“Enteric Dialysis®” – From Concept to Reality
[In conjunction with standard care of therapy]

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Abstract:
Since the article published in the Journal of Nephrology and Therapeutics in 2015, exponential advances have been made in probiotics, prebiotics, the gut microbiome, dysbiosis, and recognition of the modulation of the gut microbiome and its impact on disease. Many of these advancements have come in the form of diets, understanding environmental factors, natural products, enzymes, drugs, GMO and non-GMO molecules, genes, and microbes. Advancements in study methods such as metabolomics, proteomics, metagenomics and related technologies have provided the tools needed to study microbiome interactions with the host, the molecules these microbes synthesize, and the composition of the microbes that make up the microbiome. These technologies can now help us pinpoint which microbe produces a specific biomarker of interest. Without these technological advances and the instrumentation they utilize, this would be nearly impossible. As a result, scores of medical/scientific papers and several review articles have recently been published in relevant medical and scientific journals. As such, this article is primarily aimed in independently updating the recent scientific progress, understanding, and knowledge gained on the emerging concept of “Enteric Dialysis®”. This concept is being rapidly recognized and accepted as a potential pathway towards maintenance of good health, facilitating the healing process and promising potentials to address several diseases. This author will attempt his best efforts to provide his personal views and latest advances in connecting the importance of the Gut Microbiome and dysbiosis resulting in inflammation attributing to various disease states. This article is mainly designed to educate patients, and healthcare professionals who may not be familiar with the subject matter described herein. With the recent gains in research and knowledge, Enteric Dialysis® is transforming from a concept to reality, and can potentially provide a promising future for those with Chronic Kidney Disease (CKD) along with standard care of therapy.

Introduction:
Dr. Ranganathan and his colleague, Usha Vyas’ review article: “Probiotics, Prebiotics and Synbiotic: Gut and Beyond” was published in Gastroenterology Research and Practice Journal in 2012 [1]. Their 2012 article has inspired researchers in the field of the kidney and gut microbiome and as a result modulating the gut microbiome to improve health and treat disease has raced ahead of its time. There are hundreds of probiotic/prebiotic products and various formulations commercially available in the form of foods, beverages and dietary supplements. Probiotics and prebiotics are manufactured in c-GMP/US FDA approved facilities either as medical foods or dietary supplements only. As of now, there exists no probiotic manufacturing facility with a Drug Master File (DMF) documentation needed for manufacturing these products as a drug product. Thus, no probiotic or prebiotic formulation can be considered a drug. Over 76% Americans buy and consume one or more dietary
supplements on their own discretion. This is mainly because of the belief that in general, dietary supplements are safe, inexpensive, and mostly efficacious for intended claims made. They’re also conveniently sold over the counter at pharmacies and online. These products are mainly targeted toward gut, immune and digestive health. It is also becoming more apparent that with the availability of newer instrumentation and technology, and greater understanding of the role of the gut microbiome and its modulation with various kinds of natural, synthetic and biological actives towards various healthcare applications are rapidly being accomplished both for veterinary and human uses. Several more review articles have been published by host of scientific experts pertaining to the Gut-Brain and Gut-Kidney connection. This book chapter is specifically intended on the role of uremia, uremic toxins, and Gut Microbiome targeted to understanding the field of Chronic Kidney Disease applications. In this aspect, several recent reviews related to Gut-kidney connection and, as well as modulation of the Gut microbiome have been cited for added knowledge and scientific progress made as of this writing.

**Probiotics**: They are defined by the Food and Agriculture Organization (FAO) and World Health Organization (WHO) as “live microorganisms which when administered in adequate amounts, confer a health benefit on the host” (2002) [2]. Probiotics are characterized and named according to its Genus, Species and Strains. In addition, only those well characterized and precisely defined strains possessing specific health benefits are classified as Probiotics. Probiotics are quantified as Colony Forming Units (CFU, generally billions of CFU/gm). In humans, the probiotics which are used for various applications need to be well documented and proven to be safe for consumption. They need to have a “Generally Regarded As Safe” status termed as ‘GRAS’ certified [3].

Probiotic bacteria have a large role to play in our health and well-being. They work by different mechanisms in the body, depending on the strain of the bacteria leading to various beneficial or therapeutic properties. (Figure 1). Many strains produce bacteriocins namely lactacin and bisin which inhibit the growth of pathogenic bacteria [4, 5, 6]. Many strains also modulate inflammation in the gut. They lower the levels of pro-inflammatory bio markers like IL-1β, and C-reactive protein and also middle molecules like IL-6 and TNF-α and up-regulate the levels of anti-inflammatory markers like IL-10 [7-11]. *L. acidophilus* metabolizes uric acid and decreases production of dimethylamine, trimethylamine, TMAO and nitrosamines. Secondly it also reduces small intestinal bacterial overgrowth (SIBO) in renal failure patients [12, 13].
Not all probiotic bacteria give the same beneficial effects. Each species of probiotic bacteria is further characterized by a strain number which imparts its unique property like a DNA fingerprint.

As shown in figure 2, two different strains of Lactobacillus acidophilus when consumed give different beneficial effects. Supplementation with *L. acidophilus* NCFM® tended to increase the specific serum IgA [10]. The strain significantly reduced the incidence and duration of fever, upper respiratory infection symptoms and antibiotic use compared to a placebo [14] whereas *Lactobacillus acidophilus* LA-05®, which is a proprietary strain from Chr-Hansen has the property to reduce constipation, diarrhea, lactose intolerance and side effects associated with antibiotics [15-18]. *Lactobacillus acidophilus* LA-05® and *Bifidobacterium lactis* BB-12® are generally used together.

The US Food and Drug Administration (FDA) has designated the strains LA-5® and NCFM® as Generally Recognized As Safe (GRAS). This is a very important criteria to be looked into when buying any probiotic containing products for human consumption.
Figure 2: Comparison of two strains of L. Acidophilus. L. acidophilus NCFM® and Lactobacillus acidophilus LA-05®

https://www.optibacprobiotics.co.uk/live-cultures/probiotics-database/lactobacillus-acidophilus-ncfm

A large number of probiotic products are available commercially as dietary supplements on the market for various applications (Table 1). They now appear with increasing frequency in various foods, beverages, supplements, and are readily utilized in alternative and complementary medical practice strategies. Due to direct consumer advertising, the average population has been convinced of the positive role that probiotics play in health and disease. This has led to marketing and consumption of a number of probiotic supplements available for purchase online or in pharmacies without their benefit being scientifically proven in a rigorous clinical trial. Probiotic microbes are also predominantly found in fermented dairy foods such as yogurt, kefir, cheese and other fermented foods.

Table 1: Commercially available probiotic products

<table>
<thead>
<tr>
<th>Product</th>
<th>Company/Manufacturer</th>
<th>Use (Label Claims)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align®</td>
<td>Proctor &amp; Gamble</td>
<td>Digestive Health</td>
</tr>
<tr>
<td></td>
<td>(1 billion CFU) 1 probiotic strain</td>
<td></td>
</tr>
<tr>
<td>VSL#3®</td>
<td>Sigma-Tau Pharmaceuticals</td>
<td>Dietary management of IBS and Ulcerative Colitis</td>
</tr>
<tr>
<td></td>
<td>(112 billion CFU) 3 Bifidobacterium strains 4 Lactobacillus strains 1 Streptococcus strain</td>
<td></td>
</tr>
<tr>
<td>Colon Health®</td>
<td>Phillips</td>
<td>Digestive Health</td>
</tr>
<tr>
<td></td>
<td>(1.5 billion CFU) 1 Lactobacillus strain 2 Bifidobacterium strains</td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>Company</td>
<td>CFU/Strain Description</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Renadyl™</strong></td>
<td>Kibow Biotech, Inc.</td>
<td>(45 billion CFU) 1 Streptococcus strain 1 Lactobacillus strain 1 Bifidobacterium strain</td>
</tr>
<tr>
<td><strong>DelPro™</strong></td>
<td>Pure Research Products, LLC</td>
<td>(10 billion CFU) 3 Lactobacillus strains 2 Bifidobacterium strains</td>
</tr>
<tr>
<td><strong>Ultimate Flora®</strong></td>
<td>ReNewLife</td>
<td>(3 billion CFU) 1 Bacillus strain 3 Lactobacillus strains 2 Bifidobacterium strains</td>
</tr>
<tr>
<td><strong>Culturelle® Kids Packets</strong></td>
<td>Culturelle</td>
<td>(5 billion CFU) 1 probiotic strain</td>
</tr>
<tr>
<td><strong>Florastor Kids</strong></td>
<td>Biocodex</td>
<td>(5 billion CFU) 1 Saccharomyces strain</td>
</tr>
<tr>
<td><strong>Protectis™</strong></td>
<td>Bio Gaia</td>
<td>(100 million CFU) 1 Lactobacillus strain</td>
</tr>
</tbody>
</table>

**Prebiotics:** They are defined as “non-digestible, but fermentable, foods/ingredients that allow specific changes, both in the composition and/or activity, in the gastrointestinal microflora that confers benefits upon host well-being and health [19]”. Well known examples of prebiotics include inulin, oligofructose, galacto-oligosaccharide, lactulose [20], xylo-oligosaccharides [21] and Beta-glucans [22]. Commercially available fibers are all mainly formulated for digestive health. Some of these are Benefiber, Metamucil and Citrucel manufactured by large pharmaceutical companies.

Prebiotics stimulate the growth or activities of specific microbial genera and species in the gut microbiota, in order to confer health benefits to the host. In general, prebiotics favor the growth of bifidobacteria and lactobacilli over potentially harmful proteolytic and putrefactive bacteria. All currently known prebiotics are carbohydrates, and there are many different carbohydrates marketed world-wide as prebiotics. Dietary fibers contain prebiotics and consumption of dietary fiber has been shown to be beneficial [23, 24]. Commercially available prebiotics are manufactured from various plant sources and have been shown to impart various health benefits. Some of the prebiotics available on the market are shown in table 2.
### Table 2: Commercially available Prebiotics

<table>
<thead>
<tr>
<th>Prebiotic</th>
<th>Structure</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin</td>
<td><img src="image" alt="Inulin Structure" /></td>
<td>Chicory, wheat, onion, bananas, garlic, asparagus, Jerusalem artichoke.</td>
</tr>
<tr>
<td>β(1,3)(1,6)-glucans</td>
<td><img src="image" alt="β(1,3)(1,6)-glucans Structure" /></td>
<td>Mushrooms, Yeast cell walls</td>
</tr>
<tr>
<td>Arabinogalactan</td>
<td><img src="image" alt="Arabinogalactan Structure" /></td>
<td>Larch wood, gum Arabic</td>
</tr>
<tr>
<td>Xylo-oligosaccharide</td>
<td><img src="image" alt="Xylo-oligosaccharide Structure" /></td>
<td>Bamboo shoots, fruits, vegetables, milk, and honey</td>
</tr>
<tr>
<td>β(1,3)(1,4)-glucans</td>
<td><img src="image" alt="β(1,3)(1,4)-glucans Structure" /></td>
<td>Oats, Barley</td>
</tr>
<tr>
<td>Galactooligosaccharide</td>
<td><img src="image" alt="Galactooligosaccharide Structure" /></td>
<td>Lactose</td>
</tr>
<tr>
<td>Fructooligosaccharide</td>
<td><img src="image" alt="Fructooligosaccharide Structure" /></td>
<td>Jerusalem artichoke, chicory, Blue Agave garlic, asparagus, jícama, and leeks</td>
</tr>
</tbody>
</table>

### Table 3: Fiber supplements available in the US market

<table>
<thead>
<tr>
<th>Product</th>
<th>Company/Manufacturer</th>
<th>Use (Label Claims)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metamucil®</td>
<td>P&amp;G 2 Prebiotics</td>
<td>Digestive Health</td>
</tr>
<tr>
<td>Benefiber®</td>
<td>GSK 1 Prebiotic</td>
<td>Digestive Health</td>
</tr>
<tr>
<td>Mirafiber®</td>
<td>Bayer 1 Prebiotic</td>
<td>Digestive Health</td>
</tr>
<tr>
<td>Product</td>
<td>Company/Manufacturer</td>
<td>Use (label Claims)</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Probiolicious Probiotic Gummies™</td>
<td>Rainbow Light (1 billion CFU) 4 Prebiotics 1 Probiotic</td>
<td>Digestive Health</td>
</tr>
<tr>
<td>Primadophilus® Children</td>
<td>Nature’s Way (3 billion CFU) 1 Prebiotic 7 Probiotics</td>
<td>Digestive Health</td>
</tr>
<tr>
<td>Probiotics with Colostrum®</td>
<td>ChildLife (4 billion CFU) 1 Prebiotic 3 Probiotics</td>
<td>The probiotic blend is for intestinal health, the colostrum is for immune support, and the prebiotics support good bacterial growth for healthy digestion and immune function</td>
</tr>
<tr>
<td>FloraTummys® Probiotic Sprinkles Kids</td>
<td>FloraTummys (5 billion CFU) 1 Prebiotic 2 Probiotics</td>
<td>Supports immune health, restore friendly bacteria, and reduce diarrhea, constipation and gas</td>
</tr>
<tr>
<td>Pro-Kids®</td>
<td>Hyperbiotics (3 billion CFU) 1 Prebiotic 4 Probiotics</td>
<td>Immune System Health</td>
</tr>
<tr>
<td>Little Ones®</td>
<td>LoveBug (3 billion CFU) 1 Prebiotic 5 Probiotics</td>
<td>Digestive Health</td>
</tr>
</tbody>
</table>

**Synbiotics:** The combination of probiotics and prebiotics is generally known as synbiotics. Many products are available on the market which contains both of these (Table 4).

Table 4: Synbiotic products on the market
Berry-licious Fruit Punch®  |  GoLive  (15 billion CFU)  
6 Prebiotics  
15 Probiotics  |  Gut health  
|  Just For Kids®  |  SunBiotics  (5 billion CFU)  
5 Prebiotics  
5 Probiotics  |  Digestive Health  

The expansion of our awareness and use of probiotics, however, has raced ahead of the scientific basis for the mechanisms by which they impact health. Probiotics are increasingly utilized in clinical settings for various health applications [25]. In kidney failure, there are multiple factors associated; the role of digestive [26] and immune systems [27], as well as inflammatory [28] and oxidative stress [29, 30] functions in the progression of kidney disease have been emphasized by researchers in the past decade. Current data have highlighted an integrated and perhaps a causal relationship between the observed clinical outcomes and the role of an activated immune system in uremia [31].

**Human Microbiome:** The Human Microbiome Project by the NIH in US and the MetaHIT project in Europe showed that we have diverse groups of microbes in and on our body systems [32]. The Human Microbiome Project (HMP) is a United States National Institutes of Health (NIH) initiative with the goal of identifying and characterizing the microorganisms, which are found in association with both healthy and diseased humans (the human microbiome) using tools such as metagenomics (which provides a broad genetic perspective on a single microbial community), as well as extensive whole genome sequencing. The microbiology of five body sites was studied: oral, skin, vaginal, gut, and nasal/lung. Tools for deep sequencing of bacterial 16S rRNA sequences amplified by polymerase chain reaction from human subjects were used. HMP researchers reported that this plethora of microbes contribute more genes responsible for human survival than humans contribute. Where the human genome carries some 23,000 protein-coding genes, researchers estimated that the human microbiome contributes some 8 million unique protein-coding genes or 360 times more bacterial genes than human genes. The Human Microbiome Consortium published findings showing that even within healthy individuals that is a lot of diversity [33].

**Gut Microbiome:** During coevolution with microbes, the human intestinal tract has been colonized by thousands of bacterial species [34, 35]. Gut-borne microbes outnumber the human body cells by a factor of ten – i.e. =>100 trillion versus 10 trillion [36]. Recent metagenomics analysis of human Gut microbiota has revealed the presence of **3.3 million** genes, compared to a mere **23,000** known human genes [37-39] (Figure 3). Microbial communities perform the majority of biochemical activities on the planet and play integral roles in human metabolism and immune homeostasis in human physiology and function [40]. Evidence for various beneficial roles of the intestinal microbiota and, concomitantly, probiotic microbes in human health and disease have been expanding rapidly in recent years [41-45]. Beneficial impacts have been noted for gastrointestinal disorders, functional bowel disorders, inflammatory bowel disease and ulcerative colitis, diarrhea, cardiovascular disorders, cancer, hepatic function, metabolic conditions including obesity/diabetes, lipid metabolism, neuropsychiatric disorders (depression and anxiety), chronic fatigue syndrome, autism, psychoneuroimmunity, and neurodermatology, immune function (incl. immunomodulation/ inflammation), allergies and, autoimmune disorders[46](Figure 4). In Chronic Kidney Disease the gut microbiome has been shown to be altered [47-50].
Figure 3: Comparison of the Human Genome and Gut Microbiome

The microbiota can be viewed as a metabolic organ exquisitely tuned to our physiology that performs functions we have not had to evolve on our own.


Figure 4: Diseases influenced by gut microbiota
Gut Dysbiosis, Leaky Gut Syndrome, Small Bowel Bacterial Overgrowth (SBBO) or Small Bowel Intestinal Over (SIBO) growth:

With the recent research and knowledge gained from it, Enteric Dialysis® is transforming from a concept to reality, and can potentially provide a promising future for those with Chronic Kidney Disease (CKD) with standard care of therapy.

Due to the expanded understanding of the complexity of the gut microbiome, it is evident that CKD patients have a distinctly altered microbiome composition [47]. This altered composition is commonly known as dysbiosis. Dysbiosis can be explained as an imbalance of beneficial and pathogenic microbes. An individual with dysbiosis will have higher quantities of pathogenic microbes and lower quantities of beneficial microbes. Dysbiosis will cause impairment in the epithelial barrier, and structure and function of epithelial tight junctions. This is commonly known as “leaky gut syndrome” and is related to almost all gut diseases [27]. CKD causes dysbiosis; the pathogenic bacteria convert urea into ammonia, and generate several other toxins. This disrupts enterocyte tight junctions, resulting in translocation of bacteria and toxins into circulation [48-50]. Once in circulation, the bacteria and toxins cause systemic chronic inflammation. Small Bowel Bacterial Overgrowth (SBBO) is a condition describing the growth of large numbers of bacteria in the small intestine [51, 52]. Dr. Simenhoff and his fellow researchers were the first to report SBBO in dialysis patients [13]. Dr. Simenhoff attributed SBBO to increased toxicity due to the production of various amines like methylamine, dimethylamine, N, N-nitrosoamine, trimethyl amine, and trimethylamine-oxide. The researchers also showed that biomodulation of the toxic and nutritional effects of small bowel bacterial overgrowth in end-stage kidney disease using freeze-dried Lactobacillus acidophilus [12].

A study published in 2004, showed that SBBO is also a common cause of chronic diarrhea [53]. Already established common causes of chronic diarrhea include inflammatory bowel disease, irritable bowel disease, celiac disease, giardiasis and idiopathic secretory diarrhea. In this study involving 87 subjects, the cause of chronic diarrhea SBBO was found in 48% of those with chronic diarrhea.

While the large intestine typically harbors a high number of bacteria, the small intestine does not. Too many bacteria living in the small intestine (SBBO) will metabolize nutrients that would otherwise be utilized by the host. The breakdown of these nutrients in the small intestine can also damage the intestinal lining making it more difficult for the host to absorb nutrients. This can result in malnutrition, loss of body mass, increased inflammation/oxidative stress and ultimately resulting in poor quality of life among CKD patients.

There are two tests commonly used to diagnose SIBO, one is to perform anaerobic and aerobic colony counts of small intestine luminal contents [54]. The other test is a breath test, which measures small bowel bacterial contamination indirectly [55]. The breath tests are more popular and rely on the recovery and quantification of gas produced by bacteria living in the small bowel. Subjects will ingest substrate, and the gas produced by the breakdown of said substrate by bacteria (which is exhaled) is analyzed via gas chromatography to measure exhaled hydrogen and/or methane [56-58]. While the breath test is easy to perform it is difficult to interpret, lactulose or glucose hydrogen breath tests are the most common. Proof of SIBO is said to be found when hydrogen concentrations are greater than 10 parts per million after a 50 gram glucose load [59].
**Chronic Kidney Disease:** General awareness of the rising global prevalence of kidney disease has been steadily growing among medical and public health professionals [60-62]. Kidney disease is the eighth leading cause of death in the U.S. [63], with approximately 600,000 patients in end-stage renal disease (ESRD, most receiving dialysis) and over 26 million in earlier stages of chronic kidney disease (CKD) [64]. As the population continues to age and the epidemiological shift from acute infectious to chronic metabolic diseases progresses, contributing factors to kidney disease (obesity, diabetes, and hypertension) become epidemic. Kidney disease may turn into a major health crisis in the USA and globally. Existing worldwide statistical data on the incidence and prevalence of kidney disease and kidney failure, the resulting mortality, the high cost of treatment, and associated socioeconomic and political consequences present a compelling and urgent need for an effective, easy to use and affordable alternative adjunct treatment modality to be available to the global kidney patient population. A latest research by the George Institute for Health published in the Lancet [65] shows that every year over two million people globally die as they do not have access to treatment for kidney failure (dialysis or transplantation). Despite ongoing R&D drug developments by several pharma/biotech firms, the use of dietary supplements is also a promising and inexpensive approach and should be included in any strategy to reduce the likelihood of such epidemic CKD crisis.

**The Uremic syndrome:** It is said to consist of nitrogenous waste retention, deficiency in kidney derived hormones such as erythropoietin and vitamin D (anemia and renal osteodystrophy) and the enzyme renin, and reduced acid excretion with acidosis. Untreated uremia may progress to coma and eventual death. Toxicity due to the accumulation of various uremic toxins (recent findings and literature reports to include Indoxyl Sulfate and para-Cresyl Sulfate, in particular) is a concern for CKD and ESRD patient populations. Concentrations of uremic solutes have been shown to increase as the disease progresses from CKD to ESRD [66, 67]. The European Toxin workgroup (EUTOX) has classified many uremic toxins based on their molecular weights and their protein binding property [68]. Though urea is generally nontoxic, it can degrade to the highly toxic cyanate, which, in turn, binds to proteins by carbamylation, including serum albumin, and modifies them. Recent studies by Berg et al. [69] have shown that carbamylated serum albumin is a risk factor for mortality in patients with kidney failure. As early as 1998, it was shown that CKD patients are at a higher risk of cardiovascular problems. The renal axis has a role to play in the blood pressure [70]. Death due to cardiovascular disease is higher by 10 to 20 times in these patients as compared with the general population [71]. Increased levels of uremic toxins also cause dysregulation of the Gut Microbiome (Dysbiosis) which in turn promotes inflammation and oxidative stress. This further accelerates the progression of CKD symptoms including progressive decline of the GFR to End Stage Renal Disease requiring dialysis. Therefore, some believe it to be necessary to reduce the levels of urea in chronic renal failure patients by medication or other interventions and strategies, such as a probiotic therapy (some representatives of the lactic acid bacteria population have the capacity to metabolize urea). Probiotics and prebiotics have for centuries been reported to enhance intestinal health [72]. Scientific proof has now been obtained that confirms their positive effects on human health in general [73]. Recently, the application of probiotics/prebiotics in various diseases has intensified, as understanding of how the gut microbiota shapes human health and how their composition changes significantly in any disease conditions and, more so, in CKD progression [74-78] (Figure 5).
The Gut Kidney Axis:

As mentioned earlier, the dysbiosis seen in CKD patients has been known for several decades as well as its role in metabolic disturbances in CKD. CKD stages III-V (ESRD) are complicated further by alterations in bowel microbes throughout the gastrointestinal tract. Advancing CKD brings advanced dysbiosis in the gut thus leading to higher concentrations of urea, uric acid, oxalate, creatinine and other toxins. Some of these “other toxins” are produced by pathogenic bacteria residing in the gut, which results in disruption of the epithelial lining and systemic inflammation. In addition to causing several physiological issues, these other toxins promote the growth of more harmful bacteria, accelerating the dysbiosis. Short Chain Fatty Acids (SCFAs) are important molecules for humans as they help to regulate inflammation and the immune system. When a state of dysbiosis is achieved, lower levels of SCFAs are produced, thus helping to facilitate a chronic state of inflammation and decrease immune system function. As a result of dysbiosis, restrictive diets and medication, people with CKD suffer from GI conditions frequently [47, 79, 80]. In an effort to combat dysbiosis, Dr. Ranganathan and his research team have developed a probiotic/prebiotic formulation known as Renadyl™. Renadyl™ has undergone a pharmaceutical like validation in in vitro models, animal models (rats, mini-pigs, cats, and dogs) [81-84], and three clinical trials in humans (CKD III and IV, and Dialysis patients). These studies have shown that Renadyl is able to metabolize and remove uremic toxins [85-90] in patients with various stages of CKD. While microbiome composition studies have not been completed in human models, three customer surveys have been carried out so far. Improved quality of life has been seen in customers using Renadyl (figure 6) [91, 92] and, in the most recent survey given to Renadyl users, 88% of survey respondents indicated that Renadyl had improved their overall quality of life [93].
Quality of life in customers using Renadyl Treatment modalities for CKD:

In CKD patients there are profound changes in the colonic structure and function resulting in abnormal generation and absorption of toxins, dysbiosis, impaired epithelial disarray and as well SBBO. Generally most of these patients are treated with one or more distinct drug therapies such as antibiotics, EPO, Vit D, ACE drugs or ARB inhibitors, K or P binders, diuretics etc., to address the corresponding symptoms. Dietary changes are also recommended. A supplement called ketoacids is one of the dietary supplements recommended. These supplements provide protein without overloading the diseased kidneys with too much phosphorus or urea that would come from foods. However, in the United States, these supplements are expensive and not routinely covered by insurance companies. Likewise it is also quite expensive for CKD patients who have little or no financial resources worldwide. Another treatment to remove uremic toxins is by using an adsorbent called kremezin or AST-120. Oral charcoal sorbents like AST-120 (9 gm/day, about USD$270/ month supply), manufactured by Kureha Chemical Industry Co. Ltd. and marketed as a drug under the brand name Kremezin is being used mainly in Japan and has been reported to have mixed clinical findings in other countries. AST-120 has little affinity for urea but does bind with uric acid, creatinine, indole and phenol metabolites. In addition, it also possesses the negative impact in binding to several of the drugs that most of the CKD patients consume every day. AST-120 is a specially coated charcoal and possesses similar properties of activated charcoal in binding characteristics to scores of aromatics, steroidal and heterocyclic compounds. Table 5 shows a comparison of both treatment modalities and pro/prebiotics.

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2015</th>
<th>2017*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of Three Consecutive Biennial Customer Survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Surveys Sent</td>
<td>998</td>
<td>834</td>
<td>600</td>
</tr>
<tr>
<td>Number of Respondents</td>
<td>147 (14.7%)</td>
<td>168 (20.1%)</td>
<td>214 (35.6%)</td>
</tr>
<tr>
<td>Breakdown of Respondents</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Respondents in ESRD (%)</td>
<td>17%</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>Respondents in CKD III and IV (%)</td>
<td>57%</td>
<td>58%</td>
<td>73%</td>
</tr>
<tr>
<td>Respondents indicating Renadyl improved quality of life (%)</td>
<td>73%</td>
<td>72%</td>
<td>88%</td>
</tr>
<tr>
<td>GFR Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average change in GFR since taking Renadyl</td>
<td>.**</td>
<td>.**</td>
<td>3.5 mL/min/1.73m²</td>
</tr>
</tbody>
</table>

Table 5: Comparison of treatment modalities and pro/prebiotics.
Table 5: Comparison of different treatments for reduction of uremic toxins

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Application/Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacids</td>
<td>Provide essential amino acids</td>
<td>Expensive. Not covered by insurance</td>
</tr>
</tbody>
</table>
| Kremezin      | Binds to Uric acid, creatinine, phenoles and indoles.  
**Does not bind to Urea** | Dosage 9g/day. Cost $270/month. Can bind to many other aromatic, steroidal and heterocyclic compounds including drugs. |
| Pro/Prebiotics| Restore gut balance. Reduce production of some toxins.  
Metabolize some uremic toxins. Safe and well tolerated. | Large number of RCT needed to get statistically significant data.          |

Concept of “Enteric Dialysis® - Addressing the causes and not the symptoms:

The kidney/s is a single organ system possessing three distinct functions. These are: secretory (hormonal), regulatory (homeostasis) and excretory (urinary elimination). The currently existing drug interventions address only the individual deficiencies on the pathophysiology and biochemical functions of the kidney. These three functions are in a dynamic equilibrium in any healthy individual, and so is the Gut Microbiome with trillions of microbes.

Using Probiotics and Prebiotics: Probiotics, prebiotics and their combination termed as synbiotics could also play a role in reducing the generation and elimination of uremic toxins, more so in conjunction with standard care of therapy according to individual CKD patient, nutritional needs and disease conditions. The modulation of the intestinal microbiota composition with the use of probiotics/prebiotics could potentially minimize the deleterious effects of its imbalance, thereby improving the health of the gastrointestinal tract, strengthening the immune system, restoring the bioavailability of micronutrients, exerting anti diabetic actions, improving dyslipidemia and allergic disorders, and reducing the risk of other health problems. The mechanism by which probiotics exert their favorable effects seems due to direct utilization of several uremic toxins as its nutrients for the gut microbial growth with its inherent capabilities of multiplying and doubling every 20 to 25 minutes. The increased growth of these gut microbes are then eliminated by the natural defecation process which has been referred to as “Enteric Dialysis” in this chapter. In addition, the probiotics change the intestinal pH, inhibits the growth of pathogens (through the production of antibacterial compounds, competitive exclusion of pathogens in receptor binding sites and competition for available nutrients), and suppression of mutagenic and carcinogenic processes and ultimately affords protection of the intestinal/gut barrier. Despite several reported observational or pilot scale/small scale studies, quality intervention trials investigating this novel treatment in CKD are still lacking for its full clinical validation. Hence, a well-designed RCT protocol with the power needed for subject enrollment and statistical significance changes in defined primary or secondary end points are needed. The published studies and, as well the proposed “SYNERGY” [94] clinical trials are aimed to assess the effectiveness of synbiotics (co-administration of pre- and probiotics) as a potential treatment targeting the synthesis of uremic toxins, specifically, indoxyl sulfate (IS).
and p-cresol sulfate (PCS). These and other biomarkers evaluated like doubling of the serum creatinine has been re-evaluated and being proposed with the general acceptance of GFR decline as an end point for clinical trials in CKD. The earlier end point “doubling of serum creatinine” is a late event in several CKD patients and also subject to several of the aforementioned variable subject matters discussed. It is also subject to enrolled patients primary disease status, diet, life style and several other factors including genetic makeup and dysbiosis of the gut Microbiome. This also requires a long time of follow-up and large sample size in clinical trials. Thus, there is a great interest in alternative GFR-based end point to shorten the duration of clinical trials, reduce sample size, and extend their conduct to patients with earlier stages of CKD.

**Possible pathways or mechanism of “Enteric Dialysis®”**

**The probiotic strains in Renadyl work in the gut by three distinct mechanisms**

(Figure 7):

1. All three strains in Renadyl produce bacteriocins namely lactacin and bisin which inhibit the growth of pathogenic bacteria [4-6]. This, in turn, leads to reduced generation of gut related uremic toxins. Secondly, it also reduces small intestinal bacterial overgrowth (SIBO) in renal failure patients [12, 13].
2. The three strains metabolize various uremic toxins thus reducing the burden on the failing kidneys. *S thermophilus* metabolizes urea, uric acid and creatinine. *L acidophilus* metabolizes uric acid and also decreases production of dimethylamine, trimethylamine, TMAO and nitrosamines. *B longum* metabolizes creatinine and reduces levels of protein bound uremic toxins like phenols and cresols [87-89].
3. These strains also modulate inflammation in the gut. They lower the levels of pro-inflammatory bio markers like IL-1β, and C-reactive protein and also IL-6 and TNF-α and up regulate the levels of anti-inflammatory markers like IL-10 [7-11].

Figure 7: Possible pathways for Renadyl’s action
**Drug like validation of a dietary supplement:**
Probiotics and Prebiotics are widely used for digestive and immune health. Renadyl™, a Pro/Prebiotic dietary supplement has demonstrated its potential to reduce serum uremic toxins in a drug like validation with in vitro (Lab and SHIME), animal studies (5/6th nephrectomized rats, minipigs, cats and dogs) [81-84] and human clinical trials [85-90].

**Routine Dialysis Versus the concept of “Enteric Dialysis”:** Previous research has suggested that longer dialysis sessions can provide benefits without increasing the risks of complications [95-97]. However, some nephrology professionals find this view highly debatable. (http://kidney.niddk.nih.gov/about/ResearchUpdates/KidneyWin13/1.aspx). The controversy centers on the invasive nature of hemo/peritoneal dialysis that has significant potential for causing greater infections and higher mortality, particularly when sessions are frequent. However, the use of a well-researched, clinically documented and safe probiotic/prebiotic dietary supplement formulation has the potential to safely perform continuous 24/7 uremic toxin removal and stabilize the gut Microbiome and its dysbiosis. Table 6 and figure 8 show the advantages of Enteric Dialysis with standard care of therapy.

Table 6: Benefits of Enteric Dialysis over hemo and peritoneal dialysis:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Dialysis Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peritoneal</td>
</tr>
<tr>
<td>Surgical procedure needed</td>
<td>Y</td>
</tr>
<tr>
<td>Invasive</td>
<td>Catheter</td>
</tr>
<tr>
<td>Chances of Infection</td>
<td>Y</td>
</tr>
<tr>
<td>Dietary restrictions</td>
<td>Y</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Figure 8: Benefits on adding Renadyl™ with standard care of therapy in Pre-dialysis and Dialysis patients.
New end points proposed for CKD clinical trials [US FDA/NKF]:

Enteric Dialysis is safe and well tolerated. It is non-invasive and less expensive. Hemo/Peritoneal Dialysis are unable to reduce protein bound uremic toxins like indoles and cresols and other middle molecules. It is painful and associated with poor quality of life (yo-yo effect) and blood associated infections like Hepatitis C. Imbalanced gut microflora is not restored and gut associated uremic toxins are produced. Renadyl™ on the other hand, by removing uremic toxins, reducing levels of protein bound uremic toxins, production of bacteriocins to restore gut imbalance and reducing inflammation, provides benefit to patients in all stages of pre dialysis and dialysis and with a variety of comorbid conditions. It appears to have a stabilizing effect on the overall health status and improved quality of life (QoL).

We also conducted three biennial customer surveys (2013, 2015 and 2017). The results of the first two surveys have been published [91, 92]. However due to HIPPA regulations we were unable to get the detailed medical records. In the recent 2017 survey, the customers voluntarily provided us with their eGFR before and after taking Renadyl. The data was analyzed independently by Prof Alan Weinberg at the Mount Sinai Health System in NY (http://www.mountsinai.org/profiles/alan-d-weinberg). Results show an increase of 3.5 mL/min/1.73m² which translates to an 11.6% improvement in GFR. [93]. The summary of this recent survey is shown in figure 9.

“The US Food and Drug Administration currently accept halving of glomerular filtration rate (GFR), assessed as doubling of serum creatinine level, as a surrogate end point for the development of kidney failure in clinical trials of kidney disease progression. A doubling of serum creatinine level generally is a late event in Chronic Kidney Disease (CKD); thus, there is great interest in considering alternative end points for clinical trials to shorten their duration, reduce sample size, and extend their conduct to patients with earlier stages of CKD. However, the relationship between lesser declines in GFR and the subsequent development of kidney failure has not been well characterized. The National Kidney Foundation and Food and Drug Administration sponsored a scientific workshop to critically examine available data to determine whether alternative GFR-based end points have sufficiently strong relationships with important clinical outcomes of CKD to be used in clinical trials. Based on a series of meta-analyses of cohorts and clinical trials and simulations of trial designs and analytic methods, the workshop concluded that “a confirmed decline in estimated GFR of 30% over 2 to 3 years may be an acceptable surrogate end point in some circumstances, but the pattern of treatment effects on GFR must be examined, specifically acute effects on estimated GFR. An estimated GFR decline of 40% may be more broadly acceptable than a 30% decline across a wider range of baseline GFRs and patterns of treatment effects on GFR. However, there are other circumstances in which these end points could lead to a reduction in statistical power or erroneous conclusions regarding benefits or harms of interventions. We encourage careful consideration of these alternative end points in the design of future clinical trials” [98].
Summary and Conclusions:

A marker of dialysis adequacy in the eighties of last century, Kt/V (urea) helped to improve dialysis efficiency and to standardize the procedure. However, in 2015 Vanholder [99] based on various clinical studies and modifications of dialysis concluded that Kt/V (urea) is too simple a concept for the complexities of uremia and today’s dialysis. However, clinical research after 2015 showed that urea had an important role to play in diabetes [100] and a study at the Albert Einstein College of Medicine NY showed that elevated serum levels of BUN was associated with an increased burden of coronary artery disease on cardiac catheterization [101]. This led back to the importance of urea in renal failure with a publication again by Vanholder in 2017 [102] titled “Urea and chronic kidney disease: the comeback of the century? (in uraemia research)”. Therefore, the use of a well-researched, clinically documented and safe probiotic/prebiotic dietary supplement formulation has the potential to safely perform continuous 24/7 uremic toxin removal and stabilize the gut Microbiome and its dysbiosis. Hence, the concept of “Enteric Dialysis” with continuous removal of uremic toxins may be the key to reducing the GFR by at least 30 to 40% assuming that standard patient care and therapeutic regiments are maintained. Several additional multi-site clinical trials are needed to document US FDA’s recently accepted 30% to 40% reduction in GFR and to document the delayed progression of CKD in various randomized clinical trial (RCT) interventional studies. In summary, probiotics and prebiotics offer safe, inexpensive, convenient adjunctive therapy for the care of CKD patients worldwide. By modulating the gut Microbiome, probiotics and prebiotics also possess an attractive potential to reduce inflammation with the ultimate outcome of an improved quality of life for CKD patients worldwide.

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