Objectives

• Review GI uses for probiotics supported by "some" evidence (limited)

• Safety of probiotics
Definition

- Probiotics (Greek “pro bios” - “for life”)

Living microorganisms which when administered in adequate amounts confer a health benefit to host

Challenges to Providing Advice

- Many products on the market
  - Regulated as Health Product or Food Product with Probiotic Claims by Health Canada

- Low Quality Evidence
  - Small studies - underpowered
  - Some lack control group
  - Meta-analysis
    - Heterogenous – different strains, concentrations
    - Publication bias
Factors Affecting Efficacy

- Specific Strain
- Dose
- Delivery Vehicle

How Do Probiotics Work?

- Anti-Bacterial Peptides
- Enhance Mucosal Barrier
- Neuropeptides – motility and sensation
- Modulate Immune/Inflammatory Response
Uses in GI

- Irritable Bowel Syndrome (IBS)
- Inflammatory Bowel Disease (IBD)
- Antibiotic-associated Diarrhea
- HP Eradication
- C. difficile

• RCT / Meta-analyses
• Guidelines

Irritable Bowel Syndrome

• Many RCTs published however:
  - Small studies
  - Study designs
    - Varying endpoints – some not clinically relevant
  - Different species and doses
  - Large placebo effect

• Systematic Reviews / Meta-analyses
  - Better than placebo in improving IBS symptoms
    - RR – 0.72-0.77 (NNT=4)
  - Heterogeneity of studies, possible publication bias, <50% of studies fulfilled selection criteria

Am J Gastro 2008  Gut 2010
Small Sample Size

Irritable Bowel Syndrome - Guidelines

- Advise people who choose to try probiotics to take the product for at least four weeks, at the dose recommended by the manufacturer, while monitoring the effect.

- Overall some evidence to support use of probiotics in IBS

- Not enough evidence to recommend which probiotic
  - Larger studies
    - *Bifidobacterium infantis*
    - *Lactobacillus plantarum*

NICE Guidelines
Uses in GI

- Irritable Bowel Syndrome (IBS)
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Inflammatory Bowel Disease

- Crohn’s disease
  - Probiotics have no effect on induction or maintenance of remission

- Ulcerative colitis
  - VSL #3
    - 4 strains of *Lactobacillus*
    - 3 strains of *Bifidobacterium*
    - 1 strain of *Streptococcus*

  - ? E. coli Nissle 1917 (Mutaflor)
Probiotics in CD and UC

Probiotics in UC

Shen J et al. Inflammatory Bowel Disease 2014
Inflammatory Bowel Disease - UC

Statement 34: In patients with UC, we recommend against probiotics to induce or maintain complete remission outside the setting of a clinical trial.
GRADE: Strong recommendation, very low-quality evidence.
Vote: strongly agree, 48%; agree, 43%; uncertain, 9%.

- Insufficient quality of evidence to support use in conjunction to or in place of standard therapy
- Most evidence (although limited quality) is for VSL #3
  - Addition to standard therapy (5-ASA)

Gastroenterology May 2015

Uses in GI

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Antibiotic-Associated Diarrhea (AAD)

• Incidence
  – 5-39%

• Mechanism
  – Some antibiotics stimulate motility (erthromycin, clavulanate)
  – Decrease fecal anaerobes
    • Decrease metabolism of CHO – osmotic diarrhea
    • Decrease rate of breakdown of bile acids – secretory diarrhea

AAD

• Meta-analysis
  – 34 studies (10 pediatrics)

  – Probiotics
    • Lactobacilli bulgaricus, casei, paracasei, acidophilus, plantarum, rhamnosus, salivarius
    • Bifidobacterium infantis, bifidum, lactis, longum, breve
    • Enterococci faecium
    • Streptococci thermophilus
    • Saccharomyces boulardii

  – Probiotics Duration
    • Duration of probiotic therapy up to 28 days

NEJM 2002

Aliment Pharmacol Ther 2012
ADULTS

- Pooled RR over placebo (overall)
  - 0.53 (0.44-0.63)
  - **NNT = 8**

- Pooled RR during *H. pylori* treatment
  - 0.37 (0.20-0.69)
  - **NNT = 5**

- Preventive effect remained significant when grouped by
  - probiotic species
  - duration of antibiotics/probiotics
Guidelines?

• No guidelines from GI associations for this indication

• Appears to be effective from available evidence

• No specific strain demonstrated to be more effective

Uses in GI

• Irritable Bowel Syndrome (IBS)

• Inflammatory Bowel Disease (IBD)

• Antibiotic-associated Diarrhea

• HP Eradication ✔

• C. difficile
H. Pylori

Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy

J. L. TONG*, Z. H. RAN*, J. SHEN*, C. X. ZHANG† & S. D. XIAO*

- **14 RCTs**

- **Pooled eradication rates:**
  - 83.6% (with probiotics)
  - 74.8% (without)
  - OR 1.84 (1.34-2.54)

- **Side effects**
  - 24.7% (with)
  - 38.5% (without)
  - OR 0.44 (0.30-0.66)

### Table: Comparison of Outcome

<table>
<thead>
<tr>
<th>Study of sub-category</th>
<th>Probiotic (n)</th>
<th>Control (n)</th>
<th>OR (fixed)</th>
<th>Weight</th>
<th>OR (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cagauco 2000</td>
<td>5/60</td>
<td>5/60</td>
<td>7.23</td>
<td>1.00</td>
<td>[0.30, 3.39]</td>
</tr>
<tr>
<td>Armuzzi-Diapermin</td>
<td>26/60</td>
<td>37/60</td>
<td>29.08</td>
<td>0.48</td>
<td>[0.23, 0.96]</td>
</tr>
<tr>
<td>Charleston 2002</td>
<td>11/64</td>
<td>12/61</td>
<td>20.04</td>
<td>0.14</td>
<td>[0.05, 0.44]</td>
</tr>
<tr>
<td>Chen 2004</td>
<td>6/47</td>
<td>15/50</td>
<td>16.98</td>
<td>0.34</td>
<td>[0.12, 0.97]</td>
</tr>
<tr>
<td>Tang 2004</td>
<td>5/36</td>
<td>13/39</td>
<td>14.92</td>
<td>0.39</td>
<td>[0.09, 0.91]</td>
</tr>
<tr>
<td>Sialkana 2005</td>
<td>20/23</td>
<td>22/24</td>
<td>3.76</td>
<td>0.61</td>
<td>[0.09, 4.01]</td>
</tr>
<tr>
<td>Sialkana 2006</td>
<td>7/59</td>
<td>6/67</td>
<td>6.97</td>
<td>0.92</td>
<td>[0.31, 2.76]</td>
</tr>
<tr>
<td>Total (meta. CI)</td>
<td>329</td>
<td>287</td>
<td>100.00</td>
<td>0.44</td>
<td>[0.30, 0.66]</td>
</tr>
</tbody>
</table>

Total events: 81 (probiotic), 114 (control)

Test for heterogeneity: $Q_9 = 8.01$ [df = 9] ($P = 0.33$), $I^2 = 25.6$

Test for overall effect: $Z = 6.04$ ($P < 0.0001$)
H Pylori

European Consensus Report

Statement 12: Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects.

Evidence level: 5

Grade of recommendation: D

Gut 2012
## Uses in GI

- Irritable Bowel Syndrome (IBS)
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- C. difficile

## C. Difficile

### Role
- Prevention of CDAD
- Prevention of Recurrent CDAD

### Strains
- *Saccharomyces boulardii*
- *Lactobacillus GG*
- Mixtures
- Fecal transplant
C. Difficile

• Systematic Reviews / Meta-analyses
  – Cochrane Review 2008
    • Overall no sufficient evidence to recommend for probiotics
      – as an adjunct to antibiotic therapy
      – to prevent recurrence

  – 2 of 5 studies found that *S. boulardii* may be effective in secondary prevention of CDI

C. Difficile

• *S. boulardii*
  – Mechanism
    • Produces serine protease that directly degrades toxin A and B
    • Destroys colonic receptor for C. Diff

  – Survives best at 37°C
  – Resistant to antibacterial agents and stomach acid

McFarland L WJG 2010
C. difficile & S. boulardii

~ 50% initial and 50% recurrent

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Treatment groups</th>
<th>Study population</th>
<th>Daily dose (mg/d)</th>
<th>Duration of treatment (wk)</th>
<th>Follow-up (wk)</th>
<th>C. difficile recurrence in probiotic group</th>
<th>C. difficile recurrence in placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>McFarland et al(25)</td>
<td>S. boulardii vs placebo</td>
<td>124 adult patients on varied doses of vancomycin or metronidazole; recurrent and initial CDAD cases; 3 referral sites, US</td>
<td>$5 \times 10^9$ (5000 mg)</td>
<td>4</td>
<td>4</td>
<td>15/37 (40.5%)</td>
<td>30/67 (44.8%)</td>
</tr>
<tr>
<td>François et al(26)</td>
<td>S. boulardii vs placebo</td>
<td>168 adult patients recurrent CDAD on vancomycin (2 g/d, n = 32) or V (3000 mg/d, n = 33) or M (1 g/d, n = 33); 4 referral sites, US</td>
<td>$2 \times 10^9$ (2000 mg)</td>
<td>4</td>
<td>4</td>
<td>17/38 (44.7%)</td>
<td>13/27 (48.1%)</td>
</tr>
</tbody>
</table>

rCDAD 35% vs 65%

C. Difficile

- Overall insufficient evidence to recommend use in recurrent C. diff or to prevent C. diff
Safety

• **Common side effects**
  – Bloating, distension, diarrhea, constipation, nausea, dyspepsia

• **Are probiotics safe:**
  – Bacteremia / endocarditis / liver abscess from LGG have been reported
  – Fungemia from *S. boulardii*
  – **Risk factors**
    • Severely immunocompromised
    • Premature infants
    • Central vein catheters
    • Severe pancreatitis – NJ feeding

My Take

**Some** evidence to support possible benefit of probiotics in certain GI conditions (poor quality)

- For GI diseases with effective established treatments, no role for probiotics
  - IBD
  - *C. difficile*

- For GI diseases with less effective conventional therapy, consider probiotics (healthy outpatients)
  - IBS
  - AAD / HP eradication
Bifidobacterium infantis
Saccharomyces boulardii
Lactobacillus plantarum

Health Canada

How do I know if a product has been authorized?

To be licensed in Canada, natural health products must be safe, effective, of high quality and carry detailed label information to let people make safe and informed choices.

You can identify products that have been licensed for sale in Canada by looking for the eight-digit Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label.

A NPN or DIN-HM means that the product has been authorized for sale in Canada and is safe and effective when used according to the instructions on the label.