The use of probiotics to prevent antibiotic induced diarrhoea.

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Bacteria Nomenclature

- Division e.g. Firmicutes
- Class e.g. Bacilli
- Order e.g. Lactobacillales
- Family e.g. Lactobacillaceae
- Genus e.g. Lactobacillus
- Species e.g. casei
- Strain e.g. shirota or DN114-001
What is the problem?
Gut microflora changes with ageing

- Bacteroides and bifidobacteria (total numbers and species diversity)
- Amylolytic activity
- Total SCFA (acetate, propionate and butyrate) (ABE)

Gut microflora

- Facultative anaerobes
- Fusobacteria, clostridia, eubacteria
- Proteolytic activity (ABE)

Total anaerobes = stable

Shifts in dominant species within bacterial groups
## Consequences

<table>
<thead>
<tr>
<th>Potential changes</th>
<th>Consequence to health</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ SCFA formation</td>
<td>↑ risk of diarrhoea, Changes in microflora, ↓ in faecal output</td>
</tr>
<tr>
<td>↑ Proteolytic activity</td>
<td>Toxic metabolites, ↑ risk of Cancer</td>
</tr>
<tr>
<td>Breakdown of bile acids</td>
<td>Toxic metabolites, ↑ risk of Cancer</td>
</tr>
<tr>
<td>Alterations in colonisation resistance</td>
<td>↓ Resistance to disease, ↑ in pathogenic bacteria</td>
</tr>
<tr>
<td>Changes to immunity within the gut</td>
<td>↑ risk of infection</td>
</tr>
</tbody>
</table>
**Mechanism**

- **Bacteroides fragilis**
- **Bacteroides distasonis**
- **Enterobacteriaceae**
- **Clostridial rRNA cluster IV**
- **Clostridial rRNA cluster XIVa**
- **Bifidobacteria**

Scanning Electron Micrograph of *Clostridium difficile*

Clostridium difficile adhering to the microvilli of the gut.
Antibiotic associated diarrhoea

25 studies including 2810 patients

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Number of RCT</th>
<th>Combined RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharomyces boulardii</td>
<td>6</td>
<td>0.37</td>
<td>0.26, 0.52</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>6</td>
<td>0.31</td>
<td>0.13, 0.72</td>
</tr>
<tr>
<td>Single strains of probiotics</td>
<td>6</td>
<td>0.46</td>
<td>0.21, 1.03</td>
</tr>
<tr>
<td>Mixtures of two probiotics</td>
<td>7</td>
<td>0.51</td>
<td>0.38, 0.68</td>
</tr>
</tbody>
</table>

McFarland LV, Am J Gastroenterol 2006;101:812–822
C. Diff associated diarrhoea

<table>
<thead>
<tr>
<th>Probiotic Combination</th>
<th>n</th>
<th>Dose (cfu per day)</th>
<th>Study period (days)</th>
<th>CDAD rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus acidophilus, Bifidobacterium bifidum&lt;sup&gt;1&lt;/sup&gt;</td>
<td>138</td>
<td>2x10&lt;sup&gt;10&lt;/sup&gt;</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>L acidophilus, Lactobacillus bulgaricus, B bifidum&lt;sup&gt;1&lt;/sup&gt;</td>
<td>100</td>
<td>NA</td>
<td>Var</td>
<td>11</td>
</tr>
<tr>
<td>Lactobacillus casei DN 114 001, L bulgaricus, S thermophilus&lt;sup&gt;2&lt;/sup&gt;</td>
<td>135</td>
<td>2x10&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Var</td>
<td>0</td>
</tr>
<tr>
<td>S boulardii&lt;sup&gt;3&lt;/sup&gt;</td>
<td>180</td>
<td>2x10&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Var</td>
<td>3</td>
</tr>
<tr>
<td>S boulardii&lt;sup&gt;3&lt;/sup&gt;</td>
<td>246</td>
<td>1x10&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Var</td>
<td>3</td>
</tr>
</tbody>
</table>

Study period: Treatment 20 days, Follow up 0 days

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>0.08</td>
</tr>
</tbody>
</table>

n=number of patients recruited on an intention to treat basis. NA=data not available. NS=not significant. Var=variable treatment and follow-up periods.

*Table 2: Trials of probiotics as primary prophylaxis against CDAD in hospitalised patients.*

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Power estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding</td>
<td>Concurrent medications for diarrhoea treatment</td>
</tr>
<tr>
<td>Precise strain</td>
<td>Patients group – disease specific v mixed; treated with specific type of Abx v any</td>
</tr>
<tr>
<td>Dose</td>
<td>Definition of diarrhoea and clear method of assessment</td>
</tr>
<tr>
<td>Duration</td>
<td>Testing for pathogenic bacteria – C Diff</td>
</tr>
<tr>
<td>Quality control of probiotic</td>
<td>Outcomes – simple incidence or other measures such as duration or severity</td>
</tr>
<tr>
<td>Method of administration</td>
<td>Monitoring for Adverse events</td>
</tr>
<tr>
<td>Length of follow up</td>
<td>Intention to treat analysis and good follow up</td>
</tr>
</tbody>
</table>
The Probiotic Trial

• Randomised double-blind, placebo-controlled study of a commercially available probiotic preparation on elderly patients receiving antibiotics while in hospital.

• Was there a reduction in the incidence of AAD and CDAD while on probiotic compared to placebo?
Who did we include?

- In-patients aged over 50 years
- Prescribed antibiotic therapy
- Able to take food and drink orally
- Excluded people who had a possibility of getting diarrhoea for other reasons – bowel problems, previous antibiotics
- Milk or lactose intolerance or using probiotics
- Safety
Intervention

• Probiotic drink containing *Lactobacillus casei* DN-114001, *Streptococcus thermophilus* and *Lactobacillus bulgaricus*

• Placebo group - a UHT milkshake drink.

• Started within 48 hours of antibiotic therapy and continued for one week after

• 100ml was given twice daily half an hour before or 1-2 hours after meals.
Results

• No reported adverse events related to the study drinks.
• Quality control lactobacillus counts were carried out on a sample of the Actimel® drinks: Mean count = $2.2 \times 10^8$ cfu/ml (range: $0.35 \times 10^8$ - $4.6 \times 10^8$).
• Yazoo was also tested for bacterial content and no growth was found.
Baseline data

• Average age = 74yrs
• Most patients received 1 antibiotic, about 40% received 2
• Reasons for antibiotic use
  – respiratory infection (49%)
  – prophylaxis before or after surgery (25%) (usually orthopaedic).
Results – Any Diarrhoea

Placebo Group
- 66%
- 34%

Probiotic Group
- 88%
- 12%
Results – C. Difficile

Placebo Group
- 17%
- 83%

Probiotic Group
- 0%
- 100%
Numbers needed to treat

- Any Diarrhoea = 5
- (95% CI: 3-15)

- C. difficile = 6
- (95% CI: 4-14)
Cost of Treatment

- No calculated costs for AAD
- Additional treatment costs for CDAD
  - £1835 (USA); £4000 (UK)
- Average cost of the probiotic = £10 per patient.
- The cost to prevent one case of:
  - AAD = £50
  - CDAD = £60
# Time of Treatment

<table>
<thead>
<tr>
<th>Time of Treatment</th>
<th>Probiotic N=65</th>
<th>Control N=62</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During antibiotic treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (6%)</td>
<td>5 (8%)</td>
<td>0.74</td>
</tr>
<tr>
<td>No diarrhoea</td>
<td>61 (94%)</td>
<td>57 (92%)</td>
<td></td>
</tr>
<tr>
<td><strong>Post antibiotic treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (6%)</td>
<td>14 (28%)</td>
<td>0.003</td>
</tr>
<tr>
<td>No diarrhoea</td>
<td>50 (94%)</td>
<td>37 (72%)</td>
<td></td>
</tr>
</tbody>
</table>
How might it work?

S.C. Ng et al.
Inflamm. Bowel. Dis
2008; online first
Improves immune response to C. diff infection

- *S. boulardii* up-regulates total and specific anti-toxin A secretory IgA expression in animals.

Colonisation resistance

- Lactobacilli inhibit C.diff growth
- Bifidobacteria inhibit growth and adhesion of C.diff
- ? via antimicrobials
- ? alterations of lumen pH hindering pathogenic proliferation (achieved through production of SCFA)
- Limited evidence specific to C.diff

Adhesion and mucosal invasion

- No *C. diff* specific data
- Lactobacilli and bifidobacteria reduce adhesion of other pathogenic bacteria (*E coli*).
- Antibacterial substance production?
- Suggests mechanism only works when probiotic present BEFORE pathogen.

Toxin inhibition

- S.boulardii resulted in reduced binding of toxin A
- Reduced intestinal fluid secretion
- Reduced intestinal permeability
- Probably due to protease that breaks down the toxins

Safety

“Current evidence suggests that the risk of infection with probiotic lactobacilli or bifidobacteria is similar to that of infection with commensal strains, and that consumption of such products presents a negligible risk to consumers, including immuno-compromised hosts.”

Will any probiotic do?

• NO
• Other strains may well be effective in preventing diarrhoea but research is needed
• Each strain must be shown to be effective for a given problem with a controlled trial
Expert recommendations

• **A**: Prevention of antibiotic associated diarrhoea in ambulatory and hospitalized adult patients. *LGG* and *S.boulardii* shown to be effective. *L.casei, L bulgaricus* and *S.Thermophilus* drink also good evidence.

• **B**: Prevention of *C.difficile* associated diarrhoea and its use in recurrent *C.difficile* disease. Best data for *LGG* and *S.boulardii*

42(supp 2) S104-S108
Future studies

• Well powered RCT to demonstrate effectiveness against *C. difficile*
• RCTs of different strains & dose regimens with quality control
• Need to demonstrate in routine use
  – Less exclusions and inclusion of more at risk patients
  – Use of routine data to avoid consent issues
  – Before and after study monitoring *C. difficile* rates.
Designer Probiotics

Key messages

• Strain specific actions of probiotics
• Effective for PREVENTION
• We want a well defined proven intervention - more high quality research is needed.