Networking with your microbiota
Prophylactic use in all hospital patients?

S. Schneider (France)
Prophylactic use in all hospital patients?

Stéphane M. Schneider, MD, PhD
Nice, France
„Critical illness“

Trauma/Infection

Acute Stress Response

Iatrogenic Factors

Immunological Response

Neuroendocrine Response

Metabolic Response
Outline

- Why should we go for it?
  - Bases for a generalized use

- What are the results in selected and non-selected hospital populations?

- What are the cons?
  - Sincerity and safety

- Why we should NOT go for it…
Acute phase reaction: a common feature of the hospitalized patient

- Rise in cytokines and coagulation factors within seconds
- Rise in acute phase reactants within hours
- Disappearance of "protective" flora in 6-8 hours
- Overgrowth with PPMs after 10-12 hrs and
- Translocation

+ antibiotics, fasting, colon preparation,...
The beneficial microbiota, probiotics and synbiotics

- Modulate the innate and adaptive immune defence mechanisms
- Synthesize & release numerous nutrient; antioxidants, growth-, coagulation and other factors
- Control GI motility
- Reduce potentially pathogenic micro-organisms
- Reduce/eliminate the content of various toxins, mutagens, carcinogens
- Promote apoptosis
- Fight immunoparesis, along with n-3 fatty acids, antioxidants and functional fibres
How to assess a probiotic?

- Not only the genus and species, but most importantly the strain
  - *Lactobacillus*
  - *Lactobacillus plantarum*
  - *Lactobacillus plantarum 299v*

- Not in a general population but in patients with a specific condition

- Not a metaanalysis, but well-powered individual studies
Metaanalysis of prophylactic probiotics in the ICU

Figure 3  Forest plot showing the effect of pro/synbiotics on proportion of patients with pneumonia.

Figure 4  Forest plot showing the effect of pro/synbiotics on hospital mortality.

Figure 5  Forest plot showing the effect of pro/synbiotics on length of ICU stay in days.
Individual studies of pro/synbiotics in the ICU

- Synbiotic 2000®
- Trevis® + Raftilose®
- Yakult® + GOS
- Lactobacillus plantarum 299

Each individual study negative in terms of septic complications

Biological endpoints (immune parameters, delaying *P. aeruginosa* colonization, …)
Metaanalysis of prophylactic probiotics in the ICU

Mortality

Infections

Length of ICU stay

Length of hospital stay

Difference

Number of trials

(95% CI)

(patients)

- 1%

(- 7% to + 4%)

10 (587)

- 21%*

(- 36% to - 7%)

9 (554)

- 5.97 days

(-14.99 to + 2.55 days)

4 (272)

- 0.58 days

(- 5.14 to + 3.99 days)

3 (209)

Favours probiotics

Favours placebo

Mortality

Infections

Length of ICU stay

Length of hospital stay

- 1%

(- 7% to + 4%)

10 (587)

- 21%*

(- 36% to - 7%)

9 (554)

- 5.97 days

(-14.99 to + 2.55 days)

4 (272)

- 0.58 days

(- 5.14 to + 3.99 days)

3 (209)
Prophylaxis of acute hospital diarrhea

Sazawal et al. Lancet Infect Dis 2006
<table>
<thead>
<tr>
<th></th>
<th>Number of trials</th>
<th>Effect size</th>
<th>Heterogeneity test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Overall effect</td>
<td>34</td>
<td>0.65</td>
<td>0.55-0.78*†</td>
</tr>
<tr>
<td>Types of diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic-associated diarrhoea</td>
<td>19</td>
<td>0.48</td>
<td>0.35-0.65*†</td>
</tr>
<tr>
<td>Travellers’ diarrhoea</td>
<td>6</td>
<td>0.92</td>
<td>0.80-1.06</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>0.66</td>
<td>0.47-0.92*†</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>12</td>
<td>0.43</td>
<td>0.29-0.65*†</td>
</tr>
<tr>
<td>Adult</td>
<td>21</td>
<td>0.74</td>
<td>0.59-0.94*</td>
</tr>
<tr>
<td>Probiotic strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Saccharomyces boulardii</em></td>
<td>5</td>
<td>0.48</td>
<td>0.24-0.96*</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>10</td>
<td>0.72</td>
<td>0.57-0.93†</td>
</tr>
<tr>
<td>Lactobacillus acidophilus plus Lactobacillus bulgaricus</td>
<td>7</td>
<td>0.70</td>
<td>0.36-1.33*</td>
</tr>
<tr>
<td>Other single strain</td>
<td>6</td>
<td>0.83</td>
<td>0.62-1.09*</td>
</tr>
<tr>
<td>Other combination of strains</td>
<td>6</td>
<td>0.48</td>
<td>0.34-0.67</td>
</tr>
<tr>
<td>Formulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule, tablet, powder, or granules (C/T/P/G)</td>
<td>25</td>
<td>0.66</td>
<td>0.52-0.83*†</td>
</tr>
<tr>
<td>Pre-mixed with a food vehicle (PFV)</td>
<td>9</td>
<td>0.57</td>
<td>0.41-0.81*</td>
</tr>
<tr>
<td>Formulation and age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/T/P/G in children</td>
<td>7</td>
<td>0.35</td>
<td>0.18-0.68*</td>
</tr>
<tr>
<td>PFV in children</td>
<td>5</td>
<td>0.54</td>
<td>0.31-0.94*</td>
</tr>
<tr>
<td>C/T/P/G in adults</td>
<td>17</td>
<td>0.80</td>
<td>0.61-1.04*</td>
</tr>
<tr>
<td>PFV in adults</td>
<td>4</td>
<td>0.62</td>
<td>0.45-0.86</td>
</tr>
</tbody>
</table>
Probiotics in prevention of antibiotic-associated diarrhea

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio</th>
<th>(95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surawicz*</td>
<td>0.37</td>
<td>(0.16 to 0.88)</td>
<td>15.1</td>
</tr>
<tr>
<td>McFarland*</td>
<td>0.46</td>
<td>(0.18 to 1.18)</td>
<td>12.1</td>
</tr>
<tr>
<td>Lewis*</td>
<td>1.67</td>
<td>(0.47 to 5.89)</td>
<td>3.5</td>
</tr>
<tr>
<td>Adam*</td>
<td>0.22</td>
<td>(0.10 to 0.48)</td>
<td>29.9</td>
</tr>
<tr>
<td>Tankanow</td>
<td>0.88</td>
<td>(0.22 to 3.52)</td>
<td>3.9</td>
</tr>
<tr>
<td>Vanderhoof</td>
<td>0.23</td>
<td>(0.09 to 0.56)</td>
<td>21.2</td>
</tr>
<tr>
<td>Orrhage</td>
<td>0.58</td>
<td>(0.07 to 4.56)</td>
<td>2.2</td>
</tr>
<tr>
<td>Wunderlich</td>
<td>0.25</td>
<td>(0.05 to 1.43)</td>
<td>5.2</td>
</tr>
<tr>
<td>Gotz*</td>
<td>0.34</td>
<td>(0.09 to 1.38)</td>
<td>7.0</td>
</tr>
<tr>
<td>Overall</td>
<td>0.37</td>
<td>(0.26 to 0.52)</td>
<td></td>
</tr>
</tbody>
</table>
**Clostridium Difficile diarrhea**

- Six RCTs for treatment of *C diff* diarrhea, total of 354 adults patients: 3 trials exclusively for recurrent CDD
- 2 trials (33%) showed a significant reduction in CDD recurrences in the probiotic treated group as compared with placebo; 4 studies showed no difference.
- Only *Saccharomyces boulardii* showed significant reduction in recurrences. *Lactobacillus rhamnosus* GG and *Lactobacillus plantarum* alone did not show significant differences.

McFarland Am J Gastroenterol 2006
Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Aas, Charles E. Gessert, and Johan S. Bakken

1Department of Gastroenterology, 2Division of Education and Research, and 3Department of Infectious Diseases, St. Mary’s/Duluth Clinic Health System, Duluth, Minnesota

*Clin Infect Dis* 2003;36:580-585

*Clostridium difficile*-associated diarrhea and colitis have emerged as major complications associated with use of systemic antimicrobials. In this study, the medical records for 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection during a 9-year period at a single institution were retrospectively reviewed. During the period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects received a total of 64 courses of antimicrobials (range, 2–7 courses; median, 3 courses). During the 90 days after receipt of treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during 90-day follow-up. No adverse effects associated with stool treatment were observed. Patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors via a nasogastric tube.
Incidence of diarrhea in tube-fed patients

% with diarrhea

General hospital population  Intensive care units

Cataldi-Betcher  Hébuterne  Pinilla  Homann  Bliss  Bleichner  Kelly  Bliss  Hart  Smith

Schneider et al. Presse Med 2003
Consequences

- Discomfort ➔ Life-threatening acidosis
- Pressure sores
- Increased costs
  - Nursing staff
  - Clothes, bed sheets,…
- Nutritional goals
  - EN reduced or put on hold
  - Amount delivered = 50% of the amount prescribed
  - Malnutrition, Dehydration ➔ Morbidity

Adam et al. Intensive Care Med 1997
Faecal microbiota in total artificial nutrition patients

**Total bacteria**

- Controls
- TEN
- TPN

**Anaerobes**

- Controls
- TEN
- TPN

**Aerobes**

- Controls
- TEN
- TPN

* p<0.01 vs. Controls
† p<0.01 vs TEN

Schneider et al. Eur J Nutr 2000
**Saccharomyces boulardii** and ETF-associated diarrhea

- **Saccharomyces boulardii** (Sb): a probiotic yeast
- Effective in 3 PRCTs in preventing EN-associated diarrhea in ICU patients

![Graph showing comparison between Placebo (n=64) and Sb 2 g/d (n=64).](Bleichner et al. Intensive Care Med 1997)
## Prevention of postoperative infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Condition</th>
<th>Probiotic-Synbiotic</th>
<th>Infections with probiotic (%)</th>
<th>Infections with placebo (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rayes</td>
<td>2002</td>
<td>Liver Tx</td>
<td><em>L. plantarum</em> 299 + oat fiber</td>
<td>4/31 (13)</td>
<td>11/32 (34)</td>
<td>0.017</td>
</tr>
<tr>
<td>Rayes</td>
<td>2005</td>
<td>Liver Tx</td>
<td><em>Synbiotic 2000</em>®</td>
<td>1/33 (3)</td>
<td>17/33 (51)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rayes</td>
<td>2007</td>
<td>Whipple’s</td>
<td>Same</td>
<td>5/40 (12)</td>
<td>16/40 (40)</td>
<td>0.005</td>
</tr>
<tr>
<td>Han</td>
<td>2009</td>
<td>Digestive surgery</td>
<td>Same</td>
<td>1/15 (7)</td>
<td>3/15 (20)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sugawara</td>
<td>2006</td>
<td>Biliary surgery</td>
<td><em>L. casei Shirota, B. breve Yakult</em> + galactooligosaccharides</td>
<td>5/41 (12)</td>
<td>12/40 (30)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Rayes</td>
<td>2002</td>
<td>Digestive surgery</td>
<td><em>L. plantarum</em> 299 + oat fiber</td>
<td>3/31 (10)</td>
<td>3/32 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>McNaught</td>
<td>2002</td>
<td>Digestive surgery</td>
<td><em>L. plantarum</em> 299</td>
<td>7/64 (11)</td>
<td>10/65 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Anderson</td>
<td>2004</td>
<td>Digestive surgery</td>
<td><em>L. acidophilus</em> La5, <em>B. lactis</em> Bb-12, <em>S. thermophilus</em>, <em>L. bulgaricus</em> + FOS</td>
<td>23/72 (32)</td>
<td>20/65 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Jain</td>
<td>2004</td>
<td>Digestive surgery</td>
<td><em>L. acidophilus</em> La5, <em>B. lactis</em> Bb-12, <em>S. thermophilus</em>, <em>L. bulgaricus</em> + FOS</td>
<td>33/45 (73)</td>
<td>26/45 (58)</td>
<td>NS</td>
</tr>
</tbody>
</table>

± enteral nutrition, ± fibre
Acute pancreatitis

- **Severe**: 20%
- **Benign**: 80%

Causes:
- Infection
- Translocation
- SIBO
- Increased mucosal permeability
- Inflammation
Synbiotics and severe AP

- Heatkilled (A) or live (B) *L. plantarum* 299 + 10 g oat fibre in 45 patients

- Pancreatic sepsis:
  - A. 7/23 patients (30%)
  - B. 1/22 patients (4.5%) (p=0.023)

- Mean length of stay:
  - A. 21.4 days
  - B. 13.7 days (NS)

- No differences in:
  - Chest infections (2/2)
  - SIRS (6/11)
  - MOF (2/2)
Synbiotics and severe AP

- **Synbiotic 2000**: $\log_{10}$ bacteria
  - *Pediococcus pentosaceus* 5–33:3
  - *Lactococcus raffinolactis* 32–77:1
  - *Lactobacillus paracasei subsp paracasei* 19
  - *Lactobacillus plantarum* 2362
  - $\beta$-glucan + inulin + pectin + resistant starch

Olah *et al.* Hepatogastroenterol 2007
## Synbiotics and severe AP

<table>
<thead>
<tr>
<th></th>
<th><strong>Synbiotic 2000®</strong></th>
<th><strong>Fibres only</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>9 (27%)</td>
<td>15 (52%) *</td>
</tr>
<tr>
<td><strong>SIRS</strong></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>MOF</strong></td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td><strong>SIRS + MOF</strong></td>
<td>8</td>
<td>14 *</td>
</tr>
<tr>
<td><strong>MOF &gt; 48 h</strong></td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><strong>Surgical drainage</strong></td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong></td>
<td>14.9 ± 6.5 d</td>
<td>19.7 ± 9.3 d</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>2 (6%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>

* P < 0.05

Olah et al. Hepatogastroenterol 2007
Synbiotics and severe AP

Ecologic 641 : $\log_{10}$ bacteria
- *Lactobacillus acidophilus*
- *Lactobacillus casei*
- *Lactobacillus salivarius*
- *Lactococcus lactis*
- *Bifidobacterium bifidum*
- *Bifidobacterium lactis*
- Corn starch + maltodextrins

Besselink et al. Lancet 2008
Patients’ characteristics

Multicentre RCT for 28 days alongside NJ feeding.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Synbiotics</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 16</td>
<td>59 ± 16</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>60%</td>
<td>58%</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 6</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>8.6 ± 4.4</td>
<td>8.4 ± 4.5</td>
</tr>
<tr>
<td>Imrie</td>
<td>3.3 ± 1.7</td>
<td>3.4 ± 1.6</td>
</tr>
<tr>
<td>Peak CRP</td>
<td>268 ± 127</td>
<td>270 ± 122</td>
</tr>
<tr>
<td>Organ failure</td>
<td>6%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Primary endpoints: infections

Besselink et al. Lancet 2008
Secondary endpoints

Besselink et al. Lancet 2008
RR = 2.53 (95\% CI = 1.22-5.25)

Mortality (%) vs Days from randomisation

- Probiotics
- Placebo

Numbers still at risk:

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>152</th>
<th>141</th>
<th>138</th>
<th>136</th>
<th>135</th>
<th>133</th>
<th>132</th>
<th>131</th>
<th>130</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>144</td>
<td>141</td>
<td>139</td>
<td>139</td>
<td>138</td>
<td>137</td>
<td>136</td>
<td>136</td>
<td>136</td>
<td>136</td>
</tr>
</tbody>
</table>

p=0.01; log-rank test
Other safety concerns

- Infection: 0.05-0.4% of infective endocarditis or bacteriemia (*Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus paracasei*)
- Reported case of liver abscess (*Lactobacillus rhamnosus*)
- Reports of *Saccharomyces boulardii* fungemia: probable role of central venous catheters
- Most of the cases are in immunocompromised patients or those with serious underlying diseases
Sincerity

- Probiotics and synbiotics are available as:
  - Functional foods (Actimel®, Yakult®, LCI®, …)
  - Dietary supplements (Synbiotic 2000®, VSL#3®, Trevis®, Lactobacillus rhamnosus GG, Lactobacillus plantarum 299v, Escherichia coli Nissle 1917, …)
  - Drugs (Saccharomyces boulardii, …)

- Not the same quality criteria are applied. Only drugs have an easy access to hospitals.
- The vector matters.
- Maintenance temperature matters.
Less guarantees with functional food

- At least $10^9$-$10^{10}$ CFU/d

<table>
<thead>
<tr>
<th>Product (brand)</th>
<th>Microorganisms declared on the label&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CFU/g determined by plate count&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Detection by PCR-DGGE</th>
<th>Detection by Species-specific PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyr (Giglio, Reggio Emilia, Italy)</td>
<td><em>L. acidophilus</em></td>
<td>$&lt; 10$</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td><em>Bifidobacterium</em> spp.</td>
<td>$8 \times 10^7$</td>
<td>B. lactis</td>
<td>B. lactis</td>
</tr>
<tr>
<td></td>
<td><em>B. bifidus</em></td>
<td>$1.5 \times 10^6$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Activia (Danone, Milano, Italy)</td>
<td><em>L. acidophilus</em></td>
<td>$&lt; 10$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td><em>B. lactis</em></td>
<td>$4 \times 10^5$</td>
<td>B. lactis</td>
<td>B. lactis</td>
</tr>
<tr>
<td>Biospega (Spegia, Vicenza, Italy)</td>
<td><em>L. acidophilus</em></td>
<td>$&lt; 10$</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td><em>B. lactis</em></td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ABC (Sitia YOMO, Milano, Italy)</td>
<td><em>L. acidophilus</em></td>
<td>$&lt; 10$</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td><em>Bifidobacterium</em></td>
<td>$1 \times 10^6$</td>
<td>B. lactis</td>
<td>B. lactis</td>
</tr>
<tr>
<td></td>
<td><em>L. casei</em></td>
<td>$&lt; 10$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mio (Nestlé)</td>
<td><em>B. lactis</em></td>
<td>$1.3 \times 10^7$</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Active-più (Parmalat, Parma, Italy)</td>
<td><em>Bifidobacterium</em></td>
<td>$5.4 \times 10^6$</td>
<td>B. lactis</td>
<td>B. lactis</td>
</tr>
<tr>
<td>Teddy (Fattoria Scaldasole®, Latina, Italy)</td>
<td><em>Bifidobacterium</em></td>
<td>$2.5 \times 10^7$</td>
<td>B. lactis</td>
<td>B. lactis</td>
</tr>
</tbody>
</table>

<sup>a</sup>: detection of positive signal; <sup>b</sup>: not detected.
Conclusions

- Probiotics are not to be used in all hospital patients at the moment. No universal harmless overefficient strain…

- Like in outpatients, specific strains need to be used in specific situations:
  - Prevention of antibiotic-associated diarrhoea
  - Prevention of enteral feeding-associated diarrhoea
  - Prevention of postoperative infections

- Follow-up of strict protocols is needed if we want to keep their current definition!
Clinical Nutrition & Metabolism International Congress

NICE - FRANCE
5-8 September 2010

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First Announcement

www.espen.org

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