

## Probiotics Separating Fact from Fiction

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## Disclosure Statement

*I have the following financial relationship to disclose:*

*Astra-Zeneca - Consultant*

*No products or services produced by this company is relevant to my presentation.*



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## Probiotics

The Commercial Blitz!



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### Probiotics



**Bifidus Regularis!**



**Regulates the digestive system.**

Breaking local news for Cleveland and Northeast Ohio  
Dannon agrees to pay up to \$45 million in damages for false advertising of its Activia and DanActive yogurt products

By James F. McCarty, The Plain Dealer  
February 23, 2010, 7:32PM

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### Probiotics

- Probiotics categories
  - Drugs (intended to cure, treat, prevent or mitigate diseases) - requires FDA approval
  - Dietary supplements } "May impact normal functioning of the body"
  - Foods } No FDA approval required
- "Probiotic foods and supplements may not contain clinically tested strains at efficacious concentrations."



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### Probiotics

- Aims
  - Why the interest?
    - The gut microbiome
  - What are probiotics?
    - How are they supposed to work?
  - Are they clinically useful?
    - What is the evidence?



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### Probiotics

- Why the interest?
  - Eczema
  - Asthma
  - Diabetes
  - Crohn's/colitis

Developed countries

Hygiene Hypothesis !



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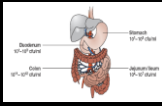




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### Probiotics

- The gut microbiome – factoids!
  - Man is Comprised of  $10^{14}$  cells
  - Of these >80% are bacterial!

Delivery: Breast vs. formula, Diet, Antibiotics

Sterile → Zoo



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### Probiotics

- The gut microbiome – factoids!
  - Humans genome +/- 23 000 genes
  - Bacterial genome >100 fold greater!



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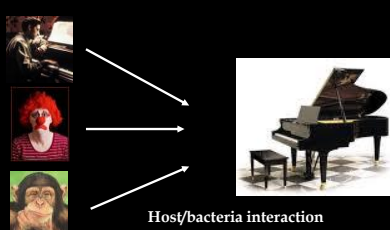
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### Probiotics

- The gut microbiome – factoids!



Host/bacteria interaction



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### Probiotics


- The gut microbiome – factoids!



Gut microbe composition has a profound impact on immunological differentiation!

“Germ free” animals: mucosal & systemic immune dysfunction

Immunological dysfunction corrected with luminal colonization with commensal microbiota



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### Probiotics

- What are probiotics?

“A live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer”

Prebiotics and Synbiotics!



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## Probiotics

### How do probiotics work?

Protective functions	Structural functions	Metabolic functions
Pathogen displacement Nutrient competition Receptor competition Production of anti-microbial factors e.g., bacteriocins, lactic acids	Barrier fortification Induction of IgA Apical tightening of tight junctions Immune system development	Control IEC differentiation and proliferation Metabolize dietary carcinogens Synthesize vitamins e.g., biotin, folate Ferment non-digestible dietary residue and endogenous epithelial-derived mucous Ion absorption Salvage of energy

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## Probiotics

### How do probiotics work?

Probiotics prevent disruption of tight junctions in STEC O157:H7- infected polarized epithelia:

K. Donato et al., Infect Immun 2008;76:1340-8

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## Probiotics

- Are probiotics clinically useful?
  - Can they treat diseases/conditions?
  - Can they prevent disease/conditions?
  - Can they promote general good health?

The evidence!

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### Probiotics

- Probiotics – more factoids!



- Not all probiotics are created equal!
  - Species
  - Number of live organisms
  - Disease entity

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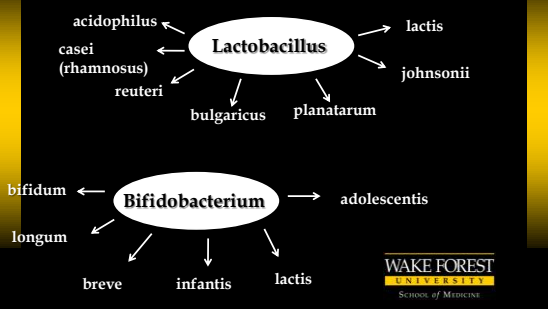
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### Probiotics



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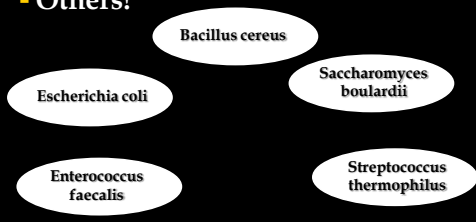
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### Probiotics

- Others!



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### Probiotics

- Sources
- Supplements
- Natural foods
  - Yogurt
  - Kefir
  - Cheese
  - Sauerkraut
  - Butter milk
- Food additives
  - Infant formulas
  - Granola bars
  - Yogurt

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### Probiotics

- Treatment roles
- Diarrhea

**L rhamnosus (GG)\***  
 RCT's x 8 - (~1000 pts)

All comers: 1 day decrease in duration	Prolonged diarrhea (> 7 days) decreased - RR = 0.25
Rotavirus: 2 days decrease in duration	Hospital duration: 1 day decrease

\* Minimum of 5 billion CFU's/day  
 No proven benefit in bacterial diarrheas

Gaundalini S, J Clin Gastroenterol 2008;42:S53-S57

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### Probiotics

- Treatment roles
- Diarrhea

**S boulardii**  
 RCT's x 5 - (>600 pts)

All comers: 1 day decrease in duration	Prolonged diarrhea (> 7 days) decreased - RR = 0.25
Rotavirus: data not extracted	Hospital duration: no data available

No proven benefit in bacterial diarrheas

Gaundalini S, J Clin Gastroenterol 2008;42:S53-S57

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## Probiotics

**ESPGHAN/ESPID Expert Working Group on Guidelines for the Management of Acute Gastroenteritis in Children in Europe.**

*"Probiotics may be an effective adjunct to the management of diarrhea. However, because there is no evidence for efficacy for many preparations, we suggest the use of probiotic strains with proven efficacy and in appropriate doses for the management of children with acute gastroenteritis as an adjunct to rehydration therapy (II, B). The following probiotics have showed benefit in meta-analyses of RCT's: Lactobacillus GG (I, A) and S. boulardii (II, B)."*

J Pediatric Gastroenterol Nutr 2008;46:supp 2.



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## Probiotics


- Treatment roles
- Atopic eczema\*

  
**L rhamnosus or B lactis**

Clinical improvement Decreased SCORAD scores Intestinal inflammatory markers decreased	Limitations: Relatively small numbers Applies only to those with food allergies
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Mechanism? - decreased intestinal permeability  
J Pediatr 2004;145:612-6

\*Isolauri E. J Clin Gastroenterol 2008;42:S91-S96



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## Probiotics



- Treatment roles
- Inflammatory bowel disease

Crohn's disease - E coli, S boulardii, L rhamnosus  
- no good evidence!

Ulcerative colitis - E coli  
- no good evidence!

Pouchitis - VSL #3 - good evidence!

IBS - B infantis - conflicting results  
B animalis, VSL #3, L plantarum  
- no good evidence



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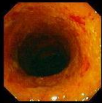
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## Probiotics



- **Treatment roles**
- **Inflammatory bowel disease**
- **Hot off the Press!\***
  - **VSL #3 in treatment of mild/moderate UC**

	VSL	Placebo
UCDAI score	63%	41%
Rectal bleeding	61%	41%
Remission	48%	32%

**VSL #3 (900 B viable bacteria)**  
*L. acidophilus, paracasei, plantarum, delbrueckii.*  
*B. longum, breve, infantis*  
*S. Thermophilus*  
 (4 pkts/day = 3600 B bacteria)

\*Tursi A, et al. Am J Gastroenterol 2010; doi: 10.1038/ajg.2010.218

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## Probiotics



- **Prevention roles**
- **Diarrhea**

**Day care centers**  
 5 RCT's - formula additive  
*L. GG, l. reuteri, B. lactis, S. thermoph.*  
**Conclusions:**  
 "Modest benefit of questionable clinical significance"

**Nosocomial diarrhea**  
 Formula + *B. lactis & S. therm.*  
 (7% vs 31%)  
 Supplement - *L. GG*  
 2 x (6x10<sup>10</sup> CFU's) - (7% vs 33%)  
 1 x (10<sup>10</sup> CFU's) - (13% vs 21%)  
**Conclusions**  
 "Weak evidence of benefit"

Gaundalini S, J Clin Gastroenterol 2008;42:S53-S57

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## Probiotics



- **Prevention roles**
- **Antibiotic associated diarrhea**
  - **Adults ~ 25%    Children ~ 11% -30%**
  - **Causes - overgrowth, motility or osmotic**

10 RCT's in children - overall suggestive benefit.  
 Problems - multiple species and doses!  
 Teasing the facts!  
 - no benefit starting after onset of diarrhea  
 - subanalysis - *L. GG* and *S. boulardii* most effective  
**Conclusions**  
 - can recommend *L. GG* or *S. boulardii*  
 - dose 5- 40 billion CFU's per day  
 - begin with start of antibiotics

J Clin Gastroenterol 2008;42:S53-S70

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### Probiotics


- Prevention roles
- C. difficile associated diarrhea
  - Epidemic of hyper virulent strain

**Questions**

- can probiotics prevent new onset CDAD?
- can probiotics prevent recurrent CDAD?

**Conclusions**

- questionable decrease in new onset CDAD.
- *L. GG* and *S. boulardii* possible benefit in RCDAD



J Clin Gastroenterol 2008;42:S53-S70

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### Probiotics

- Prevention roles
- Asthma? – no evidence!
- Atopic eczema?

**Believers!**  
Lancet 2001;357:1076-79  
Lancet 2003;361:1869-71  
J Allergy Clin Immunol 2007;119:1174

**Non believers!**  
Clin Exp Allergy 2006;36:899-906  
J Allergy Clin Immunol 2007;119:184



\*Isolauri E. J Clin Gastroenterol 2008;42:S91-S96

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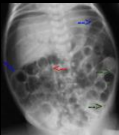
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### Probiotics

- Prevention roles
- Neonatal necrotizing enterocolitis
- Hot Off The Press!

**Updated Meta-analysis of Probiotics for Preventing Necrotizing Enterocolitis in Preterm Neonates**  
Girish Deshpande, Shripada Rao, Sanjay Patole and Max Bulsara  
*Pediatrics* 2010;125:921-930; originally published online Apr 19, 2010;  
DOI: 10.1542/peds.2009-1301



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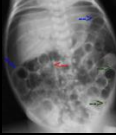
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### Probiotics

- Prevention roles
- Neonatal necrotizing enterocolitis



11 trials (2176 neonates)  
< 34 weeks & < 1500 grams  
*B. breve*, *B. bifidus*, *B. infantis*, *B. lactis*, *B. longum*  
*L. GG*, *L. acidophil*, *S. boulardii*, *S. thermophilus*,

NEC - stage 2		Mortality
Probiotic	Control	All cause RR = 0.42 (p < 0.00001)
2.73%	6.56% (p < 0.0001)	NEC mortality no difference

Time to full feeds  
Probiotic group - 5 days earlier (p < 0.0001)

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### Probiotics

- Health promotion role!
- Live cultures ≠ probiotics

Live cultures - microbes as food fermentation agents




Colds/URI's  
Decrease duration  
not frequency

Work/Day care  
absence  
(11% vs 26%)

Growth  
1.3 kg vs. 0.8 kg  
(less diarrhea)

Colic (*L. reuteri*)  
Decrease in crying  
time, GER and stools

Data suggestive of benefit - not conclusive.  
Single studies and relatively small numbers!



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### Probiotics

- Hot off the Press!!

***Lactobacillus reuteri* DSM 17 938 in Infantile Colic: A Randomized, Double-Blind, Placebo-Controlled Trial**  
Pediatrics 2010;126:e526-e533

- Breast fed infants - study 25, control 21
- 10<sup>8</sup> CFU's per day
  - Decreased daily crying rates (p = .022 on day 21)
  - No adverse effects



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## Probiotics

### Safety Profile?

**Major risk factors**

- 1) Immune compromise including malignancy
- 2) Premature infants

**Minor risk factors**

- 1) Central venous catheter
- 2) Impaired intestinal barrier
- 3) Administration via jejunostomy
- 4) Concomitant  $\alpha$ /biotic to which probiotic is resistant
- 5) Probiotics with known pathogenicity
- 6) Cardiac valvular disease.

Boyle RJ et al. Am J Clin Nutr 2006;83:1256-64

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## Probiotics

- **Conclusions**
- **Accumulating evidence of benefit**
  - Disease specific
  - Strain specific
  - Dose related
- **Safety profile**
  - Generally good
  - Cautions!

**Strong evidence**

- Viral diarrhea
- Antibiotic diarrhea
- Pouchitis
- Food induced eczema

**Good evidence**

- Recurrent CDAD
- UC relapse
- NEC

**Questionable evidence**

- Health maintenance

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## Probiotics

The ultimate benefit of a good microbiome!



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