Prevention and Therapy of Antibiotic Associated Diarrhea (ADD) through Probiotics

Prof. Rémy Meier, MD
GI-Department
University Hospital
Liestal, Switzerland

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Bacteria and the Gut

Apathogene bacteria
Lactobazilli
Bifidobacteria

Pathogene bacteria
Bacteroides
C. difficile
Pathogene E.coli
Gut barrier function

Cross-talk between Gut bacteria and the intestinal immune system

MacDonald et al, Science 2005
Mechanism of antibiotic induced diarrhea

- Reduced apathogen bacteria
- Increased pathogen bacteria

- Decreased bacteriocin production
- Decreased defensin production
- Disruption of the tight junction by pathogenic bacteria
- Inflammatory mucosal response
Pathogenic microbes and mediators (IL\(_4\), IF-\(\gamma\), TNF-\(\alpha\)) can disrupt the tight junctions barrier

Kinngasa et al, Gastroenterology 2000

Söderholm et al, Gastroenterology 2002
Bacteria and tight junctions

Control

S. Dublin

Prevention with E. Coli Nissle

Otte et al, AJP 2004

Kindly given to me by Prof. H. Lochs
Anti-inflammatory activity of probiotica

Peña et al, Infect Immun 2005
Host-bacteria interaction

Infection

Perturbed homeostasis

Protection & defense mechanisms

Bacterial signals

TLR

NOD

MAPK

NF-kB

Serpin
Galectin-3
Smad2
PP2A
PPARγ

TNF
IFNγ

1. Loss of barrier function
2. Malabsorption/diarrhea
3. Cytokine/chemokine production

Modified from Haller NGM 2005
Probiotics

Definition

Live microorganisms which when administered in adequate amounts confer a health benefit on the host!

FAO (Food and Agriculture Organization of the UN) and WHO
Probiotic claims

- [Human origin]
- Viable and hardy in human GI tract
- Acid and bile stable
- Adhesion to mucosa
- Clinically demonstrated benefit
- Safe
Probiotics

- Bifidobacteria
- Lactobacilli
- Enterococcus faecium SF 68
- [Saccharomyces boulardii]
Probiotics: Mechanisms of Action I

- Inhibit growth of pathogenic enteric bacteria
  - Decrease luminal pH
  - Secrete bactericidal proteins
  - Stimulate defensin production
  - Occupy ecological niche
- Block epithelial attachment or invasion by pathogens
  - Block epithelial binding by inducing MUC-2
  - Stimulate mucous production to alter biofilm
  - Inhibit epithelial invasion
- Elimination of pathogenic toxins
  - Several mechanisms (pH, proteolytic, binding)

Probiotics: Mechanisms of Action II

- Improve epithelial and mucosal barrier function
  - Produce SCFA
  - Enhance barrier function
  - Helps maintain normal motility patterns
  - Enhance mucosal blood flow
  - Stimulates Nitric Oxide

Adapted from Sartor: Curr Opin in Gastro 2005, 21;44-50,
Yan: Curr Opin in Gastro 2004, 20:565-571
Probiotics: Mechanisms of Action III

- **Alter host immune response**
  - Induce IL$_{10}$, TGF-β,
  - Stimulate sIgA production
  - Decrease TNF-α, IFN-γ expression,
  - Decrease NF-κB
  - Active in regulation of T cells
  - Enhance macrophage function
    (cell free extracts and intact bacteria)
  - Enhance HSP

Adapted from Sartor: Curr Opin in Gastro 2005, 21;44-50,
Yan: Curr Opin in Gastro 2004, 20:565-571
Colonization resistance
- Competitive exclusion

Maintain barrier function
- Reduce macromolecular permeability and bacterial translocation
- Maintain tight junctions (ZO-1, claudin1)

Metabolic effects
- Bacteriocins
- Decrease pH
- Quorum sensing

Enhance microbial flora
- IgA, IgG, IgM
- Increase mucin production

Modulation of signal transduction
- NF-κB
- IFNγ
- MAPK

Innate/Adaptive Immunomodulation
- Enhance cytokines (IL-10, TGFβ)

Probiotics
Probiotics and diarrhea

- Treatment of acute diarrhea
- Prevention of diarrhea
  - Traveler‘s diarrhea
  - Antibiotic associated diarrhea
Host-bacteria interaction

Infection

Perturbed homeostasis

Protection & defense mechanisms

Probiotic activity

1. Loss of barrier function
2. Malabsorption/diarrhea
3. Cytokine/chemokine production

Modified from Haller NGM 2005
Infectious acute diarrhea: Treatment with Probiotics

<table>
<thead>
<tr>
<th>Probiotic strains</th>
<th>Studies with + outcome&lt;sup&gt;1&lt;/sup&gt; /total no of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotavirus</strong></td>
<td></td>
</tr>
<tr>
<td>● Lactobacillus rhamnosus GG</td>
<td>11/14</td>
</tr>
<tr>
<td>● Enterococcus faecium SF68</td>
<td>6/8</td>
</tr>
<tr>
<td>● Lactobacillus reuteri ATCC 55730</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
</tr>
<tr>
<td>● Saccharomyces boulardii</td>
<td>4/5</td>
</tr>
<tr>
<td><strong>Not clear defined</strong></td>
<td></td>
</tr>
<tr>
<td>● Lactobacillus paracasei NCC2461</td>
<td>1/1</td>
</tr>
<tr>
<td>● Escherichia coli Nissle</td>
<td>1/1</td>
</tr>
<tr>
<td>● Lactobacillus LB (Lactéol)</td>
<td>5/5</td>
</tr>
</tbody>
</table>

<sup>1</sup>At least one positive outcome measure
Probiotics and acute diarrhea in children (< 5 years old)

Meta-analysis

18 studies with different probiotics
10 db, placebo-controlled trials

Probiotics and ORS reduced the duration of acute diarrhoea by 1 day (p<0.01)

Huang et al, Dig Dis Sci, 2002
Acute diarrhea in children:
Treatment with Lactobacillus paracasei NCC2461

Study protocol
• 230 infants, 4-24 months
  Diarrhea < 2 days
• $10^{10}$ L. paracasei NCC2461
  or placebo for 5 days

Results
• No effect on rotavirus infected children
• Sig. benefit on non-rotavirus induce diarrhea

Study selected as one of the best interventional study by NIH

L. paracasei reduces non-rotavirus diarrhea in children less than 2 years old

Sarker et al, Pediatrics 2005
Probiotics in acute diarrhea

23 randomized controlled studies with 1917 patients

- 1449 children or adolescents (< 18 y)
- 325 adults

Results:
Probiotics reduced the risk of diarrhea at 3 days
RR 0.66 (95%: 0.55-0.77)

Probiotics reduced the mean duration of diarrhea by 30.5 h (95%: 18.5-42.5)

Probiotics reduced stool frequency on day 2 by 1.5 (95%: 1.2-1.8)

Allen et al, Cochrane Database Syst Rev 2004;(2)CD003048
Summary: Acute diarrhea: Treatment with Probiotics

- The efficacy is strain specific
- The effect is dependent on the aetiology of diarrhea
- The effect is dose dependent
- Probiotics are more efficient in children than in adults and when early administered

The effects of probiotics are moderate, but biologically relevant and can afford savings in direct health costs and loss of working days
## Diarrhea prevention: Treatment with Probiotics

<table>
<thead>
<tr>
<th>Probiotic strains</th>
<th>Studies with + outcome&lt;sup&gt;1&lt;/sup&gt;</th>
<th>/total No of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nosocomial diarrhea (all causes)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. lactis Bb12</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td><strong>AAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. boulardii</td>
<td>6/7</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>E. faecium SF68</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>L. acidophilus + L. bulgaricus</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>B. lactis Bb12 and S. thermophilus</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>L. casei DN-114001</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>B. subtilis spores</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td><strong>CDAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. boulardii</td>
<td>3/4</td>
<td></td>
</tr>
<tr>
<td>L. casei DN-114001</td>
<td>1/1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>At least one positive outcome measure
Probiotics and antibiotic associated diarrhea in children and adults

D’Souza et al, BMJ 2002
Probiotics and antibiotic associated diarrhea in children

Lactobacillus rhamnosus GG reduces the risk of antibiotic associated diarrhea

• Arvola et al, 1999 (N = 119):
  RR 0.32 (95%: 0.08-1.15)

• Vanderhoof et al, 1999 (N = 188):
  RR 0.23 (95%:0.09-0.56)
Probiotics and antibiotic associated diarrhea in children

Rand, db, placebo-controlled trial
Saccharomyces boulardii vs placebo (N=269)

Saccharomyces boulardii
• Reduces the risk of diarrhea
  8% vs 23% (RR 0.3; 0.2-0.7)
• Reduces the risk of C difficile diarrhea
  3.4% vs 17.3% (RR 0.2; 0.07-0.5)

Kotowaska et al, Aliment Pharmacol Ther, 2005
Probiotics for the prevention of antibiotic associated diarrhea in children

10 randomized controlled studies with Lb spp, Bifidobacterium spp, Streptococcus spp, Saccharomyces boulardii alone or in combination

• PP-Analysis 9 of 10 studies showed positive effects
  RR 0.49 (95%:0.32-0.74)

• ITT-Analysis showed no effects
  RR 0.90 (95%: 0.50-1.65)

# Probiotics to prevent antibiotic associated diarrhea in adults

Rand, db, placebo-controlled trial  
Lactobacillus casei, bulgaricus and Streptococcus thermophilus vs placebo

N=135

<table>
<thead>
<tr>
<th></th>
<th>Probiotic</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12%</td>
<td>34%*</td>
</tr>
<tr>
<td>Cl difficile</td>
<td>0%</td>
<td>17%*</td>
</tr>
</tbody>
</table>

**Risk reduction 22%, NT 5**

*p=0.001

Hickson et al, BMJ 2007
Probiotics for the prevention of AAD and the treatment of Clostridium difficile disease

Meta-analysis (31 studies)

• Probiotics significantly reduced the relative risk of AAD (25 studies)
  RR 0.43 (95%: 0.31-0.58), p<0.001

• Probiotics had a significant efficacy for CDD (6 studies)
  RR 0.59 (95%: 0.41-0.85) p<0.005

Saccharomyces boulardii, Lb rhamnosus GG, and probiotic mixtures) significantly reduce the development of AAD

Only Saccharomyces boulardii is effective for CDD
Prevention and treatment of diarrhea with probiotics

Probiotics significantly reduce the risk of
- Acute diarrhea of diverse causes by 34% (8-53%)
  - among children by 57% (35-71)
  - among adults by 26% (7-49%)
- AAD by 52% (95% CI 35-65)
- Travellers diarrhea by 8% (-6-21%).

Probiotics are efficient in preventing acute diarrhea and have a important role in the prevention of AAD.

Sazawal et al, Lancet Infect Dis 2006
Future direction?

Use of synbiotics
(Pre- and probiotics)
Prebiotics

- Fibre gums
- Pectin
- Guar (PHGG)
- Oligosaccharides
  - Inulin
  - FOS
  - GOS
- Lactulose
- Lactitol
Prebiotics: Mechanisms of action

Prebiotics

fermented by colonic bacteria

- Short chain fatty acids (Butyrate, Acetate, Propionate) and $H_2$, $CO_2$
- Reduction of the pH in the colon
- Bifidogenic or prebiotic effect
  (Stimulation of the growth of beneficial bacteria and inhibition of harmful bacteria)
SCFA are potent promoters for sodium and water absorption in the colon.
Prebiotics in acute diarrhea

Prosp, db, placebo-controlled trial

<table>
<thead>
<tr>
<th></th>
<th>ORS + PHGG (N = 75)</th>
<th>ORS + Placebo (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Duration of diarrhoea (h)</td>
<td>74</td>
<td>90*</td>
</tr>
<tr>
<td>- Stool output g/kg BW</td>
<td>369 ± 38</td>
<td>437 ± 46</td>
</tr>
<tr>
<td><strong>Children &lt; 10 months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Duration of diarrhoea (h)</td>
<td>70</td>
<td>97**</td>
</tr>
<tr>
<td>- Stool output g/kg BW</td>
<td>370 ± 46</td>
<td>507 ± 64*</td>
</tr>
</tbody>
</table>

* P = 0.03; ** P = 0.004

Alam, Meier et al, J Pediatr Gastro Nutr 2000
## Prebiotics in cholera diarrhea

**Prosp, open randomized trial**

<table>
<thead>
<tr>
<th>N=195</th>
<th>ORS + 25g PHGG (N = 65)</th>
<th>ORS + 50g PHGG (N=65)</th>
<th>ORS alone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoolweight 1st 24h</td>
<td>5.9kg * ± 2.9kg</td>
<td>6.5kg * ± 2.2kg</td>
<td>7.9kg ± 15kg</td>
</tr>
</tbody>
</table>

* p = 0.001

Alam, Meier et al, Digestion 2008
Prebiotics in chronic diarrhea

Prosp, db, placebo-controlled trial

<table>
<thead>
<tr>
<th>Comminuted chicken diet + PHGG (N = 57)</th>
<th>Comminuted chicken diet + Placebo (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Diarrhoea (h)</td>
<td></td>
</tr>
<tr>
<td>60 ± 39</td>
<td>81 ± 48*</td>
</tr>
<tr>
<td>No (%) children stopped diarrhea</td>
<td></td>
</tr>
<tr>
<td>within 7 days</td>
<td></td>
</tr>
<tr>
<td>46 (84)</td>
<td>36 (62) **</td>
</tr>
</tbody>
</table>

* P = 0.03; ** P = 0.009

Alam, Meier et al, Arch Childhood Dis, 2005
Prebiotics (FOS) on recurrence of diarrhea in subjects with CDAD

Rand, placebo-controlled trial (N=142 patients)

- Stool culture confirmed oligofructose as prebiotic
- Relapse of *Clostridium difficile* diarrhea:
  - 8.3% oligofructose vs 34.3% placebo, \( p < 0.001 \)
- Patients who relapsed stayed in hospital longer than those who did not (53 vs 26 days, \( p < 0.021 \)

Lewis et al, Clin Gastroenterol Hepatol 2005
Conclusion

If antibiotics are used, probiotica should be given, but the type of probiotica should be carefully selected.