OBJECTIVES

1. Critically analyze the state of the science concerning probiotics used in women’s health, including the benefits and gaps in knowledge.

2. Discuss the clinical uses of probiotics to prevent and treat a variety of women’s health problems.

3. Describe probiotic dietary supplements, including strains, dosages, and routes, in sufficient detail to make effective selection recommendations and prescriptive decisions.
Lisa Hanson, PhD, CNM, FACNM

Microbiology Meets Gynecology: The Application of Probiotics to Women’s Healthcare

YOGURT

Persian Bible: Genesis 18:8
- “Abraham owed his longevity to the daily consumption of fermented milk products”. (Rijkers et al 2010)

Melchnikoff (1907)
- Began the scientific basis of probiotics
- Investigated lactic acid bacterial composition of yogurt as a protective factor for longevity

YOGURT 1977

YOGURT NOW

Bifidus Regularis®
Bifidobacterium lactis DN-173 010
**Probiotics Defined**

- "Probiotics are live microorganisms, which when administered in adequate amounts confer a health benefit on the host." 
  (FAO/WHO 2001)

![Lactobacillus and Bifidobacterium](image)

**Probiotic Product Information:**

- Most commonly available supplements contain:
  - *Lactobacillus*
  - *Bifidobacterium*

- Not systemically absorbed in healthy individuals
- Commercially available probiotics are comprised of bacteria of human origin
- Active live culture in products is critical issue
  - Refrigeration is often recommended
  - Some products are freeze dried

**Bacterial Species Used as Probiotics**

- *Lactobacillus* species
  - *L. acidophilus*
  - *L. bulgaricus*
  - *L. casei*
  - *L. crispatus*
  - *L. fermentum*
  - *L. gasseri*
  - *L. johnsonii*
  - *L. lactis*
  - *L. plantarum*
  - *L. reuteri*
  - *L. rhamnosus GG*

- *Bifidobacterium* species
  - *B. adolescentis*
  - *B. animalis*
  - *B. bifidum*
  - *B. breve*
  - *B. infantis*
  - *B. lactis*
  - *B. longum*

Some genera and species have been omitted from this list.

Williams, 2010
MECHANISM OF ACTION: STIMULATES ACID PRODUCTION

- Produce acids on mucosal surfaces:
  - Lactic
  - Acetic
  - Others
- Effects:
  - Lowers pH
  - Impedes growth of pathogens
  - Some contribute anti-inflammatory properties (e.g., activate short chain fatty acids that enhance metabolic regulatory mechanisms)

MECHANISM OF ACTION: STIMULATES HEALTHY MUCOSA

- Produce numerous substances to maintain mucosal surface:
  - Vitamins
  - Bacteriocins
  - Metabolites
  - Enzymes
  - Lipopolysaccharides
  - Peptidoglycans
  - Superantigens
  - Biosurfactants
- Functions:
  - Improve healthy microflora
  - Alter surface tension
  - Prevents adherence
  - Displace harmful bacteria from the biofilm

MECHANISM OF ACTION: SUPPORTS IMMUNE RESPONSES

- Synergistically stimulate specific infection-fighting substances of host immune system:
  - Lymphocytes
  - Cytokines
  - Interleukins
  - IgG antibodies
  - IgA antibodies and secretory IgA
PROBIOTIC MECHANISMS OF ACTION

PROBIOTIC RISK

Healthy individuals
- “Negligible”: Fewer than 1 per million users
- One review of 143 human trials of over 7,000 people over nearly 40 years found no adverse events

Immunocompromised Adults
- Best to avoid
  - vulnerable post surgical
  - those undergoing chemotherapy or radiation
  - High mortality in client with acute pancreatitis

[Adams, 2009; Reid, 2009; Karpa, 2003]

[Adams, 2009; Reid, 2009; Karpa, 2003]

[Sharp et al., 2009]

ONGOING CONCERNS FOR CLIENTS

Positives for some
- See as CAM
- See as pharmacologic treatment, although misunderstanding
- See as gene therapy & genetic modification, which can also inspire fear

Non-traditional safety issues
- Mutated bacteria may behave unexpectedly in the host
- Genetically altered microbes may also behave unexpectedly
- Unanticipated interactions within the human host possible
- Novel bacteria could enter the external environment (e.g., wastewater can affect many ecosystems)

Bacterial DNA can always mutate by transfer mechanisms (e.g., drug resistance)

Careful informed consent needed
**GUT IS A KEY AREA**

- Few overview facts:
  - Mammals’ gut: one of most densely populated ecosystems on planet
  - Multiple (2,000) microbial species present = microbiota
  - Can contain 100 times the genes in the human genome = human microbiome
  - GI tract has 400 square meters of surface area
  - Microbes ↑ in concentration as GI transit continues
    - Estimated 50% of feces are bacteria
    - With 1 trillion microbes per 1 gram of stool

Iannitti & Palmieri, 2010

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**THE HUMAN MICROBIOME**

- Trillions of bacteria:
  - Only 20% of species identified by laboratory culture techniques
- At least 2/3 of immune response is attributable to the gut:
  - Dependent on predominance of healthy bacterial flora

Hart, 2002; Adams, 2009

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**GI EPITHELium COMPONENTS**

http://www.youtube.com/watch?v=gnZEge78_78
**GI LUMEN TO BLOOD & LYMPHATICS**

http://www.youtube.com/watch?v=gn0Ego7b_78

**COLONY FORMING UNITS=CFU**

CFUs are calculated with the following proportion:

\[
\frac{\text{# of colonies} \times \text{dilution of plate}}{\text{volume of culture on plate}} = \frac{X}{\text{ml}}
\]

The resulting CFU is then presented in scientific notation

\[10^9 = 1.0 \times 10 \times 10 \times 10 \times 10 \times 10 \times 10 \times 10 \times 10 = 1,000,000,000\]

**PREBIOTICS DEFINED**

- Contribute selectively fermented food ingredients (not live organisms)
- Used as food for growth by species of *Lactobacillus* and/or *Bifidobacterium*
- Confer health benefits upon host
- Inhibit growth of pathogenic bacteria
- Enhance acidic intestinal environment

**Examples include:**

- Banana
- Jerusalem artichoke
- Onion
- Garlic

[Gibson 2004; Roberfroid 2007]
SYNBIO蒂DIS

- Prebiotics and probiotics used in combination
- United Nations Food & Agriculture Organization (FAO) recommends “synbiotic” be used only if:
  - net health benefit is synergistic
  - prebiotic increases the population and/or function of the probiotic with which it is paired

Examples:
- Human breastmilk
- Bifidobacteria and fructooligosaccharides (FOS)
- Lactobacillus rhamnosus GG and inulins
- Bifidobacteria or Lactobacilli with FOS or inulins or galacto-oligosaccharides (GOS)

YOGURT AND CULTURED MILK PRODUCTS

- Variation in probiotic live culture contents
- Refrigeration and freshness impact CFU
- 4 oz of a live cultured milk product may contain as much as 10^9 (1 billion) probiotic microorganisms.

THE FEMALE MICROBIOME

GUT COMPOSITION

- Independent of hygiene, organisms that populate the vagina originate in the gut
- Bifidobacterium predominate in healthy gut

VAGINAL FLORA

- Healthy vaginal flora: Lactobacillus predominate
- Some strains produce H_2O_2
- Maintain acid vaginal pH: optimum=4.5
- Impacted by:
  - Sexual activity
  - Vaginal cleansing practices
  - Pathogens
PREVENTION VS TREATMENT

Overall, you will see a pattern emerge that suggests that probiotics appear to be better at preventing than treating disease.

IMPORTANT CONSIDERATIONS….

• The benefit of one probiotic cannot necessarily be attributed to another
• Note the heterogeneity of the study samples, probiotic interventions, duration of treatment etc.
• Currently insurance does not cover probiotic therapy

JARISCH-HERXHEIMER REACTION OR “DIE OFF”

• When begin probiotics, may initially experience temporary bloating & flatulence that subsides with continued use
• Although controversial:
  o Referred to as a Jarisch-Herxheimer reaction=“die off”
  o Thought to occur when toxins from dying pathogens (viruses, bacteria, parasites, fungi, etc.) overwhelm body’s ability to clear them
  o More common with oral antifungals; less with probiotics
  o Temporary ↓ of dose and/or frequency may reverse symptoms
• Rare mention of “die off” in the probiotic scientific lit
URINARY TRACT INFECTION (UTI)

**Adapted from Abad & Safdar, 2009**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Type</th>
<th>Patients</th>
<th>Strain Details</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid (1992)</td>
<td>RCT placebo-controlled</td>
<td>41 premenopausal; post abx tx</td>
<td>Intravaginal: Lactobacillus rhamnosus GR-1, 1 x 10^8</td>
<td>2x weekly post antibx tx</td>
<td>No sig diff in UTI recurrence (0.45 [0.14-0.82], P=0.36) vs 6.5% (P=0.06) in 3x5</td>
</tr>
<tr>
<td>Bruce (1992)</td>
<td>Quasi-experiment</td>
<td>10 pre/postmenopausal</td>
<td>Intravaginal: Lactobacillus rhamnosus GR-1, 1 x 10^8</td>
<td>Weekly</td>
<td>No sig diff in UTI recurrence (0.45 [0.26-0.75], P=0.001) vs 6.5% (P=0.06) in 3x5</td>
</tr>
<tr>
<td>Baerheim (1994)</td>
<td>RCT placebo-controlled</td>
<td>47 18-50 yrs</td>
<td>Intravaginal: Lactobacillus rhamnosus (≥ 7.5 x 10^8 CFU)</td>
<td>26 weeks</td>
<td>No sig diff in UTI recurrence (95% CI, 0.88-1.98)</td>
</tr>
<tr>
<td>Reid (1995)</td>
<td>RCT, single-blind</td>
<td>55 premenopausal; ≥ 3 UTI/yr</td>
<td>Intravaginal: Lactobacillus rhamnosus GR-1; Lactobacillus fermentum B54, 1.6 x 10^9</td>
<td>Weekly for 12 mo</td>
<td>RR=0.42 (0.22-0.67), P1=0.001; RR=0.62, P2&lt;0.05</td>
</tr>
<tr>
<td>Kontokiari (2001)</td>
<td>RCT, open-controlled</td>
<td>150 premenopausal</td>
<td>Oral: Lactobacillus GG, 4 x 10^10 CFU/100 ml</td>
<td>5d/week for 1 year</td>
<td>No sig diff in UTI recurrence (1.05 [0.63-1.76], P=0.5)</td>
</tr>
<tr>
<td>Uehara (2006)</td>
<td>Quasi-experiment</td>
<td>9 young women</td>
<td>Intravaginal: Lactobacillus crispatus GA 98322, 1 x 10^8</td>
<td>Every 2 days for 1 year</td>
<td>No sig diff in UTI recurrence (1.28 [0.78-2.11], P=0.45)</td>
</tr>
<tr>
<td>Beereport (2012)</td>
<td>RCT</td>
<td>252 postmenopausal women; with recurrent UTI</td>
<td>Oral: Trimethoprim-sulfamethoxazole 480 mg, daily; Oral 10^9 Lactobacillus GR-1 bid</td>
<td>12 mo</td>
<td>Probiotics significantly decreased recurrent UTI by 0.4/year (95% CI -0.4-1.5), no increase in antibiotic resistance</td>
</tr>
</tbody>
</table>

Certain probiotics appear to significantly ↓ UTI rec occurrence. More research needed.

PROBIOTIC BACTERIA AND VAGINAL FLORA

**Childbearing age women**
- **Lactobacillus plantarum** (LB931) impregnated onto panty liners
- Double blind placebo controlled RCT with 191 women
- The number of Lactobacillus was significantly related to vaginal pH (p<0.001)
- 70% of women were carriers of specific Lacto strains
  (Ronnqvist, 2006)

**Conclusion:** Women with more Lacto had:
less GBS (p=0.36) and lower pH

MENOPAUSE

- **HRT:** 1 vaginal Lactobacillus
- 1 Lacto associated with ↓ UTI and ↓ BV
- **Oral Lactobacillus GR-1** has been shown to improve vaginal flora in postmenopausal women
- **Gram Stain (Nugent score)**
- **Some studies of intravaginal probiotic administration**
  route raise concerns about participant satisfaction
  (increased discharge and/or irritation)

(Petruccic et al, 2008)
BACTERIAL VAGINOSIS TREATMENT (BV)

Cochrane Review: Probiotics for the treatment of BV (Senok, 2009)

- 4 RCTs meet inclusion and quality criteria
- Various preparations and administration routes
- Women allocated to the probiotic groups had significantly improved BV cures
  - Oral metronidazole/probiotic (OR 0.09 (95% CI 0.03 to 0.26)
  - Probiotic/estriol (OR 0.02 (95% CI 0.00 to 0.47)

Conclusion: Insufficient evidence for or against probiotics for the treatment of BV

BACTERIAL VAGINOSIS TREATMENT (BV)

Systematic Review (Abad & Safdar, 2009)

- 9 studies included
- 6 studies demonstrated a significant reduction in BV (by Arsen's clinical criteria or Nugent's Gram Stain score)

More recently, RCT (Ling, 2013)

- 60 Healthy women with BV
- Randomized to 10 days of L. delbruecki subsp. lactis DM8909 109 intravaginal suppositories OR 7 days of metronidazole
- Probiotics successfully treated the BV in comparison
  - 10 days of probiotics as effective (88% cure) as 7 days flagyl (83.3%)
  - Metronidazole decreased the diversity of vaginal flora
  - Probiotic maintained diversity of the flora

Probiotics appear to be an effective alternative treatment of BV with the added benefit of promoting diverse healthy vaginal flora

BACTERIAL VAGINOSIS RECURRENCE PREVENTION

Findings: RCT (Ya, 2010)

- 120 Healthy Chinese women with recurrent BV
- Randomly assigned to 7 days on/7 days off for 60 days
  - Daily intravaginal capsule containing L. rhamnosus, L acidophilus, & Streptococcus thermophilus
  - OR placebo

- Findings
  - Probiotic prophylaxis resulted in lower BV recurrence (15.8%) vs controls (45%) P<0.001
  - Lower recurrence sustained at 2 & 11 month follow-ups

Probiotics appear to be effective in the management of recurrent BV, although more research is needed
**STUDIES OF PROBIOTICS AND VAGINAL CANDIDIAS (VVC)**

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Type of Study</th>
<th>Participants</th>
<th>Strain</th>
<th>Length of treatment</th>
<th>RR (95%-ile)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilton (1992)</td>
<td>Prospective Crossover</td>
<td>33 pre-menopausal H/O Chronic VVC</td>
<td>Oral: Lactobacillus yogurt 10^9</td>
<td>Daily x 6 mo</td>
<td>0.39 (0.17-0.7)</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>Pirotta (2004)</td>
<td>RCT, Placebo controlled</td>
<td>235 with finished ab for gyn infection</td>
<td>Oral: L. hamnusus, L. acidovorus, L. dekbrueckii</td>
<td>Daily x 4 days</td>
<td>RR: 1.09 (0.68-1.76), P=0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vaginal lactobacillus</td>
<td></td>
<td>RR: 1.38 (0.75-2.54), P&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Hilton (1993)</td>
<td>Quasi-experiment</td>
<td>28 h/o recurrent VVC</td>
<td>Vaginal suppository: Lactobacillus GG</td>
<td>Twice daily x 7 days</td>
<td>0.20 (0.03-1.18), P=0.19</td>
<td></td>
</tr>
<tr>
<td>Williams (2001)</td>
<td>RCT, Placebo controlled</td>
<td>164 HIV positive stratified by CD4 counts</td>
<td>Vaginal suppository: L. acidophilus</td>
<td>Weekly x 19 mo</td>
<td>0.54 (0.26-1.10), P=0.14</td>
<td></td>
</tr>
</tbody>
</table>

Table from Abad & Safdar, 2009

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**VULVO VAGINAL CANDIDIA (VVC)**

**Treatment**
- Only study demonstrated effective treat of VVC
- Utility of probiotics against VVC depends on adherence to vaginal epithelium
- Hormones, vaginal pH, glycogen content can impact adherence
- In vitro, Wood & colleagues (1985) found that yogurt-based sources of Lactobacillus had lower adherence to vaginal epithelium than other exogenous probiotic sources

**Prevention**
- 4 studies
- Small samples
- Nonrandomized
- Goals varied
  - prevention vs treatment
  - Include women with diverse healthcare needs
  - HIV positive
  - Menopause
  - Show some efficacy in preventing recurrences

Lactobacillus has potential to play a role in preventing VVC.

More randomized controlled studies needed with larger samples & goal of prevention versus treatment.

---

**ALLERGIES**

Perinatal programming
- Prenatal probiotics significantly reduce atopic disease in offspring
- Opportunity to make an impact diminishes with age

- 12 RCTs of probiotics against allergic rhinitis
- Various probiotics were used
- Symptoms were measured by self-report
- Probiotic groups
  - Lower reported symptoms
  - Less medication use

Ozdemir, 2012, Bjorksten, 2005

Probiotics appear to be effective in the management of allergic rhinitis
ECZEMA

- 3 Meta-analyses of probiotics as a treatment for eczema
  - No consistent evidence of benefit
- More recently, RCT of L salivarius L301 in adults
  - Some improved quality of life measures following 16 weeks of treatment when compared to placebo (Drago et al, Int J Immunopathol Pharmol 2011; 24: 1037)

COMMON COLD SYMPTOMS

- 3 RCTs of probiotics against common cold
  - L casei, B Longum, B Bifidum (2 studies)
  - L casei (one study)
  - 2 used vitamins/minerals in addition
  - Spring/winter administration
  - Probiotics significant reduced the duration and severity of common colds symptoms
  - No effect on incidence

  [Lenoir-Wijnkoop et al., 2007]

Probiotics may reduce the duration and severity of common cold symptoms

ACUTE URI PREVENTION

- Recent RCT to explore prevention of the common cold (Berggren et al., 2011):
  - 272 adults (2/3 women)
  - 10% plantarum & L paracasei
  - Symptom duration: from 8.6 to 6.2 days (p<0.05)
  - Incidence of ARIs: from 67% to 55% (p<0.05)
  - Probiotics reduced the risk of acquiring common cold

  Hao et al. (2011)
  Cochrane systematic review:
  - 10 studies, 3,451 participants
  - Various probiotics
  - Probiotics reduced
  - Incidence of acute URI
  - Antibiotics used

  Fortney, 2013; *, Hao et al., 2011

Probiotics may prevent the common cold
Microbiology Meets Gynecology: The Application of Probiotics to Women’s Healthcare

ANTIBIOTIC ASSOCIATED DIARRHEA (AAD)

- AAD affects up to 30% of antibiotic users
- 3 meta-analyses of probiotics against AAD including up to 20 clinical trials each
- Probiotics significantly reduced the incidence of AAD by 42-66%
- No increase in adverse events
- Most studied strains (most included *Lactobacillus*):
  - *Saccharomyces boulardii* (yeast-based probiotic)
  - *Lactobacillus rhamnosus*, GG
  - Or a combination of the two

(Johnston et al 2012; Hempel et al 2012; Weichselbaum, 2010, Up to Date, 2014)

Probiotics appear to be effective in preventing antibiotic associated diarrhea

ANTIBIOTIC ASSOCIATED DIARRHEA: C DIFFICILE (CDAD)

- *C. Difficile* is a serious form of antibiotic associated diarrhea also associated with fecal oral contamination via the hands of health workers and patients
- Most at risk: elderly, immune suppressed, antibiotic exposed
- Increase in CDAD infection worldwide due to hyper virulent strain
- Meta-analysis of 6 studies of probiotics used to prevent CDAD demonstrated a significant role in prevention (RR=0.59; 95% CI, 0.41, 0.85; P=0.005)

(Avadhani 2011; Weichselbaum, 2010; Friedman, 2012, Ulbricht, etal 2011)

Prevention includes taking probiotics during the antibiotic course and then for 14 days afterwards

PROBIOTIC ADMINISTRATION DURING ANTIBIOTIC THERAPY

- Antibiotics can kill probiotic bacteria
- Negates the effect of taking probiotics

Separate antibiotic & probiotic doses by 2 hours


**CELIAC DISEASE (CD)**

- Probiotics show promise in management of autoimmune disorders such as CD
  - fermentation-derived metabolites
  - regulation of the epithelial cell barrier
  - modulation of the immune response
  - Inhibition of inflammatory markers of CD
- **Example:** *Bifidobacterium lactis* was shown to inhibit the toxicity produced by gliadin in epithelial cells (the gluten protein).
- **Although this has not been studied in persons with CD**
  
  *(Lindfors, 2008)*

The impact of probiotics on CD have yet to be studied

**TRAVELERS DIARRHEA (TD)**

**Background**
- Defined as: passing 3 or more watery stools per day, during or following travel
  - Acute: 3 or more loose stools within 24 hours (Most last 3-5 days)
  - Dysentery: with visible blood or mucus
  - Persistent: lasting 14 days or longer (5-10%)
- Cause: Ingestion of food or water contaminated with feces

**Prevention**
- Meta-analysis of 12 studies
- Probiotics significantly prevented travelers diarrhea *(RR=0.85; 95% CI: 0.79, 0.91; P<0.001)*
- Significant efficacy
  - *Lactobacillus* & *B bifidum*
  - No serious adverse reactions reported
- Prebiotic galacto-oligo-saccharide 5.5g [x 1 per day, 1 week prior to & during travel to a low risk area]
- Reduced TD incidence & duration
    *(Takahashi et al 2007; Bennett, 2012)*

Probiotics appear to be effective in preventing travelers diarrhea

**ACUTE INFECTIOUS DIARRHEA**

- Meta-analysis (2010)
  - 63 RCTs
  - Different probiotics
  - Adults and children
  - Probiotic intervention resulted in:
    - 59% reduction in the risk of diarrhea lasting for 4 or more days *(RR 0.41, 95% CI 0.32-0.53)*
    - 25 hour average reduction in the duration of diarrhea *(95% CI, 16-34 hr)*
  
  *(Allen et al, Probiotics for treating acute infectious diarrhea. Cochrane Database Syst Rev 2010)*

Probiotics reduce the duration of acute infectious diarrhea
**Microbiology Meets Gynecology: The Application of Probiotics to Women’s Healthcare**

**CHRONIC DIARRHEA**

- Diarrhea of more than 4 weeks duration
- Related to:
  - Dysregulation of the intestinal homeostasis
  - Composition of gut flora
  - Chronic bacterial or parasitic infections
  - IBS, Celiac Disease (CD), small intestine bacterial overgrowth (SIBO), lactose intolerance
  - Other functional disorders
- Probiotics of single or multiple species can modify the microbiota and result in clinically appreciable benefit
- Studies focus on specific disease entities

(Scaldaferri 2012)

Probiotics appear to be effective in the management of chronic diarrhea

**CONSTIPATION**

- Waizberg et al (2013) randomized 100 constipated Brazilian women (ages 18-75) to 2 daily doses (6g) of symbiotic or placebo for 30 days
- Symptoms were measured by self-evaluation through daily records & standardized scoring tools
- Symbiotic group women (beginning the 2nd & 3rd weeks) had significantly:
  - Increased BM frequency
  - Improved consistency
  - No increase in abdominal symptoms

(Scaldaferri 2012)

Probiotics appear to be effective in the management of chronic diarrhea

**CONCLUSION**

Higashikawa et al (2010) studied effects of 3 types of Lactic Acid Bacteria (LAB) yogurts on GI symptoms, cholesterol and liver function

- 68 healthy Japanese adults with other constipation or diarrhea were randomized to receive one of 3 LAB yogurts DB.
- Participants consumed 100g daily x 6 weeks
- Results:
  - 2 yogurts resulted in dramatic improvements in BM frequency & consistency
  - 2 other yogurts decreased LDL Cholesterol
  - One yogurt also improved liver function parameters

Higashikawa et al, 2010; Bouvier, et al 2001; Marteau et al, 2002

*Japanese Dairy Industry funding

**CONCLUSION**

- Bifido animalis (DN-173010) referred to as “Vidas Regularis” (TM Activia Yogurt)
- Marteau (2002) RCTS aimed to study transit time in women with “occasional irregularity”
- 36 Healthy women consumed 125 g cups per day of probiotic milk product or placebo
- 4 consecutive 10 day periods with washouts
- Probiotic significantly shortened transit time of feces

Conclusion*: L Plantarum SN13T yogurt improved constipation, serum lipids & liver function
IRRITABLE BOWEL SYNDROME (IBS)

- Clinical diagnosis
  - IBS with constipation
  - IBS with diarrhea
  - Mixed

- Symptoms
  - Abdominal pain
  - Straining
  - Myalgia
  - Urgency
  - Bloating

- 2 meta-analyses of placebo controlled trials:
  - Nikfar, 2008 (8 trials)
  - McFarland, 2008 (20 trials)

- Probiotic use
  - *B. infantis* 35624 was associated with modest improvement in IBS symptoms

Probiotics appear to be effective in reducing symptoms of IBS

INTESTINAL GAS

- 61 otherwise healthy adults (1/2 females) with post-prandial intestinal gas-related symptoms
- Randomized to either:
  - *B. coagulans* GBI-30, 6086
  - Control
- Results:
  - Probiotic group participants had significant improvements in abdominal pain & total symptom score

Probiotics may improve post-prandial intestinal gas-related symptoms

INFLAMMATORY BOWEL DISEASE (IBD)

Crohn’s disease
- One systematic review
  - Rolfe (2008), 7 trials
- One meta-analysis
  - Rahimi (2008), 8 trials
No evidence that probiotics prevent relapse

Ulcerative Colitis
- Systematic Review
  - Khimara, (2011), 4 trials
- Probiotics did not improve remission over mesalazine therapy

Probiotics do not appear to be effective in Inflammatory Bowel Disease
### Lactose Intolerance

- GI (or other) symptoms after ingesting lactose-containing foods
- 15% Caucasians
- >50% Mexican Americans
- >80% African Americans
- Risk for calcium and protein deficiencies especially in developing countries
- Testing: Hydrogen breath test
  - 25-50 µg lactose challenge
  - Intestinal bacteria metabolize carbs to generate hydrogen which is rapidly absorbed into blood
  - 20 ppm or more = positive test
- Digest fermented milk products more easily

Levi et al, 2005

### Diabetes and Glucose Metabolism

Dysbiosis may negatively impact production of gut hormones & substances that impact obesity & glucose metabolism:
- Glucagon-like peptide-1 (GLP-1)
- Insulin signaling
- Glucose transport
- Inflammation
- Triglyceride production
- Gut permeability
- Oxidative stress

Probiotics may prevent or reverse these

### Diabetes (DM) & Glucose Metabolism

Ejtahed et al (2012)

- 64 participants (30-60 years) with Type II DM were randomized to consume 300 grams of regular or enhanced yogurt for 6 weeks:
  - Experimental group:
    - *Lactobacillus acidophilus* La5 & *Bifidobacterium lactis* Bb12
    - 15 Billion CFU total daily
  - Control group
    - Conventional yogurt
  - FBS, HbA1-C & other anthropometric measures were collected at baseline and 6 weeks

Probiotic may improve Type II DM measures

Andreason, 2010

Luoto, 2010

NS trend found in Meta-analysis, Dugoua, 2009.

Shane-McWhorter, 2012
**OBESITY**

- **Double blind placebo controlled trial**
  - 48 male, 24 each group
  - 77 females, 38 probiotic
  - Each group receive moderate calorie restriction for 12 weeks followed by 12 weeks of maintenance
  - Body weight and composition measured at baseline, 12 and 24 weeks
  - Intervention: 2 capsules per day
    - L rhamnosis CGMCC 1 3724 (LRP) 1.6x10^8 CFU with Oligofructose and inulin (prebiotics)
    - vs
    - Placebo

  *Sanchez et al 2014*

  **SYMBIOTIC supplementation may help women achieve weight loss goals**

  

**ABDOMINAL ADIPOSE**

- Multi-center, RCT, double blind, placebo controlled trial
  - Japanese adults
  - 3 groups
  - 200 g L gasseri SBT2055
    - 10^8 CFU
    - 10^7 CFU
  - Control

  Abdominal visceral fat computed by tomography at 12 weeks

  - Abdominal adipose significantly decreased in the probiotics groups by:
    - 8.8% in the 10^7 group (95%, CI: 11.9, -5.1; (p<0.01)
    - 8.2% in the 10^8 group (95%, CI: 10.8, -5.7; (p<0.01)
  - BMI, waist and hip circumference were also significantly decreased in both groups compared with controls
  - Cessation attenuated these effects

  *Kadooka, et al 2012*

  **Probiotic supplementation appeared to lower abdominal adipose. Continued supplementation is needed to sustain the effect**

**FERMENTED MILK & BLOOD PRESSURE**

- Meta-analysis of 14 placebo controlled RCTs
  - Studies done between 1996-2010
  - Included 702 participants: gender not specified
  - Intervention
    - Fermented milk 100-450g/day
    - Controls received milk-based placebo product
  - 4-24 weeks duration (average 8 weeks)
  - Findings: Fermented milk intervention significantly reduced blood pressure compared to control milk product consumption
    - Systolic \downarrow by 3.1 mm Hg (95% CI -4.64, -1.56)
    - Diastolic \downarrow by 1.09 mm Hg (-3.98-2.09)

  *Dong et al 2013*

  **Probiotic may improve blood pressure measures**
**Microbiology Meets Gynecology: The Application of Probiotics to Women’s Healthcare**

**CHOLESTEROL**

In a double blind randomized cross over study,
- Randomized 32 healthy, moderately hypercholesterolemic women & men to 4 weeks of:
  - Probiotic drink containing 10^9 L. paracasei (LPC37) AND  
  - Bread enriched with calcium OR  
  - Bread without calcium  
- After a 2 week placebo period, the groups were switched  
- Results: Probiotic + calcium significantly:
  - Decreased total cholesterol & LDL cholesterol  
  - Increased fecal L. paracasei & other Lactobacillus  
  - Increased bile acids in feces

Trautvetter et al, 2012

**Probiotic may lower lipid parameters**

**SPECULATION: ATOPY & COLON CA RISK**

<table>
<thead>
<tr>
<th>Healthy individuals (n=15)</th>
<th>Allergic individuals (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacto &amp; Bifido</td>
<td>Clostridium &amp; Bacteroides</td>
</tr>
<tr>
<td>&gt; activity &amp; occurrence of CA-promoting enzymes &amp; metabolites</td>
<td>produce↑ metabolites &amp; problematic enzymes for a more genotoxic environment in gut lumen</td>
</tr>
<tr>
<td>Low levels, β-glucuronidase, azoreductase, &amp; nitroreductase</td>
<td>High level of these toxic enzymes</td>
</tr>
</tbody>
</table>
| Lower colon pH generally | Less acidic colon pH may↑  
  toxins  
  high level of these toxic enzymes  
  metabolites & problematic enzymes for a more genotoxic environment in gut lumen |
| NS difference in pH (6.7-6.8) | pH significantly↓ (7-6.6; P=.037) |


**HPV VIRAL CLEARANCE**

Exploratory pilot
- Prospective controlled study  
- 54 women with LGSIL  
- Followed for 6 months  
- 24 women received Intervention=Daily probiotic drink  
  - Lactobacillus casei Shirota (CFU not provided)  
  - Commercially available in Belgium  
- 27 controls

- Findings:
  - Women in the probiotic group showed twice the HPV clearance of HPV infection related cytology compared to controls  
  - 60 vs 31% (p=0.05)

(Verhoeven et al 2012. European J of Ca Prevention 22: 46-51)

In the future probiotic may provide a new option to manage HPV related cytology abnormalities
SUMMARY OF EVIDENCE

<table>
<thead>
<tr>
<th>Strong evidence</th>
<th>Substantial evidence</th>
<th>Applications showing promise</th>
<th>Potential future applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Diarrhea</td>
<td>Antibiotic Associated Diarrhea</td>
<td>BV Treatment</td>
<td>Prevention of C. Diff</td>
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<tr>
<td>Constipation</td>
<td></td>
<td>BV Prevention</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td></td>
<td></td>
<td>LRT Prevention</td>
<td>Diabetes</td>
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<tr>
<td></td>
<td></td>
<td>Allergic Reactions</td>
<td>Blood pressure</td>
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<td></td>
<td></td>
<td>Atopic dermatitis</td>
<td>Obesity</td>
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<tr>
<td></td>
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<td>Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Traveler's diarrhea</td>
<td></td>
</tr>
</tbody>
</table>

Goldin & Gorbach, 2008

SOCIOECONOMIC BENEFITS

- Probiotics themselves are relatively inexpensive, even with daily dosing
- Associated with (but more research needed):
  - ↓ absences from work (&/or day care)
  - ↓ incidence of infections & recurrences
  - ↓ duration & severity of symptoms reported
  - ↓ length of stay if hospitalization needed
  - ↓ costs of antibiotics & other treatments
  - ↓ costs of provider visits through prevention
  - ↓ cost of alternative caregivers needed

Lenoir-Wijnkoop et al., 2007

RESOURCES FOR CLINICIANS:

- Natural Medicine Database
  - Website contains a table that compares commercially available probiotic formulations

- YouTube animation
  - Immunology in the Gut Mucosa
  - http://www.youtube.com/watch?v=gn22e7878
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