Use of probiotics for management of various GI conditions

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Microbiome

- Human GI tract hosts countless microbes (estimate 100 trillions bacteria alone)
- GI bacteria carries many functions, including immunity, vitamin synthesis and metabolism
- Dysbiosis-imbalance of gut microbial ecosystem overgrowth or depletion, of bacterial or other species leading to host response

The Gut Microbiome function

- Immune system training
  - Stimulation of innate immunity
  - Inhibit pathogen growth
  - Recognition of self vs. foreign
- Production of by-products
  - Vitamins (biotin, folate, vit K)
  - Balance of metabolism (firmicides vs bacteroides)
- Digestion
  - Fermentation of food residue
  - Modification of bile acids
ACINOBACTERIA

- Bifidum bacteria gram positive
- Anti-inflammatory effect
- Production of short chain fatty acids – Butyrate
- Mainly found in colon
- Produces bacteriocins, which have bactericidal action

Bacteroides

- Gram negative bacilli
- Mostly anaerobic
- Prevotella species
- Streptococcus
  - Low in obesity patients (obesity patient have high firmicutes levels)
Firmucutes

- Gram positive cocci typically anaerobes
- Lactobacilli
- Clostridia
- Fecalubacterium
- Lactbacilli increases phagocytosis and increases IgA Secretion
- Help to protect gut barrier function

A Fine Balance

Bacteria in the Gastrointestinal Tract

1. **Stomach** (very acidic, not many viable microbes)
   - *Streptococcus*
   - *Staphylococcus*
   - *Lactobacillus*

2. **Intestines** (hundreds of microbes, both commensals and mutualistic relationships)
   - **Bacteroides**: Common to everyone, can cause disease if balance is thrown out
     - **E. coli**: Common, can produce vitamin K and B
     - **Clostridium**: Common, can cause disease, resistant to common antibiotics
     - **Bifidobacterium**: Helps to control the E. coli population to prevent infection, maintains lactic functions
Are changes in gut bacteria to dysbiosis related to changes in our diet?

- Sugar consumption
- Sodium consumption
- Saturated fat, cholesterol increases firmicutes levels, and obesity
- Vegetables and fruits
- Minerals (potassium, magnesium, calcium, chromium)
- Antioxidants

Diet determines the composition of gut bacteria

**Injurious**
- Pro-inflammatory
  - Iron, sucrose, fructose, satur, fat
  - Bacteroides vulgatus, B. theta
  - Enterococcus faecalis
  - E. coli - enterotoxigenic / invasive
  - Klebsiella pneumoniae
  - Bifidobacterium adolescentis
  - Bilophila wadsworthia
  - Fusobacterium varium
  - Intestinal Helicobacter species

**Protective**
- Anti-inflammatory
  - Fiber, prebiotics
  - Lactobacillus sp.
  - Bifidobacterium sp.
  - Non-pathogenic E. coli
  - Saccharomyces houardi
  - Bacteroides thetaiotaomicron
  - Faecalibacterium prausnitzii
  - Clostridium groups IV and XIVA
**Diet and microbiome**

- High fiber and complex carbs beneficial for healthy microbiome
  - Fermentation of complex carbs produces SCFA butyrate, protective against pathogenic bacteria and inflammation
- High protein diet with low fiber diet increases gut inflammation
  - Undigested peptides cases increase in putrefied short chain fatty acid increases IBD and colon cancer
  - High fat Western diet causes a shift in bacteria to dysbiosis and obesity

**Important Questions**

- Is a change in gut microflora contributing to the development of autoimmune disease?
- Can probiotics be taken to restore health?
  - which products?
  - under what conditions?
  - dosage and length of treatment
  - how do they work?

**Probiotics Defined**

- Defined as live microorganisms which confer a health benefit on the host. First suggested by Metchnikoff
  - Probiotic - "for life" could cause displacement of putrefactive bacteria
  - Clinical uses of probiotics were first reported in the 1970s.
  - Therapy for lactose intolerance.
- The first successful trial of probiotics was conducted in children.
  - Treatment of rotavirus gastroenteritis.

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**References**

- Isolauri 1991 and 1994
- Kaila 1995
- Majamaa 1995
- U.N. Food and Agriculture Organization and WHO, 2001
Probiotic and Maintenance of barrier function

- epithelial cell tight junctions
- mucus production
- secretory IgA production

How is the barrier between epithelial cells maintained?

Bacteria-epithelial cell cross-talk contributes to intestinal inflammation in the susceptible host

Protective activity

Colitogenic activity

Signal Transduction

Gene expression

Normal Gut

Chronic Inflammation
Probiotics influences mucus production

- Mucus secretion via cAMP
- Up-regulation of mucin-producing genes

Deplancke et al AJCN 2001
Otte et al Am J Phys 2004
Caballero-Franco et al Can J Gastro 2004
Mack Gut 2003

Common probiotics available

VSL #3 probiotic
- Lactobacillus acidophilus
- Lactobacillus plantarum
- Lactobacillus bulgaricus
- Lactobacillus paracasei
- Bifidobacterium longum
- Bifidobacterium infantis
- Bifidobacterium brevis
- Streptococcus thermophilius

OTC probiotics
- Culturelle
  - Lactobacillus rhamnosus
  - Bifidobacterium infantis
- Florastor
  - Saccharomyces boulardii
  (yeast)
- GoodBelly
  - Lactobacillus plantarum

- Multi-strain vs single-strain

Multi-strain is a product of five or more proven probiotic strain containing at least 2 Lactobacilli and two Bifidobacterium strains
Are multiple strains more effective?

- All strains are different
  - strains complement each other in their effects
  - autoimmune diseases are complex
- Strains act in different sections of the gut
  - *Lactobacillus* sp in small intestine
  - *Bifidobacteria* sp in colon
- One strain may help the other strains to survive passage

Probiotics must be taken at high concentrations...

At Least $10^6$ Organisms Per mL

Probiotics act in the small intestine and the colon.

Dosages high vs low dose probiotics

- Over the last decade there is an increase in probiotic dosing in clinical research and practice
- Higher doses for treatment of IBD, IBS and AAD has been used
- Majority of trials were using VSL #3 doses ranging from 450 bln to 3.8 trillion CFU/day up to 12 months
- Positive benefits compared to placebo were noticed in UC, pouchitis and AAD
Probiotics must be taken continually....

Probiotics for IBS

- 50 clinical trials and 10 systematic reviews and meta-analysis
- Studies are done around the world using different stains showed mixed results
- Positive benefits have been seen with relatively low doses 10 billion as well as very high doses 450 billion a day
- Probiotics are safe for IBS

Irritable Bowel Syndrome

- A common syndrome in the developed world.
  - Up to 20% of general population
  - Higher incidence in females
  - Unknown etiology
- Characterized by irregular bowel movements, bloating, gaseousness, pain.
  - Defined by ROME III criteria
- Associated with bacterial overgrowth in the small intestine by breath-hydrogen studies.
  - Often responds to antibiotic therapy.
**SIBO**

- Small intestinal bacterial overgrowth
- Results from Dysbiosis in small intestine due to
  - Antibiotic use prolonged (ex for acne)
  - Use of PPI medication
  - Genetic predisposition
  - Use of antibiotics in the young age
  - Immunosuppression
  - IgA deficiency

**Probiotics for SIBO**

- Small intestinal bacterial overgrowth diagnosed by lactulose breath test or clinical diagnosis: presence of bloating, diarrhea or constipation with low/low normal B 12 levels
- treated with antibiotic (Rifaximin 550 mg tid 2 weeks, Metronidazole 500 mg tid 10 days or quinolone
- Give 40 billions of mixed strain for prevention of recurrence

**Probiotics for antibiotic associated diarrhea**

- JAMA 2012 meta-analysis of over 80 studies, in probiotic group (mostly L. Acidophilus) relative risk was decreased by about 40%

2002 meta-analysis 9 studies, Lactobacilli strains reduced overall risk of diarrhea lasting 4 or more days by 59% and duration of diarrhea by 25 hr
Probiotics for antibiotic associated diarrhea in children

- 2015 Cochrane review by Goldberg 23 RCT 3,398 children
- Significantly reduced incidence of AAD in the probiotic group
- Author concluded Lactobacilli rhamnosus, S. boulardii 5 to 40 bln a day for preventing AAD in children receiving antibiotics

Probiotic in treatment and prevention of c. difficile

- Mechanism of probiotics
  - Create bactericidal acids promoting a competition for nutrients and epithelial adhesion, reducing favorability of environment for c diff
  - Antimicrobial activity by production of acid that lowers pH in the local gut and inhibit the growth of bacteria
  - Both lactobacilli and S. boulardi suppress growth of c diff in hamsters

Probiotics and C difficile

- Intestinal barrier protection: probiotics have the ability to interfere with binding of the c. diff to intestinal epithelial cells
- Probiotic including Lactobacilli rhamnosus and Bifidobacterium breve stabilize gut permeability increase intestinal mucins
- Ingestion of probiotic has been associated with increase in Immunoglobulin A secretion in both stool and serum
Treatment of C. difficile

- Two meta-analyses in 2012 suggest benefits of probiotic for treatment of CDAD
- Concluded that probiotics could be used as adjunct treatment with Flagyl and Vancomycin in non-severe recurrent disease
- Patients with recurrent CDAD have lower rate of treatment failure with S. buolardii than placebo (354 patient trial)
- Further evaluation is needed to evaluate Lactobacilli

Probiotic for constipation and IBS-C

- One study looked in bowel transit and stool consistency
- 3 groups: placebo, low dose Bifidobacterium and high dose Bifidobacterium
- After 14 days, high dose group had statistically significant increase in bowel frequency and decrease in functional symptoms

IBD definition

- Chronic inflammatory autoimmune conditions affecting the GI tract
- Ulcerative colitis—affecting colon and rectum, superficial ulcers manifesting by bloody diarrhea
- Crohn’s disease—anywhere in GI tract, common site small intestine, affecting all layers of intestinal wall, creating inflammatory strictures, fistulas, bowel obstruction leading to surgery and disability
IBD

• Recently on the rise- 2.5 mln people will be affected in the US in 2020
• Increased incidence in children, connected to use of antibiotics
• Clear microbiome imbalance connection, overgrowth of pathological bacteria triggers autoimmune response
• Strong multistrain probiotic may play role in prevention

How probiotics can help in the treatment of IBD

- Anti-microbial Activity
  • decrease pH
  • defensins
  • H2O2

- Stimulate an Immune Response
  • Induce sIgA

- Enhanced Barrier Integrity
  • Stimulates mucin production and secretion
  • Prevents epithelial apoptosis
  • Alters tight junctional structure

- Competitive Exclusion Of Bacterial Adhesion

- Immunomodulatory
  • Induce Treg
  • Enhance IL-10 and TGF
  • Reduce TNF/IFN

Epithelial cells can distinguish pathogenic from commensal bacteria....
UC

- Double-blind study assessing VSL#3 in UC pts (>18 yo).
  - Mild-moderate, relapsing disease receiving 5-ASA or 6-MP.
  - 144 subjects (71 intervention vs. 73 placebo) received 1 sachet (1.8 x 10^8 CFU) BID.
  - 65 in VSL#3 group and 66 in placebo group completed study.
  - Decrease in UCDAI >50% higher in VSL#3 group.
    - 63.1% vs. 40.8% (p=.01, CI 95% 0.51-0.74; ITT p=.031).

Pouchitis

- Double-blind RCT
  - 40 adults with chronic relapsing pouchitis.
  - Remission achieved by antibiotics administration.
  - Randomized to receive VSL#3 or placebo.
  - After 12 months, relapse rate of 10% in VSL#3 group (2/20) vs. 40% in placebo group (8/20).

- Gionchetti P, Gastro 2003
Necrotizing Enterocolitis

- Bowel necrosis of variable length.
  - Mucosal injury and ischemia.
  - Idiopathic, but bacterial colonization is implicated.
- Affects ~10% of VLBW (<1500 g) preterm infants.
  - 5-25% of cases occur in term infants.
- Predisposing factors include:
  - Decreased normal enteric flora compared with term infants.

Musemeche et al J Ped Surg 1986
Lee et al Sem Neonatol 2003

Pouchitis

- Patients with pouchitis associated with PDAI > 7 (0-18).
  - ≥2 flares in previous year or requiring continuous abx to maintain remission.
  - Remission induced by 4 wks of Flagyl and Cipro.
- Randomized to receive VSL#3 or placebo once daily x 1 year or until relapse.
  - Symptomatic, endoscopic, and histological eval made before, at 2 and 12 months, or at relapse.
- 36 pts randomized: 20 to VSL#3 group and 16 to placebo.
  - Remission maintained in 17/20 (85%) pts in VSL#3 group vs. 1/16 (6%) in placebo group (p=.0001).

Mimura T, Gut 2004

Hepatic Encephalopathy

- Decreased colonic pH is hostile to survival of urease-producing bacteria (e.g. Klebsiella, Proteus) and conducive to growth of lactobacillus and bifidobacteria.
  - Reduced putrefaction and absorption of ammonia.
- 55 pts with hepatic cirrhosis and MHE randomized to 3 groups for 30 days:
  - A: Synbiotic preparation with 4 strains of non-urease-producing bacteria (e.g. lactobacillus paracasei and plantarum, 10^9 CFU total) along with 10 g of fermentable fiber (e.g. inulin, pectin).
  - B: 10 g fermentable fiber alone.
  - C: Placebo of a wheat-based, non-fermentable fiber.

Liu, G, Hepatology 2004
Treatment of atopic conditions in children

• Studies evaluating administration of probiotic Lactobacillus Ramnosus strain GG alone or in combination with Lactobacillus reuteri to infants with atopic dermatitis and cow milk allergy, demonstrated significant reduction of the severity of the eczema

Probiotic food sources

• Yogurt creates great media to transport probiotic through the stomach to lower gi tract (look at label to sure active cultures added after pasteurization )
• Fermented foods sauerkraut and kimchi
• Kefer (has up to 40 bln of probiotic )
• DanActive (L. casei)

Prebiotics

• Fructooligosaccharides FOS –linear or branch chain of fructose and glucose molecules
  – Found in asparagus, onion, garlic, artichoke fermented from chicory root (inulin)  
  – Feeds lactobacilli and Bifidobacterium  
  – Promotes satiety  
  – Prevents colon cancer
Points to remember

- If prescribing antibiotic give
- Probiotic for at least 2 weeks after, especially children
- Avoid long antibiotic use for acne other than short term, if possible
- Treat patients with IBS diarrhea predominant with at least 4 bacteria stains of probiotic at least 50 bln, nothing is more rewarding, if they have SIBO, treat with Xifaxan first

Thank you