Pro-biotics or Amateur-biotics?

Probiotics for gastrointestinal illness

Faculty/Presenter Disclosure

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Abbreviations

• L.=Lactobacillus
• B.=Bifidobacterium
• E.=Escherichia
What is a Probiotic?

• “Live microorganisms which when administered in adequate amounts confer a health benefit on the host”-Expert Panel of the Food and Agriculture Organization of the United Nations

• Caveat: “Barely a paper is published without the use of a different definition, or challenging the most used one, or proposing a different nuance of it.”

1. Best Pract Res Clin Gastroenterol 2016;30(1)

How do they Work?

• There are MULTIPLE answers to this question
• Simple answer?
  • They work by “creating a more favourable gut environment, and supporting a healthy digestive tract and a healthy immune system”

1. Best Pract Res Clin Gastroenterol 2016;30(1)
GI Products on Canadian Market

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align</td>
<td>B. longum infantis 35624</td>
</tr>
<tr>
<td>BioGaia</td>
<td>L. reuteri protectis DSM 17938</td>
</tr>
<tr>
<td>Bio-K+ CL 1285</td>
<td>L. Acidophilus CL 1285</td>
</tr>
<tr>
<td></td>
<td>L. casei LBC80R</td>
</tr>
<tr>
<td></td>
<td>L. Rhamnosus CLR2</td>
</tr>
<tr>
<td>Culturelle</td>
<td>L. rhamnosus GG</td>
</tr>
<tr>
<td>Florastor</td>
<td>Saccharomyces boulardii lyo</td>
</tr>
<tr>
<td>Mutaflor</td>
<td>E. coli Nissle 1917</td>
</tr>
<tr>
<td>Proxiflor</td>
<td>L. rhamnosus R0011</td>
</tr>
<tr>
<td></td>
<td>L. helveticus R0052</td>
</tr>
<tr>
<td>TuZen</td>
<td>L. plantarum 299v</td>
</tr>
<tr>
<td>VSL#3</td>
<td>4 Lactobacillus strains, 3 Bifidobacterium</td>
</tr>
<tr>
<td></td>
<td>strains and 1 Streptococcus strain</td>
</tr>
</tbody>
</table>


History of Probiotics

- 2000s-present: explosion in research, including controlled clinical trials

- Human Microbiome Project has now identified >40 000 species in the colon

3. Clin Infect Dis 2015;60(suppl 2)
Do Patients Use Probiotics?

- Small Canadian survey\(^4\)
  - 35% taken probiotics for “overall or digestive health”
- Global retail market value $41 billion USD in 2015\(^5\)
  - Only 9% of that is probiotic supplements
- All cost roughly $1/day, except VSL#3, ~$4/day

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**Evidence is strongest for conditions in bold**

- NEC=necrotizing enterocolitis
- AAD=antibiotic associated diarrhea
- RR=reduces risk
- IBS=irritable bowel syndrome
- CID=common infectious diseases
- URTI=upper respiratory tract infection

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Strain Really Matters

- All of the following potentially influence differences in effect between probiotic studies
  - Genus, species and strain studied
  - Tolerance to acid, growth requirements and fecal recovery rates
  - Method of delivery, i.e. yogourt vs capsule
  - Disease state
  - Age group of subjects
  - Combined vs single strains
  - Treatment duration
  - Number of colony forming units (CFU)

7. Therap Adv Gastroenterol 2010;3(5)

Are Probiotics Safe?

- Lack of systematic reporting
- Poorly documented interventions
- For RCTs where adverse events were reported, no statistically significant increase (RR 1.00; 95% CI 0.93-1.07)
- “Despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence”

8. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. AHRQ. April 2011.
CDAD

• *Clostridium difficile*-associated diarrhea (CDAD)
• Cochrane Review of 23 RCTs, 4303 patients looked at probiotics for prevention of CDAD
  • Incidence of CDAD: 2% in probiotic group vs 5.5% in placebo/no treatment arm (NNT 29)
• Problems
  • 10 different strain combinations
  • Only 4 showed difference in subgroup analysis


CDAD: Impact of Funding

• 24 studies separated by public funding or industry/unclear funding\(^\text{11}\)
• Industry supported/unclear funded studies were more than twice as likely as publicly funded studies to report benefit of probiotics in preventing CDAD

11. Am J Gastro 2014;109(7)
Antibiotic Associated Diarrhea (AAD)

- **JAMA 2012**\(^{13}\)
  - 82 RCTs, multiple strains, capsules, liquids, powders, yogurts, etc.
  - 63 RCTs meta-analyzed
  - NNT 13; effect still significant for numerous subgroup analyses and specific strains

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Hold the Phone

- New large multi-centre RCT, 2981 patients, government funded\(^{10}\)
- *Lactobacilli* and *Bifidobacteria*
- At 12 weeks, no significant difference in CDAD or AAD incidence:
  - CDAD: 0.8% probiotic, 1.2% placebo
  - AAD: 10.8% probiotic, 10.4% placebo

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13. *JAMA* 2012;307(18)
10. *Lancet* 2013;382(9900)
Irritable Bowel Syndrome (IBS)

- Problem with outcomes
  - Abdominal pain improvement, pain score by VAS, IBS severity score, global improvement, “adequate general symptom improvement”
- 2010 meta-analysis of 10 RCTs with 918 patients, reporting dichotomous outcomes\(^\text{14}\)
  - NNT 4 to report symptom improvement or “cure”
  - Sub-analysis of only higher quality trials: not statistically significant

\(^{14}\) Gut 2010;59:e325-e332

Inflammatory Bowel Disease (IBD)

- Crohn’s: few very small studies, no benefit\(^\text{15}\)
- Ulcerative colitis
  - Maintaining remission\(^\text{16}\): statistically similar to 5-ASA
  - Inducing remission\(^\text{17}\): only VSL#3 shows benefit; 5 studies of 438 patients; NNT ~6

\(^{15}\) Cochrane Systematic Reviews. CD006684. 
\(^{16}\) Cochrane Systematic Reviews. CD007443. 
\(^{17}\) Inflamm Bowel Dis. 2014;20(1).
Specific Products

- Florastor: *S. boulardii*
- Dose: 1-2 capsules per day
- Prevention of AAD\(^{13}\): NNT 10
- Prevention of CDAD\(^{9}\): NNT ~55
- Treatment of acute pediatric diarrhea\(^{18}\):
  - Meta-analysis of 17 studies with 2102 patients
  - Reduced duration of diarrhea on average ~20 hours, 1 less loose stool per day
  - Only 2 studies (230 subjects) done in advanced economies

\(^{18}\) Pediatrics. 2014;134:e176-e191

Specific Products: Florastor

- Caveat on CDAD & AAD findings
- LV McFarland, listed as author on one in six meta-analyses, guidelines, and systematic reviews regarding *Saccharomyces boulardii* on PubMed
- Discloses paid speaker for manufacturer but not that from 1988 to 2001, scientific director for patent holder\(^{19}\)
- Two of her RCTs published during that time included in CDAD and AAD reviews

\(^{19}\) LinkedIn profile job history of Lynne V McFarland.
Specific Products

• **Align**: *B. bacterium longum* Infantis 35624
  • Dose: 1 capsule per day
  • Marketed for IBS symptom improvement
  • Two RCTs with specific strain\(^{20,21}\)
    • Both funded, partly conducted by manufacturer
    • Statistically significant improvement, but not likely clinically significant; 0.9-1 point improvement on 7-point symptom scale
    • Neither had same dose as current product and one was in a liquid vehicle

\(^{20}\) Gastroenterology 2005;128(3)
\(^{21}\) Am J Gastroenterol 2006;101(7)

Specific Products

• **Culturelle**: *L. rhamnosus GG*
  • Dose: 1 capsule per day
  • Management of acute infectious diarrhea in children\(^{22}\)
    • Prevention of nosocomial diarrhea and rotavirus gastroenteritis
    • Meta-analysis, only 3 studies (1043 subjects), two by meta-analysis author
    • Only one not done by author and done in advanced economy showed no effect
    • Prevention of CDAD/AAD
      • No statistically significant difference from placebo\(^{9}\)

\(^{22}\) Aliment Pharmacol Ther 2011;34(9)
Specific Products

- **TuZen: *L. plantarum* 299v**
  - Dose: 1-2 capsules per day
  - Marketed for improvement of IBS symptoms
  - 3 small RCTs done, all by manufacturer\textsuperscript{23-25}
  - Small benefit; questionable clinical significance
  - Independent meta-analysis\textsuperscript{26} concluded no benefit based on data

\textsuperscript{23. World J Gastroenterol 2012;18(30)}
\textsuperscript{24. Eur J Gastroenterol Hepatol 2001;13(10)}
\textsuperscript{25. Am J Gastroenterol 2000;95(5)}
\textsuperscript{26. PLoS ONE 2012;7(4)}

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Specific Products

- **Biogaia: *L. reuteri* protectis**
  - Dose: 5 drops
  - Treatment of infantile colic
  - Meta-analysis of 6 RCTs including 423 infants with colic\textsuperscript{27}
    - Decreased crying time at 2 weeks by 43 minutes per day
    - Treatment effect *gone by 4 weeks*

\textsuperscript{27. PLoS ONE 2015;10(10)}
Other Uses

• Meta-analysis of multiple GI uses found no evidence for traveler’s diarrhea\textsuperscript{26}

• Likely benefit
  - Necrotizing enterocolitis in <34 week infants of very low birth weight (<1500g)\textsuperscript{28}

• Unlikely Benefit
  • Prevention of URTIs\textsuperscript{29}

• No benefit
  • Weight loss\textsuperscript{30}

\textsuperscript{28.} Cochrane Systematic Reviews. CD005496
\textsuperscript{29.} Cochrane Systematic Reviews. CD006895
\textsuperscript{30.} Nutr Res 2015;35(7)

Bottom Line

• Multiple problems with CDAD/AAD findings
  • Small sample sizes, industry funding, selection bias
  • Frequent detection of publication bias in meta-analyses
  • Hodgepodge of study populations, strains, doses, vehicles, and study outcomes
Bottom Line

• Best evidence currently exists for:
  • Treatment of acute diarrhea in children
    • Small effect; if limit analysis to high income countries, reduce duration of diarrhea by <20 hours
  • Prevention of AAD
    • Only 10% of RCTs adequately powered to find result
    • Frequency of AAD in placebo abnormally high; ~35% compared to general population ~10%

35. BMC Infect Dis. 2015;15(129)

Bottom Line

• Most reviews urge caution in interpreting results due to “significant methodological limitations”
• Small sample sizes, industry funding, selection bias
• Frequent detection of publication
• Hodgepodge of study populations, strains, doses, vehicles, and study outcomes
Conclusion

Probiotics need to up their game in spring training before they’re ready for the big leagues

References

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