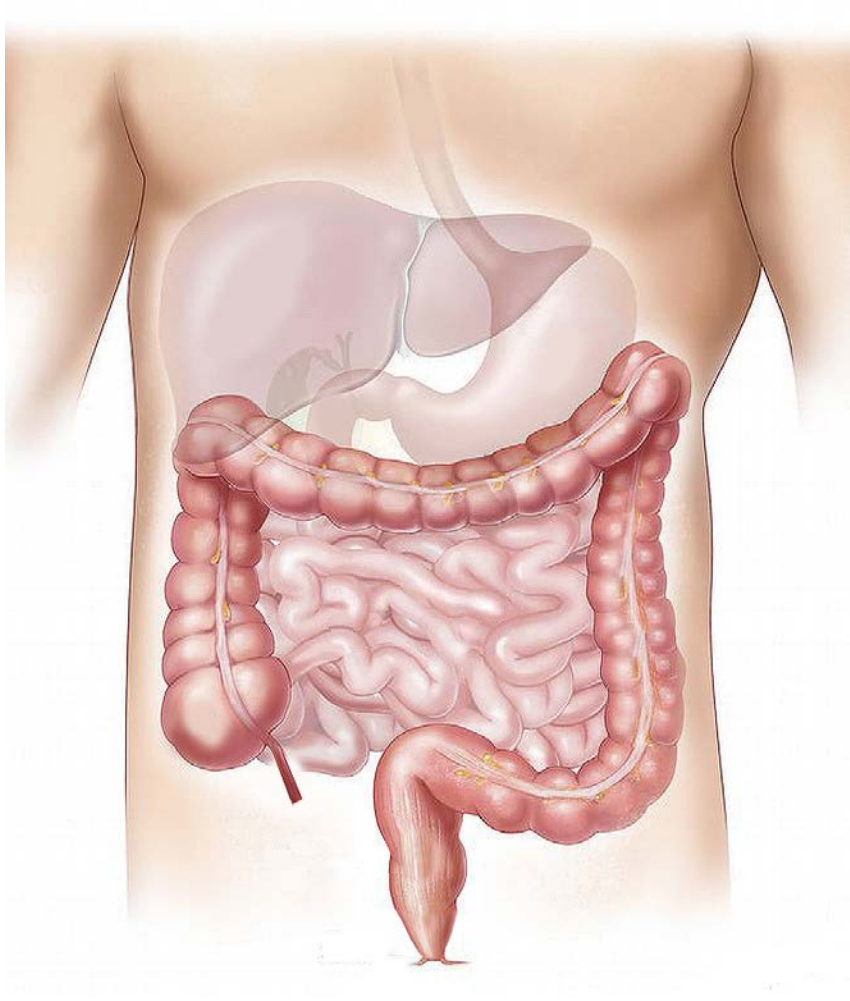


The Kidney-gut Axis: What is it, and what can renal dietitians do about it?

LINDSEY ZIRKER MS, RD, CSR

WHAT IS THE GUT MICROBIOME?

- The gut microbiome is it's own ecosystem containing more than 100 trillion bacteria.[1,2]
- A healthy individual has a rich diversity of bacteria within the gut, with the largest amount of bacteria occurring in the colon. [1,2]
- There are two main types of bacteria: saccharolytic and proteolytic[2,3]

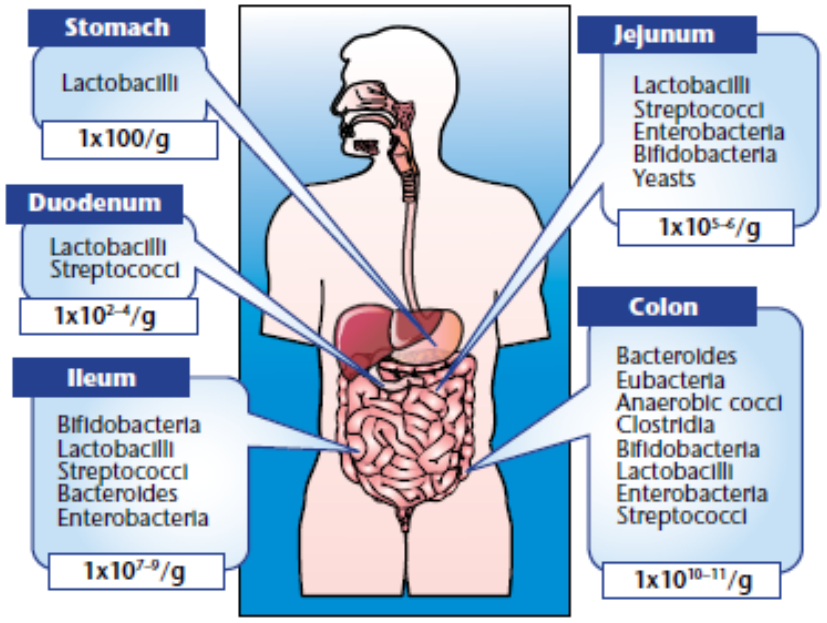


Figure 1. The type and amount of bacteria throughout the gut[1]

OBJECTIVES

- Explain the relationship between kidney disease and the gut microbiota
- Review current renal nutrition recommendations and their impact on kidney-gut axis
- Analyze current evidence to identify appropriate nutrition interventions
- Implement nutrition interventions that take the kidney-gut axis into consideration

DISCLOSURE

- I have nothing to disclose

WHAT DO THESE BACTERIA DO?

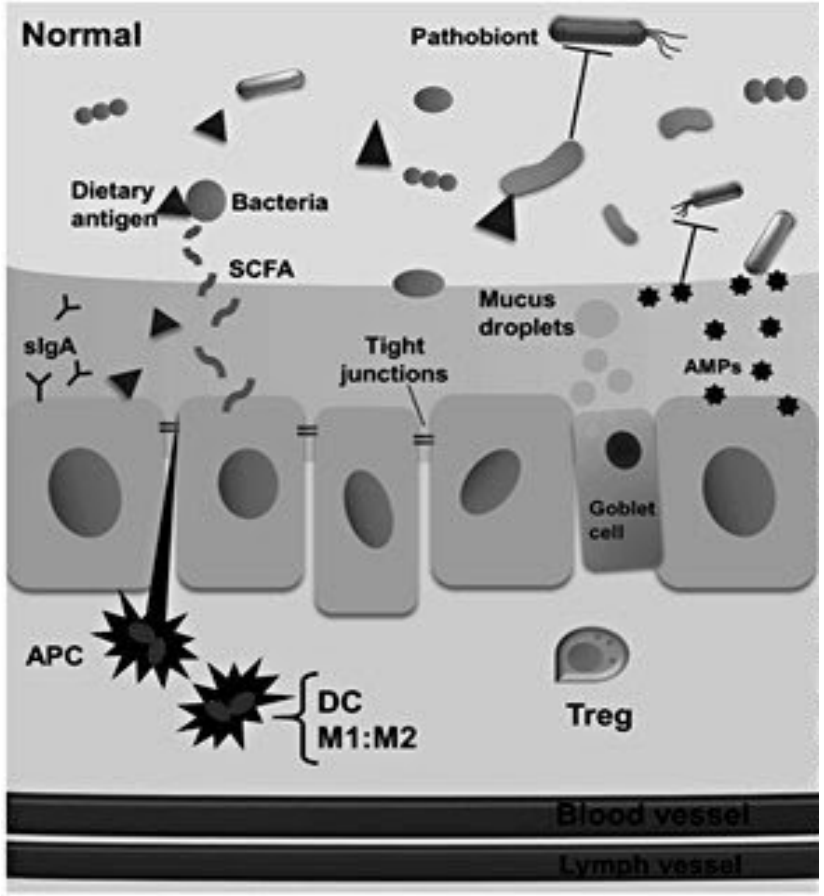
Saccharolytic bacteria:

- Primarily ferment carbohydrates (resistant starches) which produces beneficial end products such as short chain fatty acids (which support the growth of intestinal cells)[3,4,5]
- Synthesize vitamins, amino acids[2,6,7]
- Maintain intestinal barrier[2,6,7]
- Regulate immune function[5]
- Compete with pathogenic bacteria for space[7]

Proteolytic bacteria:

- Primarily ferment (putrefy) protein which produce ammonia, amines, thiols, phenols and indoles[3,8,9]
- 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[8,9]
- These end products are eliminated primarily through the kidney and rise with a decrease in GFR[8,9]

THE INTESTINAL BARRIER



- Epithelial layer along intestinal lumen[10,11]
- Mucus layer- antimicrobial proteins, lectins and defensins[10,11]
- Tight junctions to selectively allow nutrients to be absorbed. Tight junction permeability varies throughout the intestine. [7,11]

Figure 2. Tight junctions with healthy intestinal barrier[12]

WHAT DOES THE CKD GUT LOOK LIKE?

- Aerobic bacteria 100x higher in HD patients, decreased levels of bifidobacteria and *Clostridium perfringens* were increased[3]
- Bacteria that produce IS and PCS are among the most abundant bacteria found in ESRD patients[7]
- Small intestinal bacterial overgrowth (SIBO)- Increased levels of both aerobic and anaerobic bacteria in the small intestine[6,7]
- Decreased tight junction proteins[13]
- Uremia increases bacterial translocation[10]
- Uremia impairs immunity by decreasing T/B cell responses from vaccination, and decreases the memory of T and B cells[10]
- Increased nitrogen waste products (poor protein digestion, high protein diet) promotes overgrowth of proteolytic bacteria[7]
- IS and PCS increase as GFR decreases[14]

HOW KIDNEY DISEASE IMPACTS THE GUT

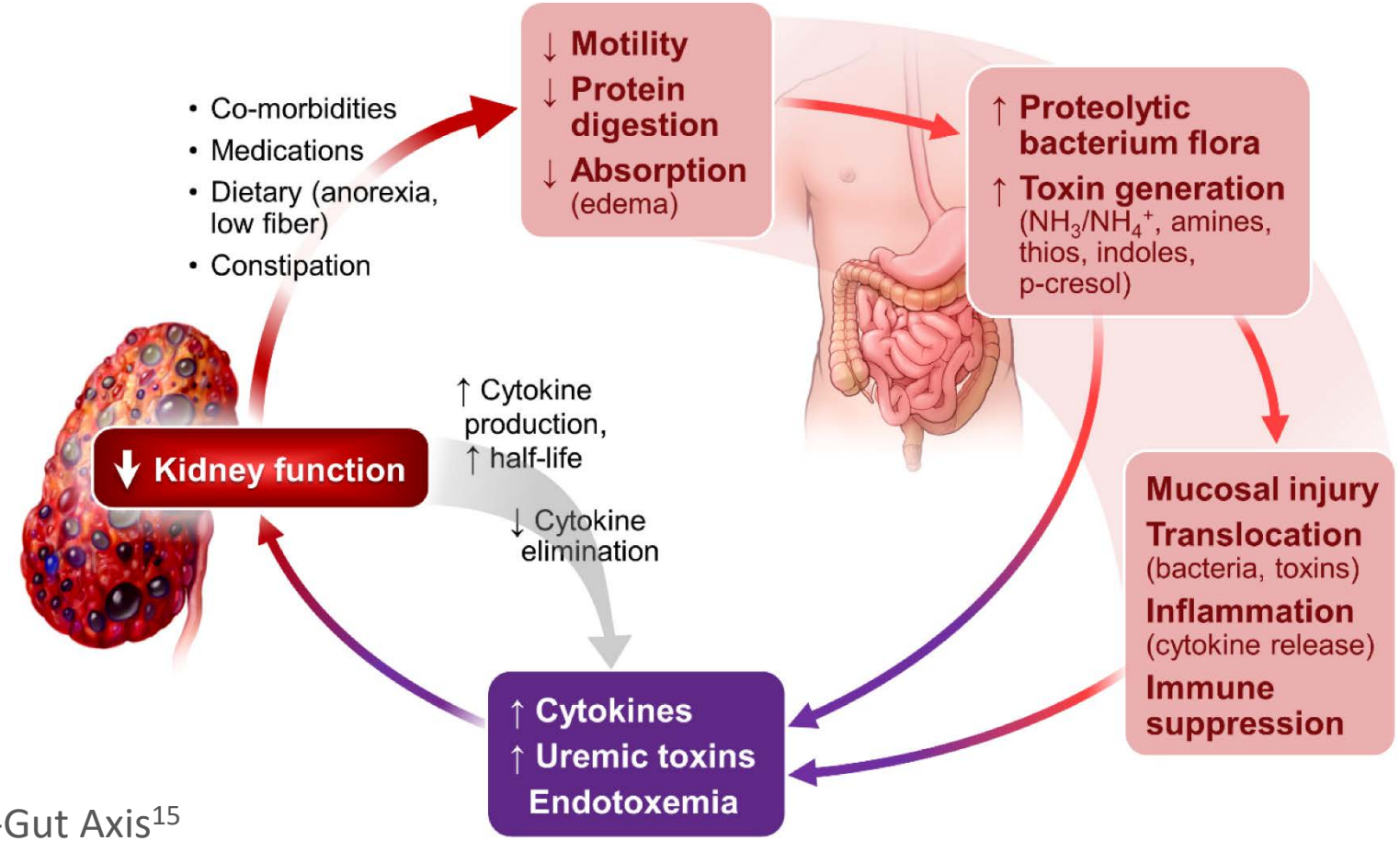


Figure 3. Kidney-Gut Axis[15]

HOW CKD CONTRIBUTES TO DYSBIOSIS[2,3,5,6,7,10,16,18,19]

Factors in kidney disease	Impact on gut
Metabolic acidosis	Intestinal pH change- supporting growth of different types of bacteria
Uremic solutes	Intestinal pH change, increased inflammation
Volume overload/ excessive ultrafiltration	Transient intestinal ischemia and hypotension
Medications- antibiotics, oral iron, anti-GERD, phosphorus binders	Increased bacterial growth or decimated population, bacterial translocation, different availability of nutrients
Renal diet	Decreased fuel for saccharolytic bacteria, increased fuel for proteolytic bacteria, increased inflammation, increased production of uremic solutes, bacterial translocation

HOW CKD CONTRIBUTES TO INCREASED INTESTINAL PERMEABILITY[5,6,7,19,20]

- 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

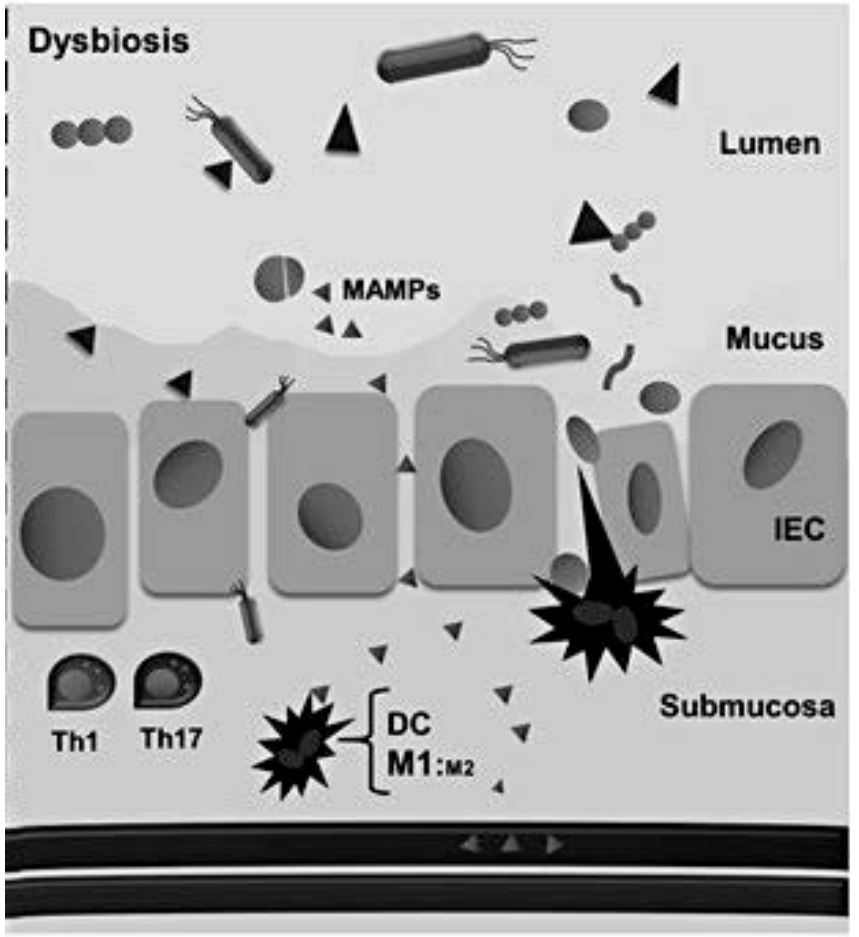


Figure 4. Damaged intestinal layer and tight junctions[12]

CONSEQUENCES OF DYSBIOSIS AND IMPAIRED INTESTINAL PERMEABILITY

- Bacteria and endotoxin translocation= PCS and IS are absorbed into the blood stream[5,7]
  - PCS and IS cause significant damage to the vascular system, including oxidative stress which prevents regeneration and healing, vascular stiffness, aortic calcification and are associated with increased mortality[3,7,13,18,20]
  - In those with CKD not on dialysis, IS and PCS contribute the to progression of kidney disease[13,20]
  - Dialysis does not filter out IS or PCS[5]
  - Bacteria translocation can contribute to uremic enterocolitis, GERD, small intestinal bacterial overgrowth, malabsorption of nutrients, food allergies/ sensitivities, obesity, other digestive issues.[20,22]
  - Endotoxins= depression and anxiety and other mental health issues[36]
- Impaired immunity and systemic inflammation[10,18,20]
  - Over stimulation from milieu flowing from impaired intestinal barrier = inflammation, but suppressed immunity as safety measures causes contradictory state of immunosuppression but systemic inflammation.

SO, WHAT CAN DIETITIANS DO?

LEARN MORE!

Resources for learning about dysbiosis and increased intestinal permeability

- AND Dietitians in integrative and Functional Medicine Practice Group www.integrativerd.org
- Institute for Functional medicine www.ifm.org/learning-center/
- Genova diagnostics www.gdx.net/clinicians/medical-education
- Diagnostic Solutions Laboratory www.diagnosticsolutionslab.com/resource-library
- CKD- Supplements, gut health and functional/ integrative nutrition principles https://kidneyrd.com/ckd-functional-integrative-nutrition-principles/
- Advancing Medicine with Food and Nutrients by Ingrid Kohlstadt
- Laboratory Evaluations for Integrative and Functional Medicine by Richard Lord and J.Alexander Bralley

REFRESH YOUR PERSPECTIVE ON "EVIDENCE-BASED"

- Sometimes we forget that an evidence-based approach requires more than peer-reviewed published research

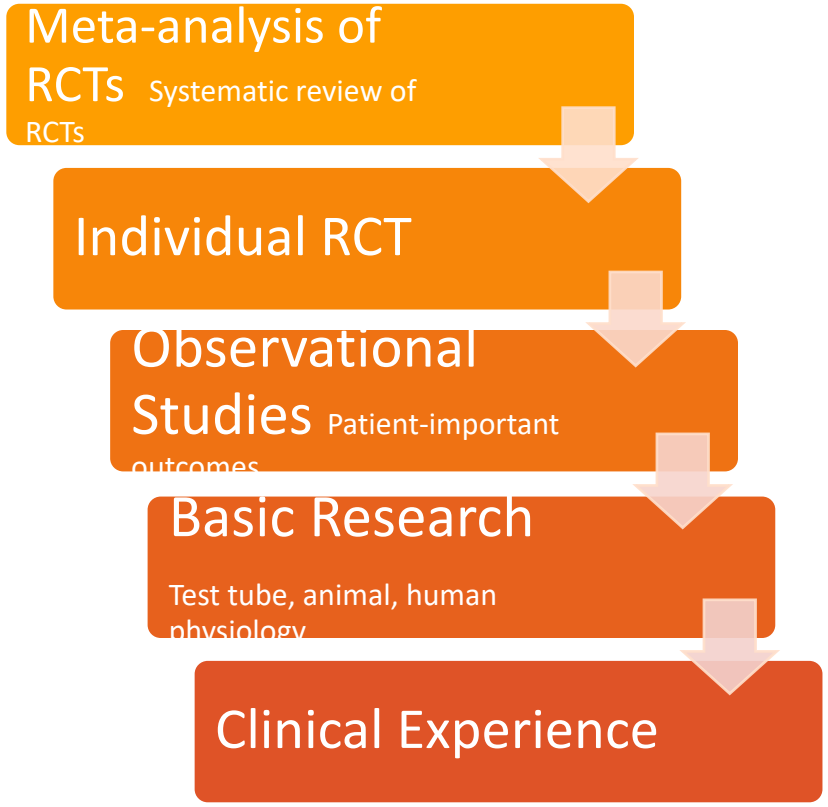


Figure 5: Hierarchy of Evidence[21]

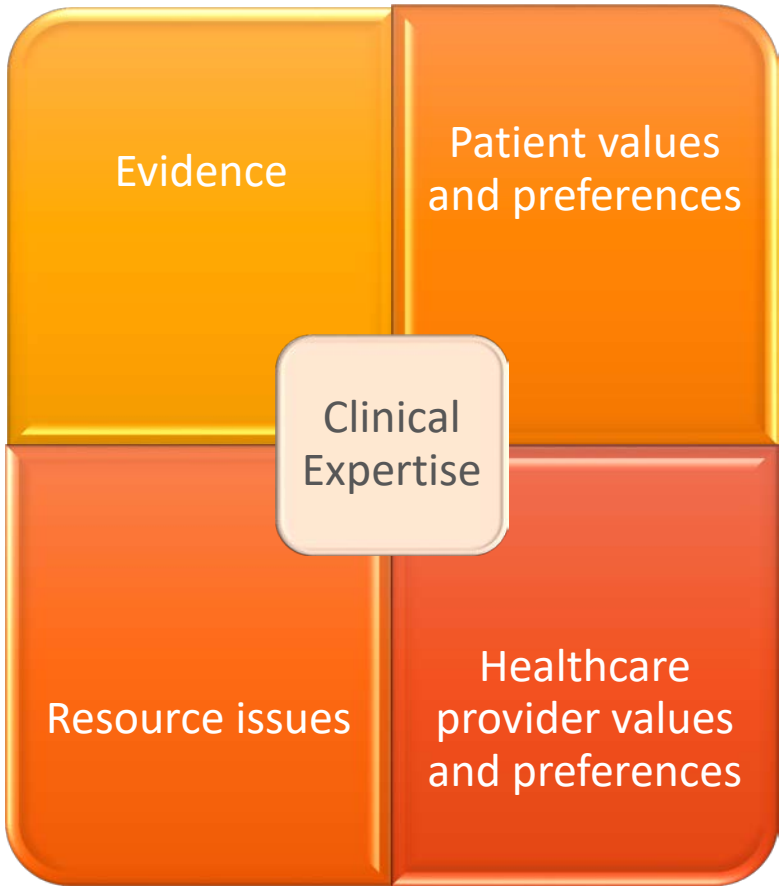


Figure 6: Model for Evidence-Based Decision-Making[21]

ASSESS PATIENT

Question	Yes	No
Have you taken an antibiotic within the past 12 months?		
Have you experienced constipation or diarrhea within the past 3 months?		
Do you experience abdominal cramping a few hours after eating?		
Is abdominal pain relieved after passing gas?		
Do you experience pain during bowel movements?		
Do your abdominal discomforts, constipation and/or diarrhea get worse with stress?		
Are you frequently bloated?		
Do you experience heart burn or burning in your stomach?		
Do you have trouble losing weight?		
Do you have food allergies?		
If your patient answers yes to 3 or more questions, there is a high likelihood of altered gut bacteria.		

Figure 7. Probiotic Screening Tool[33]

OTHER FACTORS THAT MIGHT INDICATE ALTERED GUT FLORA

- Other factors that might indicate a need for probiotics:
  - Low intake of fruits and vegetables/ low fiber[30,34]
  - Frequent use of artificial sweeteners[31,35]
  - Chronic stress[1, 34]
  - Alcohol use [1]
  - Nutrient insufficiencies/ malnutrition[1,19]
  - Iron supplementation[19]
  - Diets high in refined carbohydrates, low in fiber[34]

5 R APPROACH[22]

- Removing immune or symptom triggers such as foods, toxins, medications, and pathogenic bacteria.
- Replacing digestive enzymes, hydrochloric acid and dietary fiber
- Reinoculating the gut with friendly bacteria
- Repairing the gut lining and mucosa
- Reducing and managing stress

INCREASED FIBER

- Liberalized diet to increase fiber intake (14-27g/ day)[23,24,25]
- Increased fiber intake improves cholesterol and blood sugar levels, decreases CVD risk, increases transit time and decreases production of IS and PCS, increases growth of beneficial bacteria and decreases growth of pathogenic bacteria[25]
- Encourage intake of fruits, vegetables and whole grains as fuel for saccharolytic bacteria and less fuel for proteolytic bacteria
- It has been noted that potassium in the stool is quite high and that decreased transit time allows for increased potassium absorption- which may be the main contributor to high potassium, not diet. Increased fiber, decreasing transit time can facilitate greater potassium losses through the stool.[26]
- Consider the multiple other possible reasons for high potassium. Recent KDOQI guidelines indicate that no clinical studies have formally evaluated dietary intake on the impact of serum potassium.[27]

APPROPRIATE AMOUNT AND TYPE OF PROTEIN[27]

- CKD not on dialysis
  - Low protein diet (0.6 g/kg/day)
  - Very low protein diet + ketoanalogues (0.3g/kg/day)
  - Vegetarian or Mediterranean diet
- CKD and on dialysis
  - Increased protein intake or supplements recommended based on estimated intake (nPCR, diet recall), weight loss, SGA, malnutrition risk score
  - Plant proteins, not just animal protein recommended. Also consider that animal protein is a considerable source of potassium if you feel your patient is sensitive to dietary potassium intake

AMOUNT AND TYPE OF FAT

- Diets high in saturated fat decrease growth of beneficial bacteria and increase growth of pathogenic bacteria[28,29,30]
- Diets higher in unsaturated fats increase beneficial bacteria and are protective against the growth of pathogenic bacteria[28,29,30]
- Mediterranean style diets or supplementing with fish oil may be appropriate[27,28]
- Help patients include more healthy fats such as plant based oils (olive oil, flaxseed oil), nuts, seeds, and fish.

ARTIFICIAL SWEETENERS

- Animal studies show decreased transit time, dysbiosis and general negative impact on gut microbiome[28,29,31]
- Limited high quality studies
- May be beneficial to cut out artificial sweeteners for those who are sensitive or for those with irritable bowel[31]

PRE AND PROBIOTICS

- Both pre and probiotics have been found to improve dysbiosis and increased intestinal permeability[13,16,20,32]
- No established protocols because they are only recently recognized as legitimate, but also significant variability in individual gut bacteria- reestablishing balance is very different for every person.
- Studies in CKD populations show benefit in using pre and probiotics to address GI issues such as C. diff, constipation, inflammatory bowel etc
- Using pre and probiotics to reduce uremic toxins and slow progression of CKD is in it's infant stages with some promising studies.[33]
- Remember: diet is such a significant factor in shaping gut health, supplementing pre or probiotics without improving diet will likely have limited benefit

RESOURCES FOR USING PRE AND PROBIOTICS

- Yale University Workshop- Recommendations for probiotic use- 2015 update
- Clinical Guide to Probiotics- http://usprobioticguide.com/
- Natural Medicine Database (available for free with membership to DIFM or Renal Dietitians practice groups
- Probiotic Advisor www.probioticadvisor.com

OTHER POTENTIAL INTERVENTIONS TO CONSIDER[22]

- Use of digestive enzymes to improve protein digestion
- Evaluate use of medications that may have a negative impact on gut health
- Encourage healthy stress management
- Correct nutrient deficiencies (utilize physical assessment, food journals and medication/ nutrient interactions if lab assessment is not available)
- Improved fluid management- moderating fluid and sodium intake, less aggressive ultrafiltration.
- Consider herbal and other supplements where diet is inadequate to help sooth and heal the gut (cucurmin, zinc, melatonin, marshmallow, ginger, quercetin)

QUESTIONS?

Contact information

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