days after treatment only 26% of children had watery diarrhea compared to 81% of placebo children ($p=0.0005$). *L. reuteri* had also started colonizing the gastrointestinal tract of those children receiving the probiotic 179. Many other studies using *L. reuteri* have been done 51,80,188.

Another strain that has received a lot of attention is *Lactobacillus rhamnosus*. A large meta-analysis was done to investigate the use of *L. rhamnosus* on bacteria induced diarrhea in children and adults. The analysis included 1486 subjects age 4-65 years. The summary results showed that the risk of developing bacteria induced diarrhea was much lower in subjects on *L. rhamnosus* supplementation as compared to placebo. The combination of two Lactobacillus strains (*L. acidophilus* and *L. casei* both found in **re:iimmune**) had an even better effect on the symptoms and prevention 199.

There are many studies investigating the combination of probiotic blends. The best approach to using probiotics is to include a variety of microorganisms that complement and are beneficial to each other as well as to the host 11, 14, 15, 17, 37, 48, 51, 52, 53, 61, 64, 65, 69, 72, 73, 79, 80, 95,99,100,106,112,119,120,122,127,129,130,134,146,148,168,170,176,179,185,188,191,192,194,199.

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