Probiotiques et infections, 
*Un sujet « incertain… »*

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Toi aussi, ils t’ont mis au régime bière, choucroute, yaourt ?

M’en parle pas ! Ces probiotiques m’ont foutu de ces allergies !!
So, a strict roadmap....

- **General**:
  - Definition, Market

- **Recent findings in**:
  - Infectious diarrhea, *C. dif*, VRE, UTI, VAP, Pediatrics, Acute pancreatitis

- **Recent opinions, caveat and so forth.**
Definition and market

• « Life microbial supplement that beneficially affect the consumer by improving intestinal microbial balance ».
• Vague and uncertain alleged properties
• Drug or food : you never know…
• Multiple strains of various species
• No strain-specific properties requested
Big and highly dynamic businessness...

### Western Europe: Consumer market for probiotic and prebiotic products, 2000 to 2010

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2005p</th>
<th>00-05</th>
<th>2010f</th>
<th>05-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td>824.2</td>
<td>1,447.1</td>
<td>11.9%</td>
<td>2,100.4</td>
<td>7.7%</td>
</tr>
<tr>
<td>Prebiotics</td>
<td>365.3</td>
<td>878.6</td>
<td>19.2%</td>
<td>1,370.6</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Source: RTS Resource Ltd

By comparison antibiotic market in Eu ~7,000€m (source IMS)
Western Europe: Share of market for probiotics as industrial food ingredient by main country, 2005

% Share of market value (€m)

Source RTS Resource Ltd

A pattern very different from antibiotics: Germany 50% of French use
CDAD, and Acute Infectious diarrhea,

It’s hard to convince....
**S. boulardii et C.dif**

*The most recent review*

- 4 randomized, placebo-controlled studies
- Two for prevention of recurrences
  - One reduction of relapses (RR=0.53; p<0.05)
  - One with trend in pts with high doses of vanco only (RR=0.33; p=0.05)
- Two for prevention after ATB Rx
  - Lack of power for significance
  - Increased risk of thirst and constipation

_Tung JM et al. Can J gastroenterol, 2009_
Probiotics for treating acute infectious diarrhea: a meta-analysis

Duration of diarrhea

Allen SJ et al., The Cochrane Library 2010
Probiotics for treating acute infectious diarrhea: a meta-analysis

Diarrhea lasting >4 days

JNI Référents antibiothérapie 2011  Allen SJ et al., The Cochrane Library 2010
Probiotics for treating acute infectious diarrhea: a meta-analysis

Mean stool frequency on day 2
But no differences in comparison between:

1. Strains (LGG, Enterococcus, S. boulardii)
2. Single organisms vs combinations
3. Live vs killed organisms
4. Dose (live organisms)
5. Severity of diarrhea (outpatients)
6. Mortality stratum in the countries where trials were undertaken
But no differences in comparison:

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6. Mortality stratum in the countries where trials were undertaken

Allen SJ et al., The Cochrane Library 2010

✓ ...safe and have clear beneficial effects in [...] duration [...] 

✓ However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

JNI Référents antibiothérapie 2011
Recurrent UTIs

A promising dawn?
Rationales for prevention of rUTI with L. crispatus

- Vaginal colonisation a step for ascending UTI
- *Lactobacillus* may prevent vaginal colonisation
- Vaginal administration of *Lactobacillus* induces
  - Persistent colonisation
  - Reduction vaginal coliform counts
  - Reduction of rUTI?
- Best *Lactobacillus*
  - Produce H$_2$O$_2$, adhere to uroepithelial cells, interfere with attachment and growth of *E. coli*, persist in the vagina
- *L. crispatus* does all that (hopefully!!)
**L. crispatus** intravaginally for prevention of rUTI

Randomized, placebo-controlled Phase 2

- Lactin-V (n=48) or placebo (n=48)
- Intravaginal suppository for 5 days plus once/week for 10 weeks.
- Follow-up visit after one week and 10 weeks
- End-points:
  - rUTI
  - Levels of *L. crispatus* colonisation (qPCR)

Stapleton AE *et al.* CID 2011
**L. crispatus** intravaginally for prevention of rUTI

Randomized, placebo-controlled Phase 2

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. (%) of participants developing recurrent UTI</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactin-V (n = 48)</td>
<td>7 (15)</td>
<td>.5 (.2–1.2)</td>
</tr>
<tr>
<td>Placebo (n = 48)</td>
<td>13 (27)</td>
<td>...</td>
</tr>
</tbody>
</table>

**Intervention, L. crispatus colonization pattern**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. (%) of participants developing recurrent UTI</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactin-V, high level (n = 41)</td>
<td>2 (5)</td>
<td>.07 (.02–.3)</td>
</tr>
<tr>
<td>Lactin-V, low level (n = 7)</td>
<td>5 (71)</td>
<td>...</td>
</tr>
<tr>
<td>Placebo, high level (n = 32)</td>
<td>9 (28)</td>
<td>1.1 (.4–3.1)</td>
</tr>
<tr>
<td>Placebo, low level (n = 16)</td>
<td>4 (25)</td>
<td>...</td>
</tr>
</tbody>
</table>
VRE colonisation
Effect of probiotic on VRE colonisation in mice.
Effect of probiotic on VRE colonisation in mice.

De Regt MJA, et al. AAC 2010

Multispecies probiotic
Bifidus 4, Lactobacillus 5, Enterococcus 1

VRE colonisation

Gastro nephro

Geriatry

JNI Référents antbiothérapie 2011

De Regt MJA, et al. AAC 2010
Prevention of VAP
Probiotic prophylaxis of VAP

- Adults with ventilation for predicted >72h
- 42% exclusion for risk of probiotic infection (pregnancy; immunosuppression; prosthetic cardiac valve or vascular graft; cardiac trauma; history of rheumatic fever, endocarditis, or congenital cardiac abnormality; gastroesophageal or intestinal injury or foregut surgery during the current admission; oropharyngeal mucosal injury; and placement of a tracheostomy).
- Lacto GG $2 \times 10^9$ twice daily vs Placebo
- Microbiologically confirmed VAP on quantitative BAL

Morrow LE et al. AJRCCM 2010
LGG for prevention
of VAP: results

• Significant decreases:
  ✓ CDAD p=0.02
  ✓ Antibiotics for VAP p=0.05

• No difference:
  ✓ Death,
  ✓ Total antibiotics
  ✓ Hosp stay and charges
  ✓ Duration of ventilation

Time to VAP

Morrow LE et al. AJRCCM 2010
LGG for prevention of VAP: results

- Time to VAP: LGG (n=68) vs. Placebo (n=70) (P=0.001)
  - Significant decreases:
    - CDAD (p=0.02)
    - Antibiotics for VAP (p=0.05)
  - No difference:
    - Death
    - Total antibiotics
    - Hospital stay and charges
    - Duration of ventilation

Morrow LE et al. AJRCCM 2010

However,

- Other studies not always positive
- 2 Meta-analysis contradictory
- Adverse effects not adequately studied

Référents antibiothérapie 2011
Predicted severe acute pancreatitis
Probiotic prophylaxis in predicted severe acute pancreatitis

- Multicentre randomised, double-blind, placebo-controlled trial,
- acute pancreatitis randomly assigned within 72 h of onset
  - Multispecies probiotic preparation (n=153) *L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum, and B. lactis*
  - Placebo (n=145),
  - enterally twice daily for 28 days.
- The primary endpoint was the composite of infection 90-day follow-up. ATT

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Probiotics (N=152)</th>
<th>Placebo (N=144)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infectious complication*</td>
<td>46 (30%)</td>
<td>41 (28%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Infected necrosis</td>
<td>21 (14%)</td>
<td>14 (10%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>33 (22%)</td>
<td>22 (15%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24 (16%)</td>
<td>16 (11%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (0.7%)</td>
<td>2 (1%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Infected ascites</td>
<td>4 (3%)</td>
<td>0 (0%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoint</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of antibiotics, any indication</td>
<td>75 (49%)</td>
<td>76 (53%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Percutaneous drainage</td>
<td>14 (9%)</td>
<td>8 (6%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Surgical intervention, any indication</td>
<td>28 (18%)</td>
<td>14 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Necrosectomy</td>
<td>24 (16%)</td>
<td>14 (10%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Intensive care admission</td>
<td>47 (31%)</td>
<td>34 (24%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Intensive care stay (days)</td>
<td>6.6 (17-1)</td>
<td>3.0 (9-3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>28.9 (41-5)</td>
<td>23.5 (25-9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Organ failure during admission, any onset†</td>
<td>41 (27%)</td>
<td>23 (16%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure during admission, any onset‡</td>
<td>33 (22%)</td>
<td>15 (10%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Organ failure, onset after randomisation†</td>
<td>21 (14%)</td>
<td>16 (11%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Multiorgan failure, onset after randomisation§</td>
<td>18 (12%)</td>
<td>11 (8%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (13%)</td>
<td>23 (16%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Abdominal fullness</td>
<td>36 (24%)</td>
<td>43 (30%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>25 (16%)</td>
<td>28 (19%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Bowel ischaemia</td>
<td>9 (6%)</td>
<td>0 (0%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mortality</td>
<td>24 (16%)</td>
<td>9 (6%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%). *Patients with one or more infectious complication. †Patients with multiorgan failure are included in the organ failure group. ‡Patients with organ failure present at any time during admission, irrespective of the date of onset of organ failure, are included. §Patients in whom organ failure developed (for the first time) after the day of randomisation are included. Patients in whom organ failure (in any organ) started before the day of randomisation or on the day of randomisation are not included.

JNH Référents antibiothérapie 2011

Table 2: Endpoints

Nothing on primary endpoints!

Highly significant overmortality!
Figure 2: Kaplan-Meier time-to-event analysis for mortality in the first 90 days after randomisation. A follow-up of longer than 90 days was obtained in 266 (90%) patients. Three deaths occurred after 90 days: two in the probiotics group (day 112 and 125) and one in the placebo group (day 140).

Duration of traitement : 28days
Positions, regulators and so forth
Before use of a probiotic is considered for hospitalized patients, careful assessment of risk versus benefit must be made. To ensure patients' safety, probiotics should be properly handled during administration.
Scientific Opinion EFSA

*L. rhamnosus* GG and pathogenic GI microorganisms

- Claim “maintenance of defence against pathogenic GI microorganisms”.
- Strain sufficiently characterised.
- 45 human and 41 non-human studies.
- “cause and effect relationship has not been established....”
Probiotics in pediatrics
Guidance from American academy of pediatrics

- Modestly effective:
  - Acute viral gastroenteritis, AAD in healthy children
- Some evidence:
  - NEC (between 1000-1500g) More studies needed
- Encouraging need of confirmation:
  - H. pylori, IBS, CUC, Infantile colic, Childhood atopy
- No effectiveness:
  - Cancer, Crohndiseases
- Safety concerns:
  - Immunocompromised, debilitated, ill with catheters

Thomas DW et al. Pediatrics 2010
Au 8 Juin 2011: Des frémissements mais beaucoup d’incertitudes...