Use of Probiotics in Kidney Disease

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State of Affairs- Kidney Disease and Nutrition

• Current (most basic) nutrition therapy for kidney disease:
  – Phos/ calcium/ PTH/ vit D balance for bone/ heart health
  – Protein- to prevent malnutrition, reduce burden on kidneys, improve albumin
  – Sodium and fluid restriction for HTN management/ fluid overload
  – Renal vitamin- to support immune system, replace nutrients lost through dialysis, prevent micronutrient deficiency due to limited diet choices
  – Potassium restriction- prevent hyperkalemia
  – Weight management esp for transplant
  – Blood sugar management- for those with DM
State of Affairs- Kidney Disease and Nutrition

• What is not typically being addressed?
  – Inflammation
  – Digestive issues (poor appetite, constipation etc)
  – Nutrition quality of life
  – Metabolic acidosis
  – Fiber intake

WHY?
Why are these other aspects of nutrition and kidney disease not being addressed?

- High patient:RD ratio = lack of time
- No support from Dr or IDT or patient
- Lack of RD training (decreased awareness or ability or how to help or assess)
- Inadequate resources (RD or Patient education materials, supplements, finances etc)
- Lack of evidence-based recommendations
- Misconceptions (too expensive, not effective etc)
Objectives

1. Discuss kidney-gut axis
2. Review evidence and potential benefits of probiotics
3. Apply knowledge to practice
The Kidney-Gut Axis

The emerging role of gut health in kidney disease
Kidney-Gut Axis- Relationship Status

- There is a growing interest in the relationship between probiotics/ gut health and kidney disease.
  - A Pubmed search of “probiotics and kidney disease”
    - 2012-2019 – 208 results
    - 1999-2011- 72 results

Why the growing interest?

The reason most relationships get attention:

Sadly because they are a mess

Instead of being called KidGut- we call it kidney-gut axis
Kidney-Gut Axis: Relationship Status

• Digestive issues are common in those with kidney disease
  – Constipation\(^1,\)\(^7\) (63% in HD patients compared to 20% in healthy population\(^1\))
  – GERD (50% in HD patients\(^2\) compared to 28%\(^3\) in general population)
  – Increased transit time\(^1\)
  – Impaired protein digestion\(^1,\)\(^9\)
  – Dysbiosis\(^1,\)\(^4,\)\(^5,\)\(^6\)
  – Leaky gut/ increased gut permeability\(^4,\)\(^5,\)\(^6,\)\(^7,\)\(^8\)
Kidney-gut Axis: Relationship Status

- The gut microbiome is its own ecosystem containing more than 100 trillion bacteria.\textsuperscript{10,11}
- A healthy individual has a rich diversity of bacteria within the gut, with the largest amount of bacteria occurring in the colon.\textsuperscript{10,11}
- There are two main types of bacteria: saccharolytic and proteolytic\textsuperscript{1,11}
Kidney-Gut Axis: What do these bacteria do?

Saccharolytic bacteria:
- primarily ferment carbohydrates (resistant starches) which produces beneficial end products such as short chain fatty acids (which support the growth of intestinal cells)\textsuperscript{1,4,12}
- Synthesize vitamins, amino acids\textsuperscript{11,5,13}
- Maintain intestinal barrier\textsuperscript{11,6,13}
- Improve immunity\textsuperscript{12}
- Compete with pathogenic bacteria for space\textsuperscript{13}

Proteolytic bacteria:
- primarily ferment (putrefy) protein which produce ammonia, amines, thiols, phenols and indoles\textsuperscript{1,8,14}
- Phenols and indoles are converted to pro-inflammatory toxins like P-cresyl sulfate (PCS) and indoxyl sulfate (IS) and are of particular interest in CKD\textsuperscript{8,14}
- These end products are eliminated primarily through the kidney and rise with a decrease in GFR\textsuperscript{8,14}
Kidney-Gut Axis: The Intestinal Barrier

• Technically, the digestive system is on the outside of the body, so the intestinal barrier is a mechanical barrier to control what comes inside the body
  – It consists of an epithelial layer along the intestinal lumen which contains a mucus layer, antimicrobial proteins, antibacterial lectins and defensins.\textsuperscript{15,16}
  – This barrier prevents an immune response from the body acting on the microbiota, bacteria translocation (bacteria moving from one part of the intestine to another or into the blood stream) and prevents absorption of toxins and pathogens into the blood stream.\textsuperscript{16}
  – Tight junctions between intestinal cells selectively allow nutrients to be absorbed\textsuperscript{13,16}
Kidney-Gut Axis: Relationship Status

Intestinal barrier function - Tight junctions

- Tight junctions connect adjacent intestinal cells to each other.\textsuperscript{13,16}
- These are what allow the intestinal barrier to be selective about what is absorbed. Tight junction permeability is different throughout the intestine.\textsuperscript{13,16}

Healthy intestinal layer and tight junctions\textsuperscript{12}
Kidney-Gut Axis- What does the CKD gut look like?^{17}

How CKD alters the gut^{17}

- Co-morbidities
- Medications
- Dietary (anorexia, low fiber)
- Constipation

↓ Motility
↓ Protein digestion
↓ Absorption (edema)

↑ Proteolytic bacterium flora
↑ Toxin generation (NH₃/NH₄⁺, amines, thios, indoles, p-cresol)

↑ Cytokine production, ↑ half-life
↓ Cytokine elimination

↑ Cytokines
↑ Uremic toxins
Endotoxemia

Mucosal injury
Translocation (bacteria, toxins)
Inflammation (cytokine release)
Immune suppression
Impact of CKD on intestinal barrier and microbiota

Figure 3. How CKD impacts the gut microbiome. Adapted from Sabateino et al.7
Kidney-Gut Axis: Relationship Status

Factors in CKD that contribute to dysbiosis$^{9,15}$

• Metabolic acidosis
• Volume overload with intestinal wall congestion (↑ cytokines and endotoxins= ↑ inflammation)
• Antibiotic, oral iron, and anti-GERD- promote bacterial overgrowth
• Intestinal ischemia (vascular calcification)
• Low potassium diet and therefore low fiber diet- decreased fuel for saccharolytic bacteria$^{1,5,9}$, prolonged transit$^{1,2,9}$
• High protein diet combined with impaired digestion and increased proteolytic bacteria activity = increased production of uremic solutes- p-cresol sulfate and indoxyl sulfate
Kidney Gut Axis: Increased intestinal permeability

- Malnutrition- decreased intestinal cell turnover contributes to breakdown of tight junctions. Decreased fuel for bacteria causes breakdown of mucosal layer
- Uremia contributes to dysbiosis which contributes to inflammation which also compromises tight junctions
- Proteolytic bacteria increase ammonia production= intestinal pH change (decreasing friendly bacterial growth) and increasing inflammation= uremic enterocolitis
- Hypervolemia/ aggressive ultrafiltration - contributes to intestinal ischemia depriving intestinal cells of oxygen and increasing endotoxins and cytokines

Damaged intestinal layer and tight junctions
Kidney-Gut Axis: Relationship Status

- **Uremia**
  - Impairs intestinal barrier function and encourages intestinal inflammation\(^\text{15}\)

Figure 1 | Hypothetical concept about how a failing kidney and the intestinal microbiota affect each other. (Left part) Under physiological conditions, the predominance of symbiotic bacteria, an intact intestinal barrier, defensins production, mucus integrity, and immunoglobulin A (IgA) secretion support the symbiosis between the host and its gut microbiota. An intramural innate immunity controls pathobiont overgrowth inside the lumen of the intestinal tract. (Right part) The metabolic changes that are associated with the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD) change the balance of symbionts and pathobionts in a way that favors pathobiont overgrowth, that is dysbiosis. Pathobiont overgrowth induces inflammation and loss of barrier function that in turn promotes increased translocation of bacterial components and even living bacteria into the host's internal environment. This process will activate innate immunity characterized by production of proinflammatory cytokines that define a state of systemic inflammation. This process potentially modulates a number of clinically relevant processes in CKD such as the progression of CKD, accelerated atherogenesis, and protein wasting.
Dysbiosis and increased intestinal permeability are at the root of many unaddressed nutrition-related issues in those with kidney disease.

Is there evidence to support the use of probiotics to address these nutrition-related issues?
Review evidence and potential benefits of probiotics

Are probiotics a viable form of therapy in kidney disease?
The Evidence

Hierarchy of Evidence\textsuperscript{20}

Meta-analysis of RCTs
Systematic review of RCTs

Individual RCT

Observational Studies Patient-important outcomes

Basic Research Test tube, animal, human physiology

Clinical Experience

Model for Evidence-Based Decision-Making\textsuperscript{20,21}

Evidence

Patient values and preferences

Clinical Expertise

Resource issues

Healthcare provider values and preferences
The Evidence

Probiotics

- Digestive symptoms
- Dysbiosis/leaky gut
- Uremia
The Evidence

Definitions-

• **Probiotics**—“living organisms in food and dietary supplements that, upon ingestion, can improve the health of the host beyond their inherent basic nutritional content.”

  6

• **Prebiotics**—“Non-digestible food ingredients that stimulate the growth and/or activity of bacteria in the GI.” 6 (promote saccharolytic bacteria activity)

• **Synbiotic**—product with pro- and prebiotics combined 6
Method:
Excluded animal and *in vitro* studies (unless specifically relevant).
Prioritized meta-analysis, systemic (including Cochrane) reviews, and RCTs. A total of 70 studies were reviewed.

<table>
<thead>
<tr>
<th>Gastrointestinal Disorder</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Travellers' Diarrhoea</strong></td>
<td>A selective benefit of <em>S. boulardii</em> and a mixture of <em>L. acidophilus, B. bifidum, L. bulgaricus</em> and <em>S. thermophilus</em> probiotics as prophylaxis of travellers' diarrhoea. <em>S. boulardii</em> may be useful in treating travellers' diarrhoea where other medical treatments have failed.</td>
</tr>
<tr>
<td><strong>Irritable Bowel Syndrome</strong></td>
<td>A mixture of bacterial strains including lactobacillus and bifidobacteria may be the most effective in IBS collective symptoms with a good safety record and are thus appropriate for therapeutic trial in holistic IBS therapy.</td>
</tr>
<tr>
<td><strong>Inflammatory Bowel Syndrome</strong></td>
<td>Probiotics, especially those containing multiple strains can maintain remission in ulcerative colitis and also demonstrate efficacy in pouchitis. There is currently no evidence for probiotics in Crohn’s disease.</td>
</tr>
<tr>
<td><strong>C. difficile and antibiotic associated diarrhoea</strong></td>
<td>Lactobacillus species appear to be the most effective in preventing <em>C. difficile</em> infections.</td>
</tr>
<tr>
<td><strong>Lactose intolerance</strong></td>
<td>There is benefit from taking probiotics in lactose intolerance. There is most evidence for <em>L. rhamnosus</em> and <em>bifidobacterium</em>, often in combination.</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>Probiotics, mainly lactobacillus and bifidobacteria, have a beneficial role in the care of patients with diarrhoea associated with chemotherapy and radiotherapy.</td>
</tr>
</tbody>
</table>
### TABLE 1. Recommendations for Probiotic Use: Update 2015

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Effectiveness</th>
<th>Specific Strain of Organism and Strain References</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious childhood—treatment</td>
<td>A</td>
<td>LGG, Saccharomyces boulardii, Lactobacillus reuteri SD2112</td>
<td>27-30</td>
</tr>
<tr>
<td>Prevention of infection</td>
<td>B</td>
<td>S. boulardii, LGG</td>
<td>27,28,30</td>
</tr>
<tr>
<td>Prevention of AAD</td>
<td>A</td>
<td>S. boulardii, LGG, combination of L. casei DN114 G01, L. bulgaricus, snf Streptococcus thermophilus</td>
<td>31-33</td>
</tr>
<tr>
<td>Prevention of recurrent CDAD</td>
<td>B/C</td>
<td>S. boulardii, LGG, FMT</td>
<td>34-37</td>
</tr>
<tr>
<td>Prevention of CDAD</td>
<td>B/C</td>
<td>LGG, S. boulardii</td>
<td>34,37</td>
</tr>
<tr>
<td><strong>IBD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pouchitis</td>
<td>A</td>
<td>VSL#3</td>
<td>38-40</td>
</tr>
<tr>
<td>Preventing and maintaining remission</td>
<td>C</td>
<td>VSL#3</td>
<td>41</td>
</tr>
<tr>
<td>Induce remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ulcerative colitis</strong></td>
<td>B</td>
<td>Escherichia coli Nissle, VSL#3</td>
<td>42-44</td>
</tr>
<tr>
<td>Inducing remission</td>
<td>A</td>
<td>E. coli Nissle, VSL#3</td>
<td>43-45</td>
</tr>
<tr>
<td>Maintenance</td>
<td>C</td>
<td>E. coli Nissle, S. boulardii, LGG</td>
<td>46-48</td>
</tr>
<tr>
<td><strong>IBS</strong></td>
<td>B</td>
<td>Bifidobacterium infantis B5624, VSL#3</td>
<td>49-53*</td>
</tr>
<tr>
<td>C</td>
<td>B. animalis</td>
<td>L. plantarum 299V</td>
<td>54</td>
</tr>
<tr>
<td><strong>Necrotizing enterocolitis</strong></td>
<td>B</td>
<td>L. acidophilus NCDO1748, B. bifidum NCDO1453</td>
<td>56,57</td>
</tr>
<tr>
<td><strong>Recommendations from 2008†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune response</td>
<td>A</td>
<td>L. rhamnosus GG, L. acidophilus LAFT1, L. plantarum, B. lactis, L. johnsonit</td>
<td>58,59</td>
</tr>
<tr>
<td><strong>Allergy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic eczema associated with cow’s milk allergy</td>
<td>A</td>
<td>LGG, B. lactis</td>
<td>59</td>
</tr>
<tr>
<td>Treatment</td>
<td>A</td>
<td>LGG, B. lactis</td>
<td>59</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td>C</td>
<td>VSL#3, L. acidophilus</td>
<td>60,61</td>
</tr>
<tr>
<td><strong>Vaginosis and vaginitis</strong></td>
<td>C</td>
<td>L. acidophilus, L. rhamnosus GR-1, L. reuteri RC14</td>
<td>62-64</td>
</tr>
<tr>
<td><strong>Recommendations from 2015</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>A</td>
<td>VSL#3</td>
<td>8–12</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>C</td>
<td>VSL#3, combinations of L. plantarum, L. delbrueckii, L. bulgaricus, L. acidophilus, L. rhamnosus, B. bifidum, S. thermophilus, B. longum</td>
<td>8,9,13,15,16</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease in children</td>
<td>C</td>
<td>VSL#3, LGG</td>
<td>17</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>C</td>
<td>VSL#3, LGG, L. acidophilus, L. bulgaricus, B. bifidum, R. longum with oligosaccharides</td>
<td>8–17</td>
</tr>
</tbody>
</table>

*Guandalini et al* was made available after the workshop meeting on April 8, 2011, but believed to be significant enough to qualify this probiotic to be in a B category.

†Check 2008 references for further elaboration on strains used and their availability.

AAD indicates antibiotic-associated diarrhea; CDAD, *Clostridium difficile*-associated diarrhea; FMT, fecal microflora transplant; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LGG, *Lactobacillus GG*. 

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**ADDENDUM**

- Table 2: Additional recommendations for probiotic use.
- Table 3: Comparison of probiotic effectiveness across different clinical conditions.
- Table 4: Case studies illustrating successful probiotic treatments.

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**REFERENCES**

Clinical Guide to Probiotic Products

Available in the United States: 2016 Edition
Indications, Dosage Forms and Clinical Evidence to Date

Author: Dragana Skokovic-Sunjic BScPhm RPh NCMP
Reviewers: Dr Vivien Brown MDCM CCP FCFP NCMP, Dr Bradley C. Johnston PhD, Iris Krawchenko BScPhm RPh ACPR, Dr John Marshall MD MSc FRCPG AGAF, Dr Earnest Quigley MD FRCP FACP PMAG FRCPI, Dr Tom Smiley BScPhm PharmD
Medical Editor: Ivana Sunjic MSc

FILTER BY:

AGE/GENDER
- [ All ]

INDICATION
- [ All ]

BRAND NAME
- [ All ]

INDICATION FOR ADULT HEALTH

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Probiotic Strain</th>
<th>Dosage Form</th>
<th>CFU/Dose</th>
<th>No of Doses/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align®</td>
<td><em>B. longum</em> infants 35024</td>
<td>Capsule</td>
<td>1B/capsule</td>
<td>1 capsule</td>
</tr>
</tbody>
</table>
Many studies show support in using probiotics to improve integrity of the intestinal barrier\textsuperscript{34,35}

However, probiotics are usually not sufficient to promote complete healing. Other nutrients, diet changes and lifestyle changes may be required. The 5R protocol is a helpful therapeutic model\textsuperscript{10,32}
<table>
<thead>
<tr>
<th>Observed Benefit</th>
<th>Proposed Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Fecal vancomycin-resistant enterococci</td>
<td>Competitive colonization</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial production</td>
</tr>
<tr>
<td></td>
<td>↓ colonic pH</td>
</tr>
<tr>
<td>↑ Serum folate</td>
<td>↑ increased bacterial production of folate</td>
</tr>
<tr>
<td>↓ Serum uremic toxins:</td>
<td>↑ microbial metabolism</td>
</tr>
<tr>
<td>- Urea</td>
<td>Competitive colonization</td>
</tr>
<tr>
<td>- Uric acid</td>
<td>Antimicrobial production</td>
</tr>
<tr>
<td>- IS</td>
<td>↓ colonic pH</td>
</tr>
<tr>
<td>- PCS</td>
<td>↓ transit time</td>
</tr>
<tr>
<td>- Di-methylamine</td>
<td>↓ availability of substrate</td>
</tr>
<tr>
<td>↓ Serum phosphate</td>
<td>↓ colonic pH ↑ the ionization of Ca which bind with intestinal phos as an intrinsic binder</td>
</tr>
<tr>
<td>↓ serum triglycerides</td>
<td>↑ bacterial production nicotinic acid</td>
</tr>
<tr>
<td>↓ serum homocysteine</td>
<td>↑ bacterial production of B vitamins</td>
</tr>
<tr>
<td>↑ Quality of Life</td>
<td>↓ symptoms of uremia</td>
</tr>
<tr>
<td>↓ Urinary oxalate</td>
<td>↑ microbial metabolism of oxalate</td>
</tr>
</tbody>
</table>
The Evidence- Reducing uremic toxins

- Research is sparse and many studies are on rats. The human studies are small and of short duration
- Specifically looking at decreasing/changes in PCS, IS, uric acid, creatinine, BUN, and oxalates.
- Most comprehensive review to date (19 studies):

**Review Article**

**Pre-, Pro-, and Synbiotics: Do They Have a Role in Reducing Uremic Toxins? A Systematic Review and Meta-Analysis**

Megan Rossi,1,2,3 Kerenhaftali Klein,4 David W. Johnson,1,3 and Katrina L. Campbell1,2,3

Conclusion: “Altering the microbiota via pre-and/or probiotics is a potential treatment for reducing bacterial protein fermentation and therefore the generation of PCS and IS...”
Other papers reviewing studies in CKD populations show mainly positive results in decreasing uremic toxins, but more research is needed.\textsuperscript{6,8,9,15,37}

What do we do in the meantime?
Apply knowledge to practice

How to safely and appropriately use probiotics in kidney disease patients
Practical Application

• Use probiotics in a way that have been clinically proven.
• Use resources available to assess and better understand the whole picture of a patient’s health- not just their kidney needs
• Recognize that there are multiple ways to alter the gut flora to promote better outcomes in various areas for your patients.
Practical Application

• Safety of probiotics in those with kidney disease
  – All studies reviewed clearly state that risk associated with probiotic use is **LOW**\(^6,25,26,27\)
  – However, there is still *some* risk for probiotic sepsis\(^27\)
    • Major risk factors-
      – Immune compromise (including debilitated states or malignancy)
      – Transplant (although the little research there is inclined to support the use of probiotics)
      – Premature infants
    • Minor risk factors-
      – CVC (central venous catheter)
      – Impaired intestinal epithelial barrier (diarrheal illness, intestinal inflammation)
      – Administration of probiotic via jejunostomy
      – Concurrent use of antibiotic and probiotic- to which probiotic is resistant
      – Probiotics with high adhesion to intestine or known pathogenicity
      – Cardiac valvular disease (*Lactobacillus* only)

“We suggest that the presence of a single major risk factor or more than one minor risk factor merits caution in using probiotics.”\(^27\)
If testing is not available, there are other less specific ways to assess.

Figure 1. Probiotic Screening Tool

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you taken an antibiotic within the past 12 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you experienced constipation or diarrhea within the past 3 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you experience abdominal cramping a few hours after eating?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is abdominal pain relieved after passing gas?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you experience pain during bowel movements?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do your abdominal discomforts, constipation and/or diarrhea get worse with stress?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you frequently bloated?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you experience heart burn or burning in your stomach?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have trouble losing weight?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have food allergies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If your patient answers yes to 3 or more questions, there is a high likelihood of altered gut bacteria.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Other factors that might indicate a need for probiotics:
  – Low intake of fruits and vegetables/ low fiber\textsuperscript{31,40}
  – Frequent use of artificial sweeteners\textsuperscript{29,30}
  – Chronic stress\textsuperscript{10,31}
  – Alcohol use\textsuperscript{10}
  – Nutrient insufficiencies/ malnutrition\textsuperscript{7,10}
  – Iron supplementation\textsuperscript{7}
  – Diets high in refined carbohydrates\textsuperscript{31}
Practical Application- Recommending probiotics

• Option to recommend food or supplement
  – Factors to consider:
    • Need for specific or variety probiotic strains
    • Potassium and phosphorus level
    • Finances/availability
    • Patient preference (pill vs food)
    • Amount of probiotic needed for therapeutic benefit
Practical Application- Recommending probiotics

• Resources for specific GI issues/ products
• Each of these resources has a table with specific recommendations of amounts, strains, and/or products for various conditions
  – Clinical Guide to Probiotics (App or available online- free)
  – Yale University Workshop- 2015 update
  – Product Update- Journal of Renal Nutrition
For long term use of probiotics, it is best to rotate products to increase biodiversity and reduce chance of probiotic resistance. If using antibiotics, probiotics should be given at 2-4 hours apart from antibiotics. Most studies show benefits with 10 billion + live cultures or CFU’s. Some patients adjust better to probiotics if they start taking them every other day for the first week or two. Diet changes are key to provide maximum probiotic benefits.
Practical Application- Recommending probiotics

- Recommending probiotics for decreasing inflammation, reducing uremic toxins etc
  - There is not enough clinical evidence to be able to recommend any specific probiotic and expect any efficacy in using probiotics for ONLY these purposes at this time.
  - Only one product currently shows promise for reducing uremic toxins at this time- Renadyl by Kibow Biotech [http://www.renadyl.com/]
Possible Preventive or Therapeutic Measures in the Context of Uremic CVD

- Long slow dialysis, alternative time frames
- Convection
- Superflux
- Adsorption
- Probiotics
- Prokinetics
- Modify flora
- Diet
- Long slow dialysis, alternative time frames
- Careful application - Ca salts - Vitamin analogs
- Decrease Ca x P product
- Renagel
- New Vitamin D analogs
- Identify genetic predisposition
- Calcimimetics
- Calcitriol
- PTx
- Identify correct concentration for in vitro
- High throughput analysis
- Proteome analysis
- Decrease concentration responsible compounds
- Diminish intestinal uptake
- Enhance extracorporeal removal
- Decrease PTH
- Decrease inflammation
- Decrease metabolism
- Modify metabolism
- Regenerative medicine
- Drugs
- Folic acid
- Artificial liver
- Artificial tubule
- Vitamins C/E
- Scavengers
- Pure dialysate
- Biocompatible dialyzers
- ACEi
- Statins
- Aspirin
Practical Application- Support healthy bacteria

- Additional recommendations to support probiotics/ healthy bacteria
  - Increase fiber/ low potassium fruit and vegetable intake
    - Provides prebiotics for healthy bacteria, antioxidants, other anti-inflammatory factors
    - 10-50 g day has been used in prebiotic supplements, >5 g/day can influence gut microbiota, 15-20g needed to reduce uremic toxin concentrations.\(^ {33}\)
  - Use digestive enzymes as appropriate- esp if lower protein is not an option to improve protein digestion
  - Evaluate use of certain medications- such as long term use of anti-GERD medications
  - Increase healthy fat intake (omega 3) through supplements or food as appropriate
  - Reduce artificial sweetener/refined sugar use
  - Encourage healthy stress management
  - Correct nutrient deficiencies (use physical assessment if lab assessment is not available)
  - Those who present with impaired intestinal barrier/ leaky gut symptoms may benefit from 5 R program\(^ {32}\)
Practical Application- Pro’s and Con’s of Probiotic Foods

**Pros**
- Tend to have *significantly* higher amounts of probiotics
- Decreases pill burden
- Can be added to foods in place of less nutritious foods/condiments
- May contain other benefits that are unknown at this time
- Can make at home, which can be cost effective
- May have less diversity than a supplement

**Cons**
- Many probiotic foods are unappealing to those who like American food
- Probiotic foods can be high in potassium, sodium and phosphorus
- Some experts feel that fermented foods, since they are decaying foods, are actually not beneficial for health
- Liquids can limit some of the probiotic food options
- Probiotic options may be limited by dairy allergy or intolerance
- Making probiotic foods at home introduces an increased risk for foodborne illness
Practical Application- Prebiotics

Partial list of Prebiotics, Prebiotic Effect and Supplements/ Functional Food Products

<table>
<thead>
<tr>
<th>Fibers with prebiotic effects</th>
<th>Prebiotic effect</th>
<th>Supplement/ Food products containing prebiotic+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat dextrin</td>
<td>Increased bacteriocides</td>
<td>Benefiber, Equate Clear Soluble Powder</td>
</tr>
<tr>
<td>Inulin</td>
<td>Bifidogenic*</td>
<td>Benefiber, Luna bars, Clif bars, Builder’s bar, Kashi cereals, drink mixes and cereal bars, various Stonyfield Farms products</td>
</tr>
<tr>
<td>Acacia gum</td>
<td>Bifidogenic</td>
<td>Now Acacia fiber powder, GoLive probiotic &amp; prebiotic- (Contains 40mg K per serving)</td>
</tr>
<tr>
<td>Psyllium</td>
<td>Prebiotic potential^</td>
<td>Metamucil (Contains 30mg K per serving), various brands of psyllium husk capsules or powders</td>
</tr>
<tr>
<td>Fructooligosaccharides</td>
<td>Bifidogenic</td>
<td>Skinny Cow low-fat ice-cream sandwiches, ZonePerfect shakes, Ensure fiber, various products from Horizon Organic</td>
</tr>
</tbody>
</table>

* Increases bifidobacteria growth  
^ This table is simply identifying products that contain certain prebiotic, not making claims as to the effects of the particular product.  
^ Not currently classified as a prebiotic, only a functional fiber
## Practical Application - Prebiotics

<table>
<thead>
<tr>
<th>Type of prebiotic</th>
<th>Food source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fructans - Fructooligosaccharides, inulin, oligofructose</td>
<td>Asparagus, sugar beets, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato and rye</td>
</tr>
<tr>
<td>Isomaltulose</td>
<td>Honey, sugarcane juice</td>
</tr>
<tr>
<td>Xylooligosaccharides</td>
<td>Bamboo shoots, fruits, vegetables, milk, honey and wheat bran, whole grain breakfast cereals</td>
</tr>
<tr>
<td>Raffinose oligosaccharides</td>
<td>Seeds of legumes, lentils, peas, beans, chickpeas, mallow composite, and mustard</td>
</tr>
<tr>
<td>Soybean oligosaccharides</td>
<td>Soybean</td>
</tr>
<tr>
<td>Lactulose</td>
<td>Milk</td>
</tr>
<tr>
<td>Enzyme-resistant dextron</td>
<td>Potato starch</td>
</tr>
<tr>
<td>Arabinoxylooligosaccharides</td>
<td>Wheat bran, whole grain breakfast cereals</td>
</tr>
</tbody>
</table>
Practical Application

• Keep in mind:\(^{37}\)
  – A probiotic does more than merely introduce a new bacterial species into the gut (which may or may not take up residence). Probiotics many change the whole environment in unpredictable ways
  – Bacteria can feed or inhibit the growth of each other
  – Extreme dietary changes can produce an immediate impact on the gut microbiome
  – Normal gut microbiome increases nutrient bioavailability
  – Changing the microbiome can change the effect nutrients have on the individual
  – Diet is the primary influencer of the gut microbiome
Questions?
References


References cont.

39. Huffnagle G. The Probiotics Revolution.