The Role of Probiotics in Antibiotic-Associated Diarrhea

Elena Lionetti, MD, PhD

Department of Paediatrics – University of Catania, Italy
The Gut Microbiota

1. More than 400 species of bacteria inhabit the human gut and perform functions essentials for our survive.

2. Colonization resistance refers to the "limiting action" of the normal flora on colonization of the bowel by exogenous as well as endogenous potentially pathogenic microorganisms.

(Plos Biol 2008; 6:2383-400)
Antibiotic side effects

Nausea

Headache

Abdominal distension

Abdominal pain

Taste disturbance

Vomiting

Diarrhea

Antibiotic-Associated Diarrhea (AAD) is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics.

(NEJM 2002; 346:334-9)
Incidence of the problem

Risk factors

Hospitalization, Immunosuppression, Early age, Broad-spectrum antibiotic use Combined antibiotic therapy Prolonged antibiotic therapy

(JPGN 2003; 37:2-3)
Spectrum of clinical finding

- Nuisance diarrhoea
- Abdominal pain and cramps
- Fever
  (leukocitosis & hypoalbuminemia)
- Colitis
  (C. Difficile)

(J Pediatr 2006;149:367-72)
Any antibiotic can cause AAD

(NEJM 2002; 346:334-9)
Mechanism of AAD

**Metabolic consequences of altered flora:**
(reduction of the concentration of intestinal anaerobes)

a) Reduced digestion of CHO and increased colonic osmotic load leading to osmotic diarrhoea;

b) Reduced breakdown of primary bile acids, which are potent colonic secretory agents.

**Overgrowth of other enteric pathogens:**

a) Salmonella;

b) *Clostridium perdingens A*;

c) *Staphilococcus Aureus*;

d) *Candida Albicans*.

**Clostridium difficile:**

a) Colonisation;

b) Toxins;

(J Clin Gastroenterol 2008; 42:58–63)
AAD is responsible for:

a) longer hospital stay (8 days on average);
b) higher cost of care ($2000 - 4000 per stay);
c) 5 fold increase in the incidence of other nosocomial infections;
d) 3 fold increase in mortality (ranging from 0.7% to 38%).

There is thus considerable interest in measures capable of prevention or amelioration of this condition.

(Best Pract Res Clin Gastroenterol 2003; 17:775; Dig Dis 1998; 10:292)
Have probiotics a role in AAD?
Mechanism of action of Probiotics

1. Production of antimicrobial substances \((lactic/aceric acid, H_2O_2; reuterin)\)

2. Inhibition of epithelial and mucosal adherence of pathogens
   \((physical\ blocking\ of\ pathogen\ adhesion\ receptors,\ secretion\ of\ antibacterial\ molecules,\ stimulation\ of\ the\ secretion\ of\ antimicrobial\ substances\ such\ as\ defensin)\)

3. Competition for nutrients

4. Stabilization of the barrier function of the gut epithelium \((restoring\ paracellular\ permeability,\ increasing\ mucus\ production)\)

\(\text{(Dig Liver Dis 2002:78-80)}\)
**Mechanism of action of Probiotics**

1. **Production of antimicrobial substances** *(lactic/aceric acid, $H_2O_2$; reuterin)*

2. **Inhibition of epithelial and mucosal adherence of pathogens** *(physical blocking of pathogen adhesion receptors, secretion of antibacterial molecules, stimulation of the secretion of antimicrobial substances such as defensin)*

3. **Competition for nutrients**

4. **Stabilization the barrier function of the gut epithelium** *(restoring paracellular permeability, increasing mucus production)*

**Non immunological**

1. Stimulating cytokine production;

2. Enhancing the phagocytic capacity *(of polymorphonuclear cells and macrophages)*;

3. Prevention of apoptosis *(prolonged survival of enterocytes)*;

4. Stimulation of immunity *(especially the IgA response)*

5. Enhancing specific antibody responses to pathogenic organisms

*(Dig Liver Dis 2002:78-80)*
From bench to bedsides
From bench to bedsides

All randomized paediatric controlled trials where a specified probiotic agent has been compared to placebo (10 RCT identified)

Objective was to assess the effect of probiotics for prevention of paediatric antibiotic associated diarrhea
Effects of probiotics in children with AAD

1st Outcome

Incidence of diarrhea
Effects of probiotics in children with AAD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H-Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus GG</td>
<td>3/60</td>
<td>9/59</td>
<td></td>
<td>6.7%</td>
</tr>
<tr>
<td>Arvola 1999</td>
<td>7/93</td>
<td>25/95</td>
<td></td>
<td>10.6%</td>
</tr>
<tr>
<td>Vanderhoof 1999</td>
<td></td>
<td></td>
<td></td>
<td>0.29 [0.13, 0.63]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>153</strong></td>
<td><strong>154</strong></td>
<td>17.3%</td>
<td>0.33 [0.09, 1.15]</td>
</tr>
<tr>
<td>L. acidophilus % L. bulgaricus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinkl 1990</td>
<td>10/15</td>
<td>16/23</td>
<td></td>
<td>14.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>15</strong></td>
<td><strong>23</strong></td>
<td>14.1%</td>
<td>0.96 [0.61, 1.50]</td>
</tr>
<tr>
<td>L. acidophilus and Bifidobacterium infantis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jirapinyo 2002</td>
<td>3/8</td>
<td>8/10</td>
<td></td>
<td>9.1%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>8</strong></td>
<td><strong>10</strong></td>
<td>9.1%</td>
<td>0.47 [0.18, 1.21]</td>
</tr>
<tr>
<td>L. sporogenes</td>
<td>14/48</td>
<td>31/50</td>
<td></td>
<td>13.6%</td>
</tr>
<tr>
<td>LaRosa 2003</td>
<td></td>
<td></td>
<td></td>
<td>0.47 [0.29, 0.77]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>48</strong></td>
<td><strong>50</strong></td>
<td>13.6%</td>
<td>0.47 [0.29, 0.77]</td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benhamou 1999</td>
<td>25/327</td>
<td>16/289</td>
<td></td>
<td>12.4%</td>
</tr>
<tr>
<td>Erdeve 2004</td>
<td>14/244</td>
<td>42/222</td>
<td></td>
<td>12.7%</td>
</tr>
<tr>
<td>Kotowski 2005</td>
<td>4/119</td>
<td>22/127</td>
<td></td>
<td>8.3%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>690</strong></td>
<td><strong>638</strong></td>
<td>33.5%</td>
<td>0.45 [0.14, 1.48]</td>
</tr>
<tr>
<td>B. lactis % S. thermophilus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correa 2005</td>
<td>13/80</td>
<td>24/77</td>
<td></td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>80</strong></td>
<td><strong>77</strong></td>
<td>12.5%</td>
<td>0.52 [0.29, 0.95]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>994</strong></td>
<td><strong>952</strong></td>
<td>100.0%</td>
<td>0.49 [0.32, 0.75]</td>
</tr>
</tbody>
</table>

Total events: 93 (Treatment), 193 (Control)
Heterogeneity: Tau² = 0.28; Chi² = 27.76; df = 8 (P = 0.00052); I² = 71%
Test for overall effect: Z = 3.33 (P = 0.00088)

Probiotics are effective for preventing AAD (-11%)
Effects of probiotics in children with AAD

2\(^{nd}\) Outcome

Mean duration of diarrhea
Effects of probiotics in children with AAD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV/Random,95% CI</td>
</tr>
<tr>
<td>1 Explanatory trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arvola 1999</td>
<td>60</td>
<td>4 (1.5)</td>
<td>59</td>
<td>4 (1.5)</td>
<td>26.5 %</td>
</tr>
<tr>
<td>LaRosa 2003</td>
<td>56</td>
<td>0.7 (1.4)</td>
<td>54</td>
<td>1.6 (2)</td>
<td>24.2 %</td>
</tr>
<tr>
<td>Vanderhoof 1999</td>
<td>93</td>
<td>4.7 (1.5)</td>
<td>95</td>
<td>5.88 (1.5)</td>
<td>28.9 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>209</td>
<td>208</td>
<td></td>
<td></td>
<td>79.6 %</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.35; Chi² = 11.50, df = 2 (P = 0.003); I² = 83%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.86 (P = 0.063)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Pragmatic trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correa 2005</td>
<td>80</td>
<td>3.92 (2.47)</td>
<td>77</td>
<td>5 (2.8)</td>
<td>20.4 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>80</td>
<td>77</td>
<td></td>
<td></td>
<td>20.4 %</td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.56 (P = 0.010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>289</td>
<td>285</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.26; Chi² = 12.01, df = 3 (P = 0.01); I² = 75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.59 (P = 0.009%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Probiotics decreased the mean duration of diarrhea by \( \frac{3}{4} \) of a day
Effects of probiotics in children with AAD

3rd Outcome

Probiotic strain
Effects of probiotics in children with AAD

The effect is strain dependent (LGG and S. boulardii best)
Effects of probiotics in children with AAD

4th Outcome

Probiotic dose
Effects of probiotics in children with AAD

The effect is dose dependent
Effects of probiotics in children with AAD

5th Outcome

Antibiotic class
Effects of probiotics in children with AAD

Best preventive effect if co-administered with penicillins
Effects of probiotics in children with AAD

6th Outcome

Safety
No statistically significant difference in the incidence of adverse events between treatment and control
After the Cochrane…. 

Bifidobacterium longum PL03, Lactobacillus rhamnosus KL53A, and Lactobacillus plantarum PL02 in the prevention of antibiotic-associated diarrhea in children: a randomized controlled pilot trial. 
Szymański H, Armańska M, Kowalska-Duplaga K, Szajewska H.

The administration of the 3 probiotics did not significantly alter the rate of diarrhea, although it reduced the frequency of loose stools per day.

Clinical trial: effectiveness of Lactobacillus rhamnosus (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children

M. RUSZCZYŃSKI*, A. RADZIKOWSKI† & H. SZAJEWSKA*

L. rhamnosus to children receiving antibiotics reduced the risk of diarrhea.

Randomized, Double-blind, Placebo-controlled Trial:
Effect of Lactobacillus GG Supplementation on Helicobacter Pylori Eradication Rates and Side Effects During Treatment in Children

*Hania Szajewska, †Piotr Albrecht, and ‡Agnieszka Topeczewska-Cabanek

L. GG did not significantly improve the antibiotic side effects.

To eradicate HP we need

PPI +

- Amoxy + Clarithromycin
- Amoxy + Tinidazole
- Amoxy + Metronidazole + Clarithromycin
- Amoxy + Clarithromycin + Tinidazole

for 7, 10 or 15 days

(Gut 2007; 56:772)
Our experience with *L. reuteri* 55730

*p. reuteri* therapy to reduce side-effects during anti-*Helicobacter pylori* treatment in children: a randomized placebo controlled trial


*(Alim Pham Therap 2006; 24:1461-8)*
**L. reuteri** 55730 and antibiotic associated side effects

- Placebo: 1 cps/die
- Reuterin: $10^8$ CFU, 1 cps/die

**Eradicating Therapy**

**Follow-up**

*Gastrointestinal Symptom Rating Scale.*

It comprises 15 items describing abdominal pain, gastro-esophageal reflux, abdominal distension, diarrhea and constipation.

(Dig Dis Sci. 1988;33:129)

(Lionetti E. Alim Pharm Therap 2006; 24:1461-8)
**L. reuteri 55730 and antibiotic associated side effects**

In all probiotic supplemented children, as compared to those receiving placebo, there was a significant reduction in the GSRS score during eradicating therapy, which became markedly evident at the end of follow-up.

(Lionetti E. Alim Pharm Therap 2006; 24:1461-8)
**L. reuteri** 55730 and antibiotic associated side effects

Children receiving *L. reuteri* v. placebo complained less frequently of epigastric pain during therapy (15% vs. 45%; *p*<0.03) and abdominal distension (0% vs. 25%; *p*<0.02), diarrhea (15% vs. 45%; *p*<0.04), eructation (5% vs. 35%; *p*<0.04) and halitosis (5% vs. 35%; *p*<0.04) thereafter.

(Lionetti E. *Alim Pharm Therap* 2006; 24:1461-8)
**L. reuteri 55730 and antibiotic associated side effects**

No differences in adherence to treatment schedules (97% in both groups) and H. pylori eradication rates (85% vs. 80%; p= NS).

(Leonetti E. Alim Pharm Therap 2006; 24:1461-8)
What next

1. Probiotics are a promising option to prevent or ameliorate AAD.

2. Specific strains at high doses should be used.

3. For every 10 patients treated with antibiotics 1 will not develop diarrhea if also receiving probiotics.

4. Future studies are needed to address the cost-effectiveness of this primary prophylaxis.

5. The judicious use of antibiotics remains the best method of preventing antibiotic associated side-effects.