Prophylactic probiotics for the prevention of cancer therapy-induced diarrhea: a meta-analysis

Dr Hannah Wardill, Dr Ysabella Van Sebille, Dr Matt Ciorba and A/Prof Joanne Bowen

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The University of Adelaide (Adelaide Medical School)
The University of Groningen (University Medical Centre Groningen / Beatrix Children’s Hospital)
MICROBIOME
Evolution of the microbiome in mucositis research
Evolution of the microbiome in mucositis research

Sonis model introduced

2004
Evolution of the microbiome in mucositis research

- Sonis model introduced in 2004
- Changes in microbiome detected in preclinical models from 2007-2012, with contributions from Stringer et al., Von Bultzinglowen et al., Lin et al., and Johnson et al.
Evolution of the microbiome in mucositis research

- 2004: Sonis model introduced
- 2007-2012: 16S rRNA sequencing introduced
- Changes in microbiome detected in preclinical models by Stringer et al., Von Bultzinglowen et al., Lin et al., and Johnson et al.
- Metagenomic approaches more readily utilised
Evolution of the microbiome in mucositis research

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Clinical evidence of microbial dysbiosis

Van Vliet et al., Zvieleher et al., Montassier et al., Stringer et al., Manichanh et al., and Nam et al.

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- **2007-2012**: 16S rRNA sequencing introduced
- **2007-2012**: Metagenomic approaches more readily utilised
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- **MASCC guideline**
  - 2014

- **Metagenomic approaches more readily utilised**
“The panel suggests that probiotics containing Lactobacillus species be used to prevent diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy” Lalla et al., 2014
Evolution of the microbiome in mucositis research

- **Sonis model introduced** (2004)
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- **Meta-Analysis 1** (Wang et al. 2016)

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Meta-Analysis 1
Wang et al., 2016

2009-2016
Changes in microbiome detected in preclinical models

Meta-Analysis 2
Lui et al., 2017
Meta-analysis protocol

June 1 2000 - June 1 2017

Total of 1090 patients included in meta-analysis

Records identified through database searches n = 90

Additional records identified through other searches n = 4

Total records after duplicates removed n = 87

Records screened n = 87

Full text articles assessed for eligibility n = 14

Studies included in qualitative synthesis n = 7

Records removed based on title/abstracts n = 73

Full text articles excluded: Non-prophylactic n = 1 Case study/series n = 4 Repeated reporting n = 2

Studies included in quantitative synthesis (meta-analysis) n = 7
# Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Diagnoses</th>
<th>Treatment(s)</th>
<th>Probiotic Type/Source/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitapanarux 2010</td>
<td>N=32 (pro)</td>
<td>Cervical</td>
<td>Pelvic radiotherapy (200 cGy/fraction, 5 fraction/wk) and wkly cisplatin (40 mg/m&lt;sup&gt;2&lt;/sup&gt;, 6 wk)</td>
<td>Lactobacilli and bifidobacteria (4x10&lt;sup&gt;9&lt;/sup&gt; CFU); Laboratorio Farmaceutico SIT (Mede, Italy); Probiotic provided 1 week before treatment and for duration of treatment.</td>
</tr>
<tr>
<td></td>
<td>N=31 (cont)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delia 2007</td>
<td>N=243 (pro)</td>
<td>Sigmoid, rectal and cervical</td>
<td>Postoperative radiotherapy (60-70 Gy)</td>
<td>Lactobacilli, bifidobacteria and streptococcus (1.35 x 10&lt;sup&gt;12&lt;/sup&gt; CFU); VSL Pharmaceuticals (Fort Lauderdale MD, USA); Duration of treatment (daily)</td>
</tr>
<tr>
<td></td>
<td>N=239 (cont)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demers 2014</td>
<td>N=140 (pro)</td>
<td>Gyn, rectal, prostate</td>
<td>Radiotherapy (40 Gy) +/- chemotherapy</td>
<td>Lactobacilli and bifidobacteria (LD: 2.6 x 10&lt;sup&gt;9&lt;/sup&gt; CFU, or HD: 3 x 10&lt;sup&gt;9&lt;/sup&gt; CFU); Bifilact, virage Santé, Québec City, Canada; Duration of treatment</td>
</tr>
<tr>
<td></td>
<td>N=86 (cont)</td>
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<td></td>
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</tr>
<tr>
<td>Giralt 2008</td>
<td>N=44 (pro)</td>
<td>Endometrial adeno, advanced</td>
<td>Post-operative radiotherapy (45-50.4 Gy), concomitant weekly cisplatin (40 mg/m&lt;sup&gt;2&lt;/sup&gt;, only for patients with cervical</td>
<td>Streptococcus thermophilus, Lactobacillus delbrueckii subsp. bulgaricus + 96 ml of fermented liquid yoghurt (3x daily) containing 10&lt;sup&gt;8&lt;/sup&gt; CFU/g L.casei DN114001; Source not reported.; Probiotic provided 1 week before tx and for duration of tx.</td>
</tr>
<tr>
<td></td>
<td>N=41 (cont)</td>
<td>cervical squamous cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacatoure 2016</td>
<td>N=58 (pro)</td>
<td>Advanced NSCLC</td>
<td>Dacomitinib, (45 mg, daily, continuous)</td>
<td>VSL#3 (4 capsules daily, for duration of study); Source not reported.</td>
</tr>
<tr>
<td></td>
<td>N=59 (cont)</td>
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</tr>
<tr>
<td>Mego 2015</td>
<td>N=23 (pro)</td>
<td>Colorectal</td>
<td>Irinotecan, 5-FU, capecitabine, bevacizumab, cetuximab.</td>
<td>Colon dophilus; Harmonion International Inc. Mirabel, Canada; 10 x10&lt;sup&gt;9&lt;/sup&gt; CFU/day for 12 weeks (3 x daily)</td>
</tr>
<tr>
<td></td>
<td>N=23 (cont)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Osterlund 2007</td>
<td>N=52 (pro)</td>
<td>Colorectal</td>
<td>5-FU (370-425 mg/m&lt;sup&gt;2&lt;/sup&gt;) for 24 wk with concomitant</td>
<td>Lactobacillus rhamnosus (2x daily; 1-2 x 10&lt;sup&gt;10&lt;/sup&gt; CFU); Gefilus Valio Ltd, Helsinki Finland; Duration of treatment.</td>
</tr>
<tr>
<td></td>
<td>N=98 (cont)</td>
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</tr>
</tbody>
</table>
Results: overall risk of bias

- Overall studies were fairly robust
- Delia et al., was most problematic (multiple publications)
- Inconsistent outcome data
Results: overall risk of bias

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1. Overall diarrhea severity
Results: overall risk of bias

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1. Overall diarrhea severity
2. Incidence of severe diarrhea
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1. Overall diarrhea severity
2. Incidence of severe diarrhea
3. Use of rescue medication
Results: diarrhoea incidence

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Events</th>
<th>Total</th>
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<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
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<tr>
<td>Chitapanarux 2010</td>
<td>32</td>
<td>32</td>
<td>31</td>
<td>31</td>
<td>18.6%</td>
<td>1.00</td>
<td>[0.94, 1.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delia 2007</td>
<td>42</td>
<td>243</td>
<td>119</td>
<td>239</td>
<td>15.7%</td>
<td>0.35</td>
<td>[0.26, 0.47]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demers 2014</td>
<td>140</td>
<td>140</td>
<td>86</td>
<td>86</td>
<td>18.7%</td>
<td>1.00</td>
<td>[0.98, 1.02]</td>
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</tr>
<tr>
<td>Lacouture 2016</td>
<td>49</td>
<td>59</td>
<td>49</td>
<td>58</td>
<td>17.8%</td>
<td>0.98</td>
<td>[0.84, 1.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mego 2015</td>
<td>9</td>
<td>23</td>
<td>14</td>
<td>23</td>
<td>10.6%</td>
<td>0.64</td>
<td>[0.35, 1.18]</td>
<td></td>
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</tr>
<tr>
<td>Osterlund 2007</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>594</strong></td>
<td><strong>488</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.81</strong></td>
<td><strong>[0.60, 1.09]</strong></td>
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<td></td>
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</tr>
<tr>
<td>Total events</td>
<td>369</td>
<td>350</td>
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</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 991.21$, df = 5 ($P < 0.000001$); $I^2 = 99\%$

Test for overall effect: $Z = 1.41$ ($P = 0.16$)

<table>
<thead>
<tr>
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<td>[0.01, 2.58]</td>
<td></td>
<td></td>
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<td>8</td>
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<td>44</td>
<td>15</td>
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<td>1.24</td>
<td>[0.74, 2.08]</td>
<td></td>
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<td>0.11</td>
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<td>Total events</td>
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<td>144</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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Heterogeneity: $\tau^2 = 0.77$; $\chi^2 = 44.33$, df = 6 ($P < 0.000001$); $I^2 = 86\%$

Test for overall effect: $Z = 1.58$ ($P = 0.11$)
Results: diarrhoea incidence

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Heterogeneity: Tau² = 0.77; Chi² = 44.33, df = 6 (P < 0.00001); I² = 86%

Test for overall effect: Z = 1.58 (P = 0.11)
Results: use of rescue medication

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<tr>
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<td>3</td>
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</tr>
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<td>Giralt 2008</td>
<td>16</td>
<td>44</td>
<td>12</td>
<td>41</td>
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</tr>
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<td>41</td>
<td>59</td>
<td>36</td>
<td>58</td>
<td>49.9%</td>
<td>1.12 [0.86, 1.46]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>135</td>
<td></td>
<td>130</td>
<td></td>
<td>100.0%</td>
<td>0.93 [0.53, 1.65]</td>
</tr>
<tr>
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<td>60</td>
<td></td>
<td>58</td>
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</tbody>
</table>

Heterogeneity: Tau² = 0.15; Chi² = 5.29, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.24 (P = 0.81)
What does it mean for the future of probiotics?

• Most **comprehensive** meta-analysis (including all forms of cancer treatment, excl. surgery)

• **No overall benefit** of probiotics for the prevention of “cancer therapy” induced diarrhea

• Negative results reflect breadth of studies included (e.g. Lacouture et al., 2016)

• Data support continued use in patients with pelvic malignancy
Obstacles encountered and future directions

Obstacles

• Variation in endpoint analyses (e.g. mucositis/diarrhea assessment, self-reported vs clinician-reported)

• Lack of objective biomarker that is uniformly applicable
Obstacles encountered and future directions

Obstacles

• Variation in endpoint analyses (e.g. mucositis/diarrhea assessment, self-reported vs clinician-reported)
• Lack of objective biomarker that is uniformly applicable

Recommendations

• **Take a step back** … characterise ‘ideal’ microbial composition (likely to be different for each treatment type)
  • These studies should involve an experienced microbiologist or bioinformatics expert
  • Pair specific forms of toxicity with unique microbial phenotype
• **Intelligent study design** … uniform grading systems, inclusion of gastroenterologist or ‘onco-gastroenterologist’
Acknowledgements

Cancer Treatment Toxicities Group The University of Adelaide
The Mucositis Research Group University Medical Centre Groningen
Dr Matthew Ciorba Washington University School of Medicine

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Prophylactic probiotics for cancer therapy-induced diarrhoea: a meta-analysis

Hannah R. Wardill\textsuperscript{a,b}, Ysabella Z.A. Van Sebille\textsuperscript{c}, Matthew A. Ciorba\textsuperscript{d}, and Joanne M. Bowen\textsuperscript{a}

Purpose of review
Strong preclinical data support prophylactic probiotics as an effective preventive strategy for diarrhoea secondary to anticancer therapies. To determine the composite evidence that this approach translates to the clinic, we performed a meta-analysis of randomized controlled trials (RCTs) of prophylactic probiotics for the prevention of cancer therapy induced diarrhoea.

Recent findings
A three-step search strategy was used to identify relevant studies (1 June 2000–1 June 2017) investigating probiotic intervention for diarrhoea secondary to any cancer therapy (cytotoxic, targeted and immunotherapies). RCTs across PubMed, Embase, CINAHL and CENTRAL were assessed for eligibility and assessed using RevMan 5.3 (The Cochrane Collaboration). Seven trials with a total of 1091 patients were included in this meta-analysis. Compared with placebo, prophylactic probiotics did not prevent or reduce the overall incidence of diarrhoea or severe CTCAE Grade at least 3 diarrhoea [relative risk (RR) = 0.81, 95% confidence interval (95% CI) = 0.60–1.09, \( Z = 1.41 \), \( P = 0.16 \); RR = 0.54, 95% CI = 0.25–1.16, \( Z = 1.58 \), \( P = 0.11 \)], nor did it influence the use of rescue medication (RR = 0.93, 95% CI = 0.53–1.65, \( Z = 0.24 \), \( P = 0.81 \)).

Summary
Current evidence does not support widespread implementation of probiotics for diarrhoea secondary to anticancer therapy.