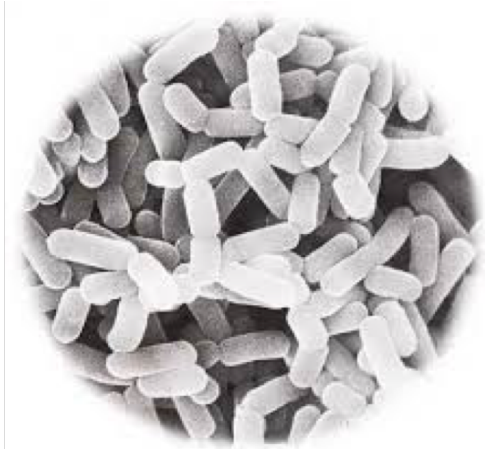


# ***Efficacy of Probiotics in Pediatric Gastrointestinal (GI) Diseases***



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# Outline (Efficacy of Probiotics)

- I. Acute diarrhea
- II. Neonatal necrotizing enterocolitis (NEC)
- III. Constipation
- IV. Irritable bowel syndrome (IBS)
- V. *Helicobacter pylori* (*H. pylori*) infection
- VI. Inflammatory bowel disease (IBD)
- VII. Short bowel syndrome

# 益生菌的定義

- Probiotics are defined as live microorganisms which, when administered in adequate amounts confer a health benefit on the host. [\(FAO/WHO. 2001.\)](#)
- 益生菌是活的益生菌，適量給予能對宿主產生健康效應  
(世界衛生組織/國際農糧組織)



# History



- Elie Metchnikoff (1845-1916),  
Russian microbiologist, received Nobel Prize in Medicine  
in 1908
- *“The Prolongation of Life” 1908*
  - *Developed a theory that lactic acid could prolong life and drank sour milk every day prove it*
  - *The potential life-lengthening properties of lactic acid bacteria*



# History

- **Probiotics**, comes from the Greek word meaning "for life", first introduced in 1953 by Kollath
  - contrasting antibiotics, probiotics were defined as microbially derived factors that stimulate the growth of other microorganisms
- In 1989 Roy Fuller suggested a definition of probiotics which has been widely used
  - a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance.

# Yogurt Formation



# Regular Yogurt vs. Greek Yogurt



# Yale University Workshop 2006: Advance in Clinical Use of Probiotics

**TABLE 1.** Guidelines for Probiotic Use

Clinical Condition	Clinical Effectiveness*	Organisms**
Adult and childhood diarrhea		<i>Lactobacillus reuteri</i> <sup>13,14</sup>
Prevention	B	<i>Lactobacillus GG</i> <sup>15,16</sup> <i>L. casei</i> , <sup>17,18</sup> <i>L. acidophilus</i> , <sup>19-21</sup> <i>S. boulardii</i> <sup>21,22</sup>
Treatment	A	<i>Bifidobacteria</i> <sup>24,25</sup>
Antibiotic-associated diarrhea	A	<i>S. boulardii</i> , <sup>25-27</sup> L GG <sup>28-30</sup>
Radiation	C	VSL no. 3 <sup>31</sup>
Vaginosis	C	<i>Lactobacillus acidophilus</i> <sup>32,33</sup>
H pylori	C	<i>L. johnsonii</i> <sup>34,35</sup>
Ulcerative colitis	C	<i>E. coli</i> (Nissle), <sup>36,37</sup> <i>Bifidobacteria</i> and <i>Lactobacillus</i> , <sup>38</sup> VSL no. 3 <sup>39,40</sup>
Crohn disease	C	<i>E. coli</i> (Nissle), <sup>41</sup> <i>S. Boulardii</i> , <sup>42,43</sup> L GG (variable) <sup>44</sup>
Pouchitis	A	VSL no. 3 <sup>45-47</sup>
Irritable bowel syndrome	C	<i>L. plantarum</i> , <sup>48,49</sup> VSL no. 3, <sup>50</sup> <i>B. infantis</i> <sup>51</sup>
Prevention of cardiovascular disease	C	<i>Lactobacillus</i> in milk and yogurts <sup>52,53</sup>
To improve immune response	B	<i>L. acidophilus</i> , <sup>54</sup> <i>L. Plantarum</i> , <sup>55</sup> <i>B. Lactis</i> , <sup>56,57</sup> L GG, <sup>58,59</sup> <i>L. Johnsonii</i> <sup>60,61</sup>

\*A indicates strong evidence; B, suggestive evidence; C, inadequate studies to be certain.

\*\*Exact dosage used is in appropriate reference.

VSL no. 3 indicates *Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbreueckii*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, and *Streptococcus salivarius*.

# 不同適應症益生菌證據等級

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Probiotics may reduce the incidence of antibiotic-related diarrhea.	A	5-7, 9	Most validated products are <i>Saccharomyces boulardii</i> and <i>Lactobacillus rhamnosus</i> GG
Probiotics may reduce the duration and severity of all-cause infectious diarrhea.	A	5, 10-12	A large meta-analysis of all-cause infectious diarrhea included studies with viral diarrhea and traveler's diarrhea
Probiotics may reduce the severity of pain and bloating in patients with irritable bowel syndrome.	B	17-19	Small trials to date
Probiotics may reduce the incidence of atopic dermatitis in at-risk infants. There is preliminary support for treatment of symptoms.	B	20-23, 25-28	—

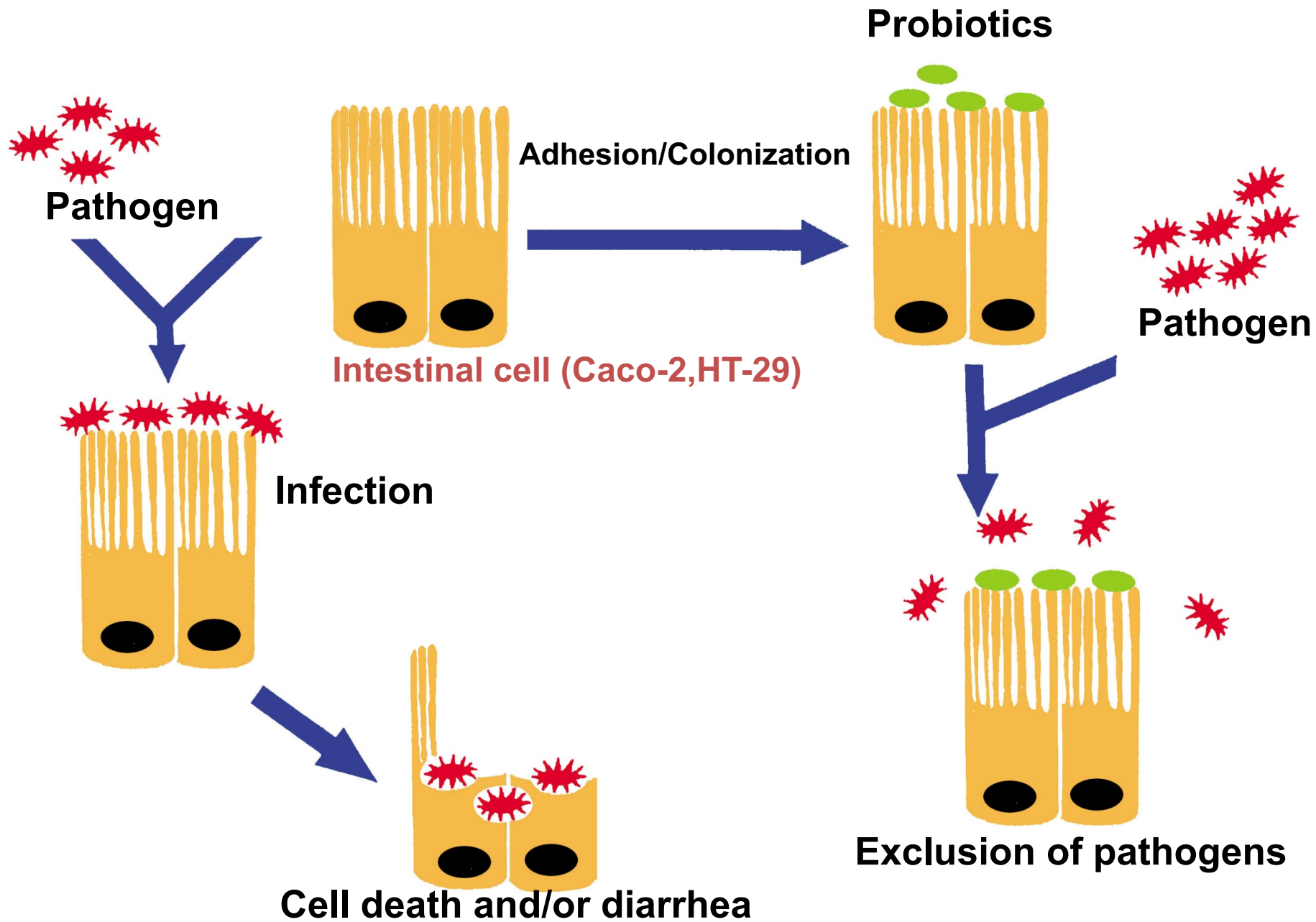
A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

- Probiotics. November 1, 2008 ◆ Volume 78, Number 9

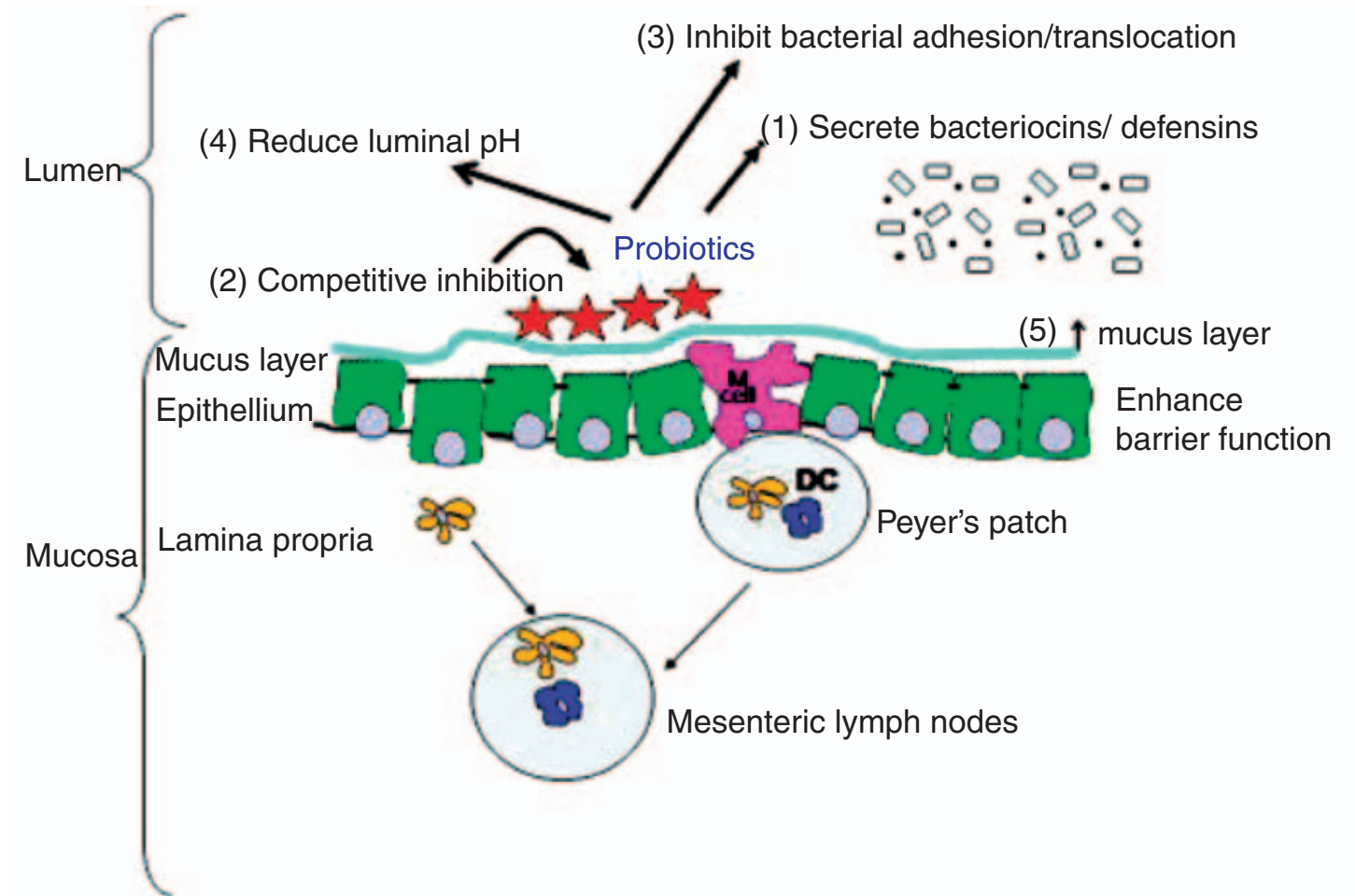
高度證據等級證明  
益生菌能幫助腹瀉改善

# ***I. Effect of Probiotics in Acute Diarrhea***



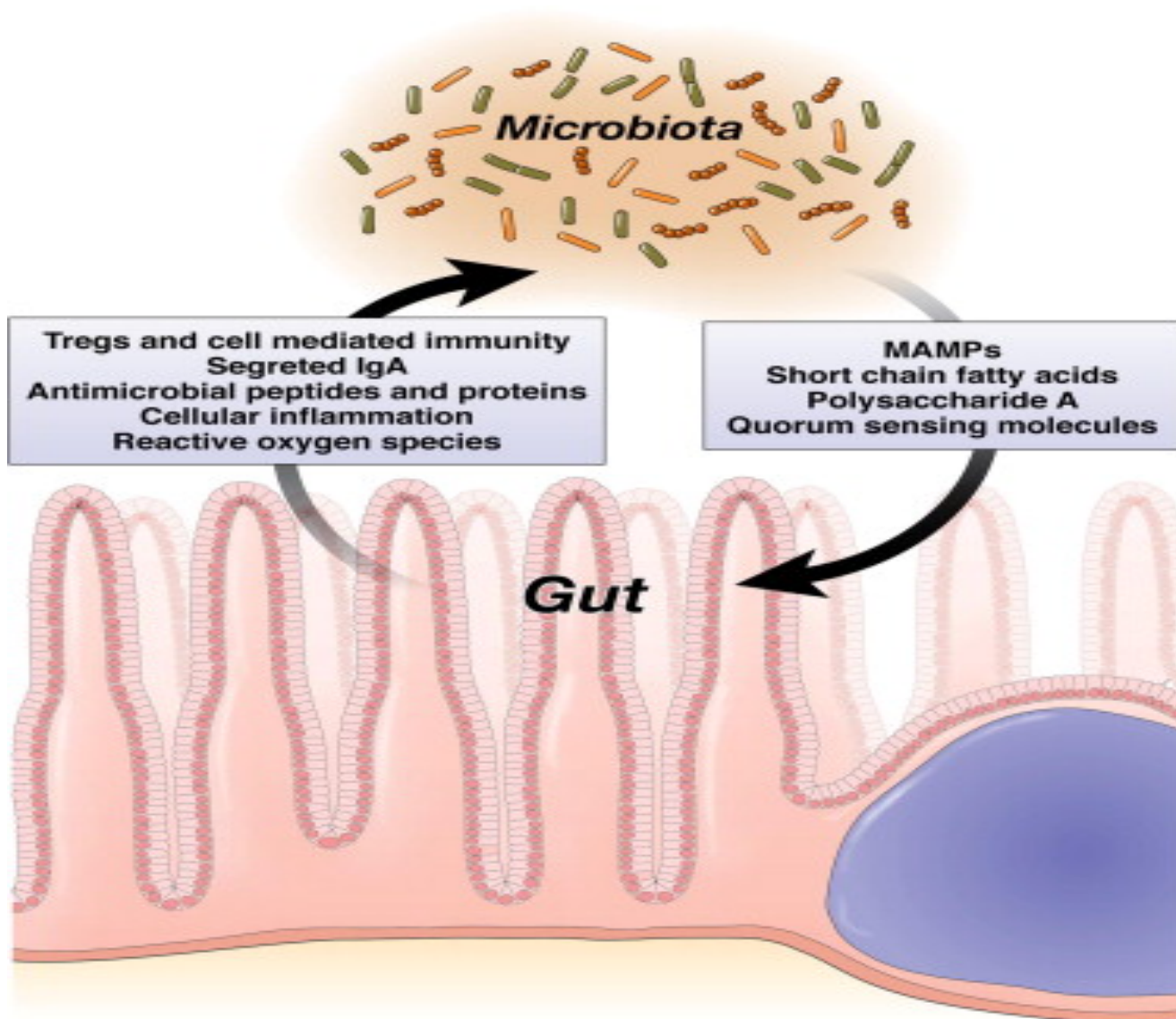


# Effect of Probiotics on GI Tract





# Mechanisms of Crosstalk



# Influences of Microbiota

- Metabolic/nutritional/energy utilization
  - Vitamin synthesis
  - SCFA as energy source – role in obesity
- Innate immune regulation
  - Dampening of inflammatory responses
- Adaptive immune regulation
  - Induction of immunosuppressive T cells (Tregs)
- Epithelial development and survival
  - Stimulation of proliferation and restitution
  - Cytoprotective effects of PRR signaling
- Competitive exclusion of pathogens

# 益生菌需耐胃酸膽鹼並可附著於腸道

菌種	胃酸耐受性	膽鹼耐受性	腸道附著能力
<i>L. rhamnosus</i>	+	+	強力附著
<i>L. casei</i>	—	+	附著
<i>L. acidophilus</i>	+	+	不附著
<i>L. paracasei</i>	+	+	不附著
<i>L. fermentum</i>	+	+	不附著

篩選47株乳酸桿菌進行in vitro試驗，並挑選5株表現最好的進行人體試驗，受試者連續18天服用 $2 \times 10^{10}$ cfu之益生菌



# 抗生素耐受性

## Characterization of Oral *Lactobacillus* as Potential Probiotics for Oral Health

*Oral Microbiol Immunol.* 2008 23(2):139-47

### 研究結果：

由健康人體篩選出67株乳酸桿菌，分別檢驗其抗菌、耐酸鹼、溶菌酶耐受性，以及抗生素耐受性。其中*L. rhamnosus*乳酸桿菌對於抗生素及酸鹼等環境壓力皆有良好耐受能力。

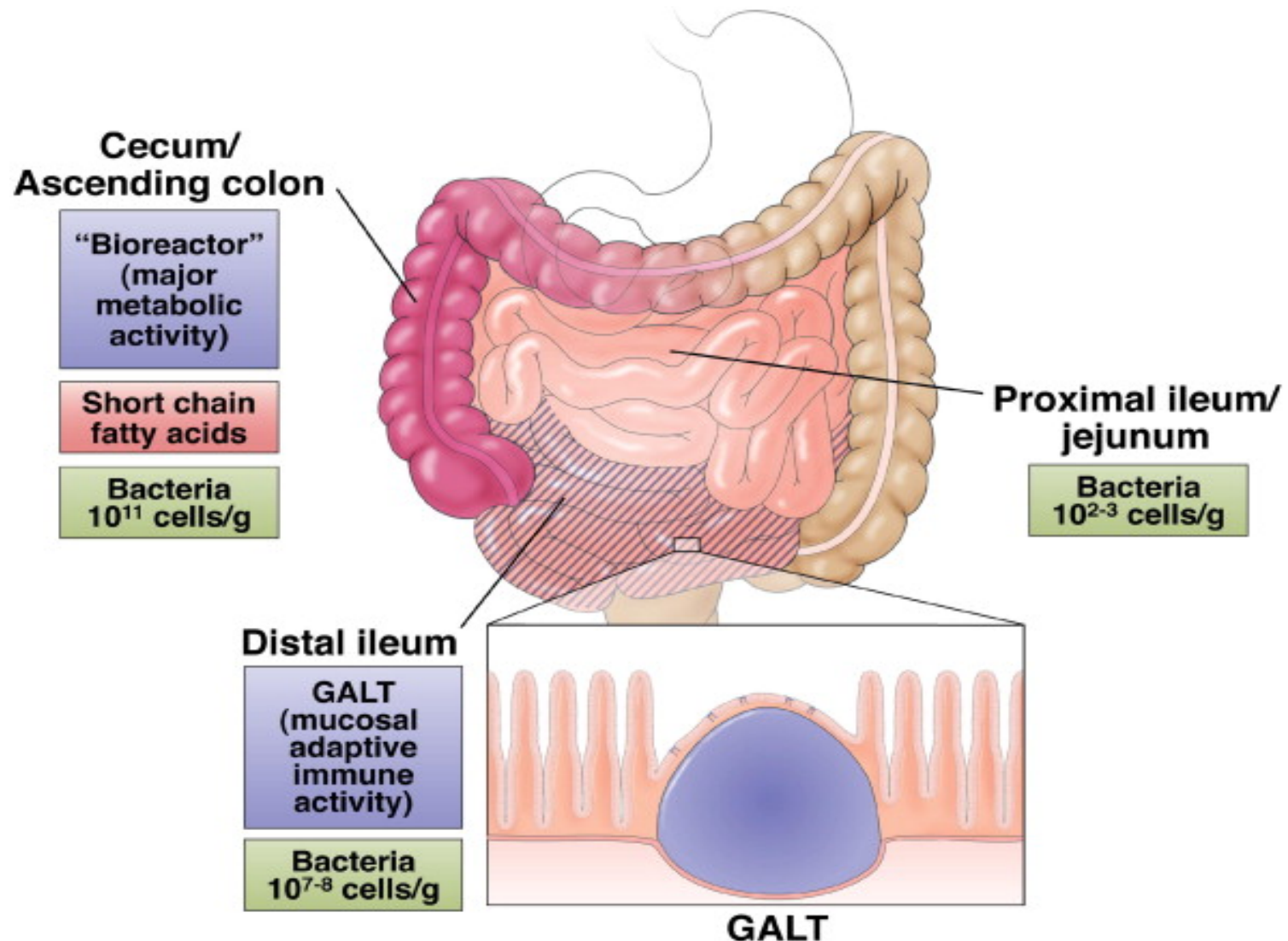
*L. rhamnosus* 對於抗生素耐受能力表現

各抗生素最小抑菌濃度										
	AC	FP	CT	GM	EM	DC	TC	CM	CL	CI
<i>L.rhamnosus</i>	0.75	8	6	12	0.25	0.5	0.5	0.75	3	4
<i>L.paracasei</i>	1	6	6	4	0.19	0.75	0.75	0.09	3	2
<i>L. salivarius</i>	0.19	0.75	0.25	2	0.25	0.25	0.25	0.19	1.5	≥32
<i>L. gasseri</i>	0.38	3	1	8	0.19	2	3	8	6	≥32

FX : cefoxitin ; FP : cefprozil ; CT : cefotaxime ; VA : vancomycin ; GM : gentamicin ;  
TC : tetracyclin ; CL : chloramphenicol ; CI : ciprofloxacin ; MZ : metronidazole

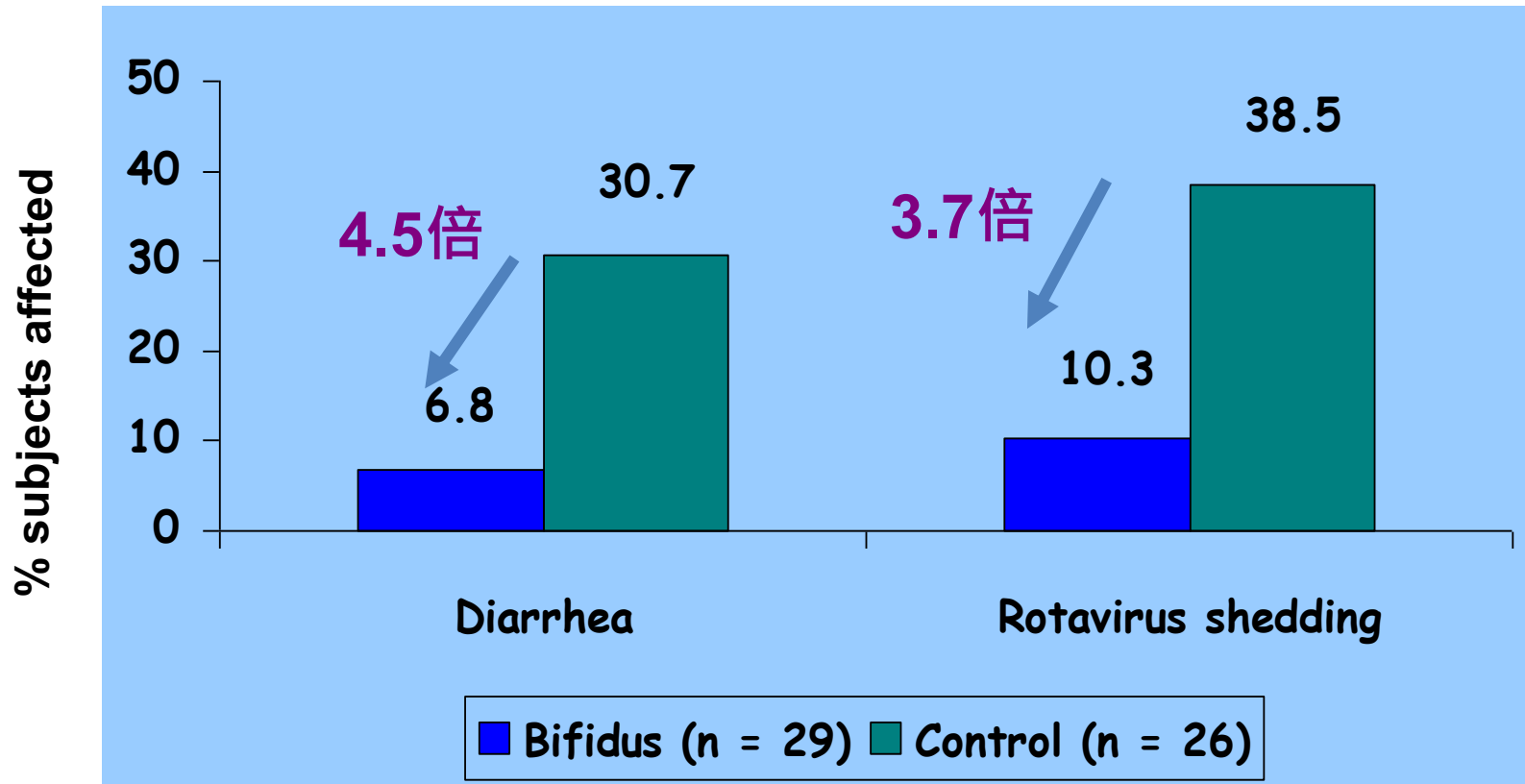
最小抑菌濃度：菌不能生長的藥物濃度，數值越高表耐受性越好

# Preferred Sites of Probiotics Interaction



# ***I. Effect of Probiotics in Acute Diarrhea***

# Prevention of Diarrhea and Rotavirus Infection by *Bifidus/thermophilus* Enriched Formula (Hospital Setting, 5-24 months)



(Saveedra JM et al, Lancet 1994;344:1046-9)



# *L. rhamnosus*

## 臨床功效研究文獻

### ◆ 腹瀉：

#### — 有助於改善急性腹瀉症狀

縮短腹瀉時間達**1.5**天

服用第2天起排便次數減少

提升糞便硬度，使糞便硬度恢復正常時間由**6天縮短為3天**

*BMJ. 2007 335(7615):340*

#### — 能有效減輕因輪狀病毒腸胃炎腹瀉造成之脫水現象

縮短因輪狀病毒感染而腹瀉時間達**1.5**天

因輪狀病毒腹瀉脫水時間**減少近1天**

*Aliment Pharmacol Ther. 2006 23(2):247-53*

#### — 與抗生素合併使用，降低因使用抗生素而引起腹瀉的風險

*Aliment Pharmacol Ther 2015; 42: 1149 - 1157*



# Infectious Diarrhea-1

- Probiotics shorten duration of diarrhea, especially in children, and prevent recurrence of diarrhea in the treatment of acute infectious diarrhea.
- Well-controlled clinical trials have shown that probiotics *L. rhamnosus GG*, *L. reuteri*, *L. casei*, and *B. lactis* can shorten the duration of acute rotavirus diarrhea.<sup>1,2</sup>
  - These trials outline the role of probiotics as therapy and their role in limiting malnutrition associated with diarrhea in a meta-analysis of 18 probiotics therapy clinical trials involving children younger than 5 years of age with acute-onset diarrhea
  - A systemic review article stated that co-administration of probiotics with standard rehydration therapy reduced the duration of diarrhea by approximately 1 day.<sup>3</sup>

1. Szajewska H, et al. JPGN 2001;33:S17–25.

2. Isolauri E, et al. Gut 2002; 50(suppl III):54–9.

3. Huang JS, et al. Dig Dis Sci. 2002;47:2625–2634.

# Infectious Diarrhea-2

- Rosenfeldt V et al described the effect of *L. rhamnosus* and *L. reuteri* administered twice daily for 5 days to a cohort of children with acute diarrhea in local day-care centers.<sup>1</sup>
  - In children treated with a mixture of the two *Lactobacillus strains*, the mean duration of diarrhea was reduced by 40 hours ( $P = 0.05$ ). Rotavirus infection was found in 63% of the children.
- This same group randomized 69 children hospitalized for acute diarrhea to the same mixture of *L. rhamnosus* and *L. reuteri* twice daily for 5 days.<sup>1</sup>
  - Duration of diarrhea was reduced by 19 hours and the length of hospitalization by 48% in the probiotic-treated group. 10% of the probiotic group versus 30% of the control group still had loose stools at the end of the study period ( $P = 0.03$ ).
  - Rotavirus infection identified in 66% of patients, at the end of intervention, rotavirus antigen persisted in 12% of patients in the probiotics group versus 46% of patients in the control group ( $P = 0.02$ ).

# Infectious Diarrhea-3

- **Costa-Ribeiro H, et al similarly measured the effect of *L. casei* subspecies *rhamnosus* GG on male children younger than 2 years of age. In their randomized, double-blinded, placebo-controlled trial, *Lactobacillus* GG did not reduce diarrhea duration or stool output. <sup>1</sup>**
  - **Whether this signifies the fact that probiotics are not effective in more severe forms of diarrhea**
  - **The duration of probiotics administration was too short to permit colonization remains to be determined.**
- **The effects of dietary supplementation with the prebiotic oligofructose in the prevention of acute diarrhea**

1. Costa-Ribeiro H, et al JPGN 2003 Jan;36(1):112-5.

# Infectious Diarrhea-RCT Studies

- A meta-analysis (2010, 63 randomized controlled trials) using several different probiotics preparations) in adults and children found that probiotics reduced the overall risk of diarrhea lasting four or more days by 59 percent (relative risk 0.41, 95% CI 0.32-0.53) and the mean duration of diarrhea by 25 hours (95% CI 16-34 hours). The two most commonly studied probiotics were *Lactobacillus GG* and *Saccharomyces boulardii*)<sup>1</sup>
- A meta-analysis (2002) included nine studies that evaluated the efficacy of several strains of *lactobacilli* in reducing the duration of symptoms in children with acute infectious diarrhea. Probiotics reduced the duration of diarrhea by 0.7 days (95% CI 0.3-1.2) and diarrhea frequency on day two by 1.6 stools per day. A minimum of 10 billion colony-forming units during the first 48 hours was needed to reduce the duration of diarrhea by more than one-half a day.<sup>2</sup>
- Probiotics (*VSL#3*, *L. rhamnosus*) may have a role in hastening recovery from acute rotavirus diarrhea in children.<sup>3-5</sup> In a double-blind, placebo-controlled trial of 230 children with acute rotavirus diarrhea, *VSL#3* significantly decreased stool frequency.<sup>4</sup> In another randomized trial, *Lactobacillus GG* demonstrated a dose dependent decrease in fecal shedding of rotavirus.<sup>5</sup>

1.Allen SJ, et al. Cochrane Database Syst Rev 2010; :CD003048

2. Van Niel CW, et al. Pediatrics 2002; 109: 678)

3.Dubey A), et al. J Clin Gastroenterol 2008; 42 Suppl 3 Pt 1: S126.

4. Teran CG, et al. Int J Infect Dis 2009; 13: 518.

5. Fang SB, et al. J Trop Pediatr 2009; 55: 297

# *L. rhamnosus* 有助於改善急性腹瀉症狀

571 位3~36個月大之急性腹瀉病童隨機分成6 組

	Dose (twice daily)	腹瀉時間	平均排便次數	糞便硬度
Placebo(口服電解質溶液) (n=92)		115.5小時	3~4天後開始減少	第6天恢復正常
<i>L. rhamnosus</i> (n=100)	6 x 10 <sup>9</sup> cfu/dose	78.5小時*	第2天起減少	第2天起明顯提升 第3天起恢復正常
<i>Saccharomyces boulardii</i> (n=91)	5 x 10 <sup>9</sup> cfu/dose	105.0小時	未減少	第6天恢復正常
<i>Bacillus clausii</i> (n=100)	1 x 10 <sup>9</sup> cfu/dose	118.0小時	未減少	第6天恢復正常
<i>L. delbrueckii</i> var <i>bulgaricus</i> <i>L. acidophilus</i> <i>Streptococcus thermophilus</i> <i>B. Bifidum</i> (n=97)	1 x 10 <sup>9</sup> cfu/dose 1 x 10 <sup>9</sup> cfu/dose 1 x 10 <sup>9</sup> cfu/dose 5 x 10 <sup>8</sup> cfu/dose	70.0小時*	第2天起減少	第2天起明顯提升 第3天起恢復正常
<i>Enerococcus faecium</i> SF68 (n=91)	7.5 x 10 <sup>7</sup> cfu/dose	115.0小時	未減少	第6天恢復正常

\* p<0.001

# Probiotics in Acute Infectious Diarrhea- Positive Recommendation

TABLE 6. Probiotics for treating acute gastroenteritis (recommendations developed by the ESPGHAN Working Group on probiotics/prebiotics)

Strain(s)	Quality of evidence	Recommendation	Dose
Probiotics with a positive recommendation			
LGG	Low	Strong	$\geq 10^{10}$ CFU/day (typically 5–7 days)
<i>Saccharomyces boulardii</i>	Low	Strong	250–750 mg/day (typically 5–7 days)
<i>Lactobacillus reuteri</i> DSM 17938	Very low	Weak	$10^8$ – $4 \times 10^8$ (typically 5–7 days)
Heat-killed <i>Lactobacillus acidophilus</i> LB*	Very low	Weak	Minimum 5 doses of $10^{10}$ CFU for 48 h; maximum 9 doses of $10^{10}$ CFU for 4.5 days
	Quality of evidence	Recommendation	Reason
Probiotics with a negative recommendation			
<i>Enterococcus faecium</i> (SF68 strain)	Low	Strong	Safety issues (a possible recipient of the vancomycin-resistance genes)

# ***Clostridium Difficile* and Antibiotic-associated Diarrhea**

- The efficacy of probiotics in *C. difficile* diarrhea and antibiotic-associated diarrhea
  - A randomized, controlled trial of *C. difficile* associated Colitis demonstrated that *S. boulardii* was able to prevent disease recurrence.<sup>1</sup>
  - In a double-blinded, placebo-controlled trial conducted in 2003, Wullt M, et al examined the ability of *L. plantarum 299v* to prevent recurrent episodes of *C. difficile-associated* diarrhea. Recurrence of clinical symptoms was seen in 4 of 11 patients treated with metronidazole plus *L. plantarum 299v* and in 6 of 9 treated with metronidazole combined with placebo.<sup>2</sup>
  - Sambol SP, et al colonized hamsters with nontoxigenic *C. difficile* strains and found that these non-toxigenic strains were able to prevent diarrheal disease in 87% to 97% of hamsters subsequently challenged.<sup>3</sup>

1. McFarland LV, et al. *JAMA* 1994; 271:1913–8.

2. Wullt M, et al. *Scand J Infect Dis.* 2003;35(6-7):365-7.

3. Sambol SP, et al. *The Journal of Infectious Diseases* 183(12):1760-6.

# Second Prevention of CDI With Probiotics

- A subsequent study using *S. boulardii* was designed to include only patients with recurrent CDI episodes and to control for the dosing and type of antibiotic used.<sup>1,2</sup>
- A substudy of the overall trial, however, did suggest a potential benefit for those patients who were randomized to high-dose vancomycin and *S. boulardii*.<sup>1</sup>
- 3 of 18 patients (17%) randomized to high-dose vancomycin (2 g/day) for 10 days and *S. boulardii* (1 g/day) for 28 days had subsequent recurrences, compared with 7 of 14 patients (50%) randomized to vancomycin alone ( $P=0.05$ )<sup>2</sup>. There was no benefit to the patients randomized to low-dose vancomycin (500 mg/day) and *S. boulardii* or to those randomized to metronidazole and *S. boulardii*
- In summary, the promising results of the first randomized trial of *S. boulardii* for secondary CDI prevention<sup>1</sup> were not duplicated in the second randomized trial of patients with recurrent CDI <sup>2</sup>, the subgroup in the first trial that showed the most potential benefit.

1. McFarland LV, et al. *JAMA* 1994; 271:1913–8.

2. Surawicz CM, et al. *Clin Infect Dis* 2000; 31:1012–7.



# Conclusion

- The limitations and findings from the meta-analyses and RCTs suggest that there is moderate evidence on the effectiveness of probiotics to prevent primary CDI. The use of probiotics as an adjunctive therapy may provide a key intervention in reducing primary CDI.
- There are insufficient data to support use in secondary prevention of recurrent CDI. Additional studies of sufficient size are needed to further evaluate secondary prevention.

# Antibiotic Associated Diarrhea-1

- A randomized trial by Seki et al found that the use of the probiotic *Clostridium butyricum* in 110 children receiving antibiotics for upper respiratory tract infections reduced diarrhea from 59% in the placebo-treated group to 5% in the *Clostridium*-treated group. <sup>1</sup>
- *S. boulardii* used in the treatment of 57 adult patients with acute amebiasis reduced the duration of diarrhea from 48 hrs in the placebo-treated group to 12 hours in the *Saccharomyces*-treated group ( $P < 0.001$ ).
  - After 4 weeks, amebic cysts were detected in 18% of the placebo-treated group but in none of the probiotics-treated group. <sup>2</sup>

1. Seki H, et al. Pediatr Int 2003 Feb;45(1):86-90.

2. Dinieyici EC, et al. Am J Trop Med Hyg 2009 Jun;80(6):953-5

# Antibiotic Associated Diarrhea-2

- In a doubleblinded, controlled trial, 740 patients undergoing cataract surgery received preoperative treatment with ampicillin and cloxacillin (for cataract surgery), with or without *Lactobacillus*.<sup>1</sup>
  - *The incidence of diarrhea in patients receiving antibiotic alone was 13% compared with 0% in patients receiving antibiotics plus Lactobacillus.*
- Sullivan et al demonstrated that the probiotics (*yogurt*) prevented antibiotic-induced changes in *Bacteroides fragilis* microflora cultured from human feces (anaerobic culture system).<sup>2</sup>
- Payne et al demonstrated that *L. plantarum 299v* diminished antibiotic-induced overgrowth of *Candida albicans*.<sup>3</sup>

1.Ahuja MC, Khamar B J Indian Med Assoc 2002 May;100(5):334-5.

2.Sullivan A, et al. J Antimicrob Chemother. 2003 Aug;52(2):308-11

3.Payne S, et al. Curr Issues Intest Microbiol. 2003 Mar;4(1):1-8.

# ***L. GG* Decline occurrence of AAD**

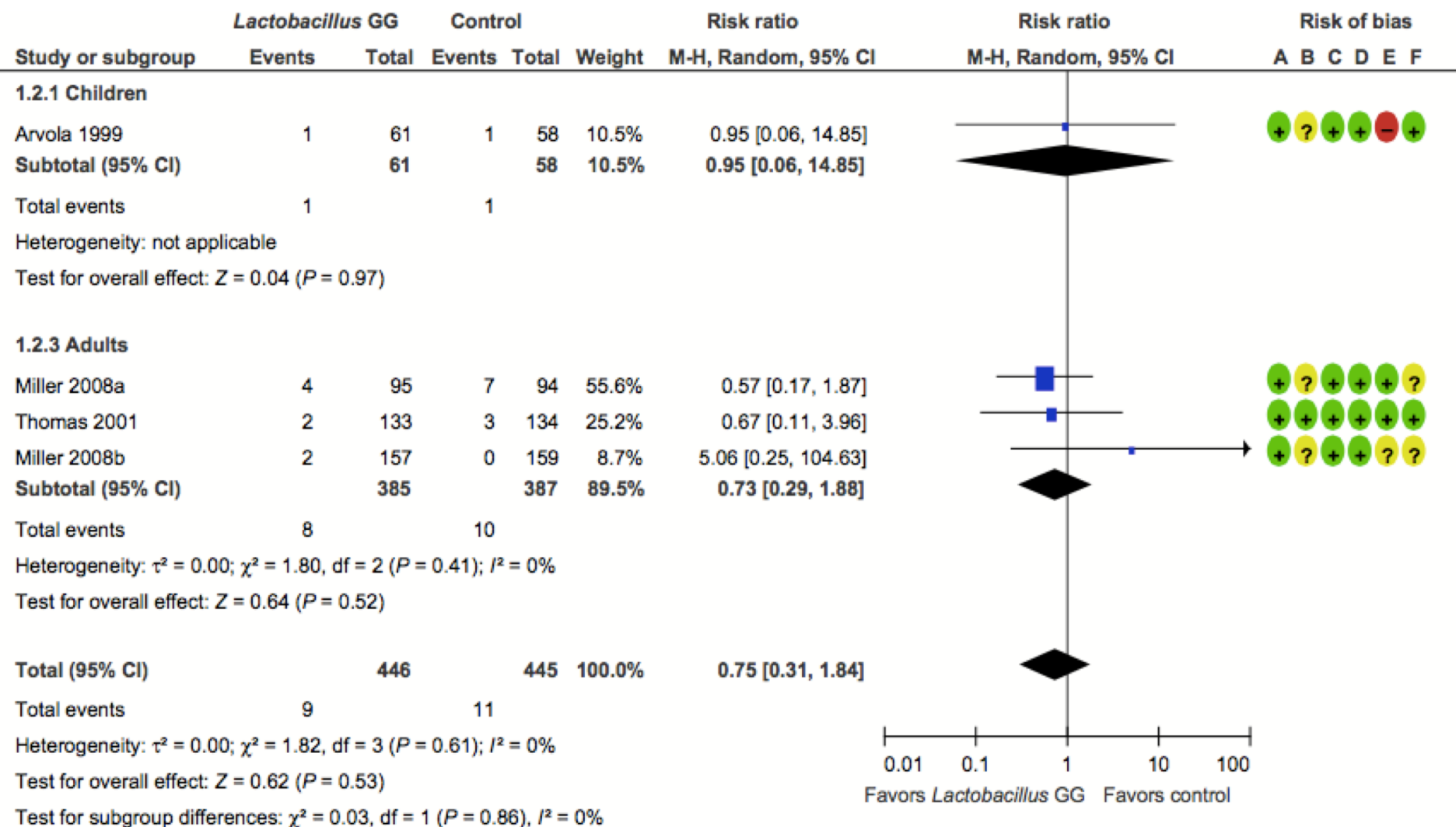
## **Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults**

H. Szajewska & M. Kołodziej

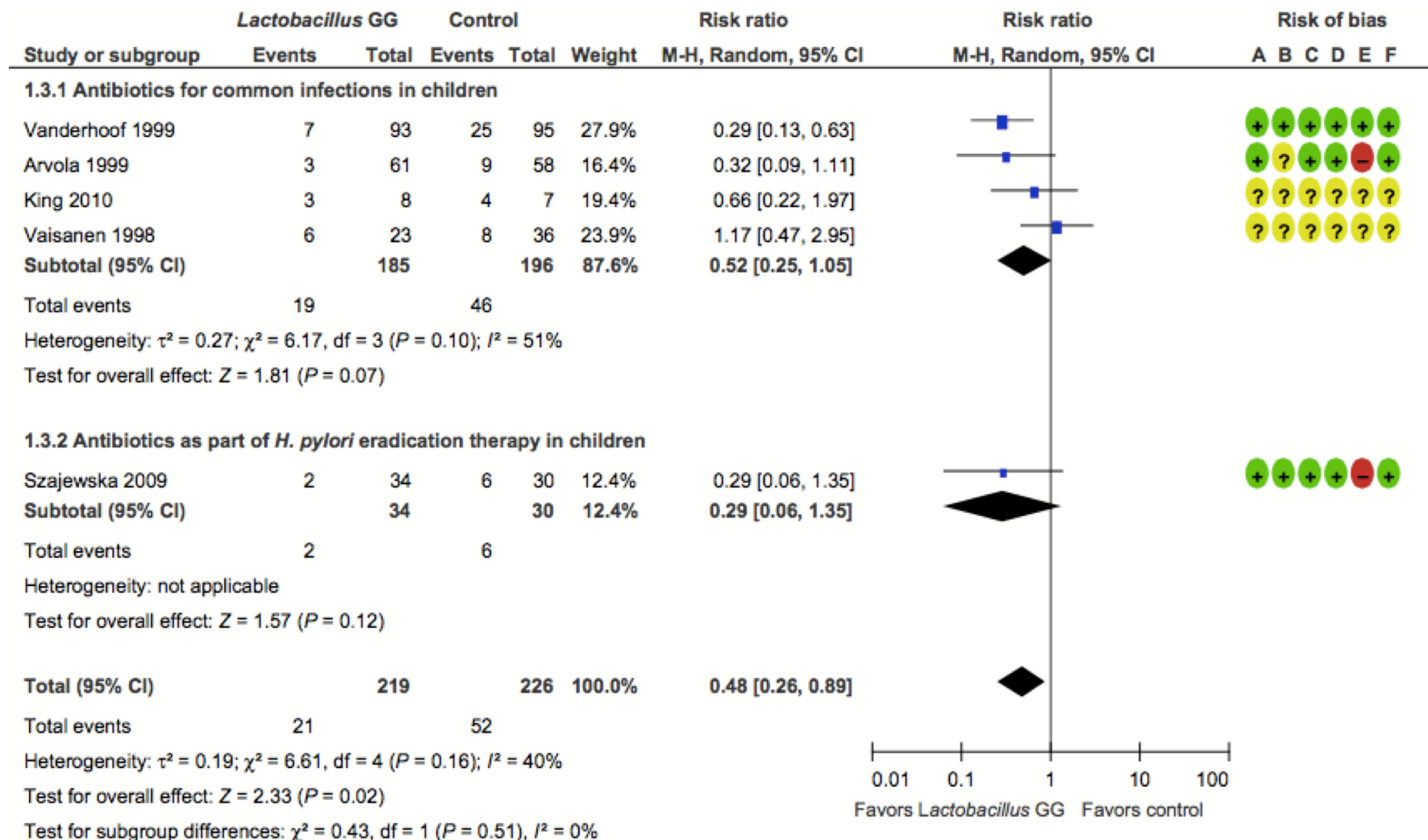
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- 設計: 收集12 RCTS，合計1499名參與者，使用LGG和placebo比較
- 分別針對兒童與成人AAD治療結果分析

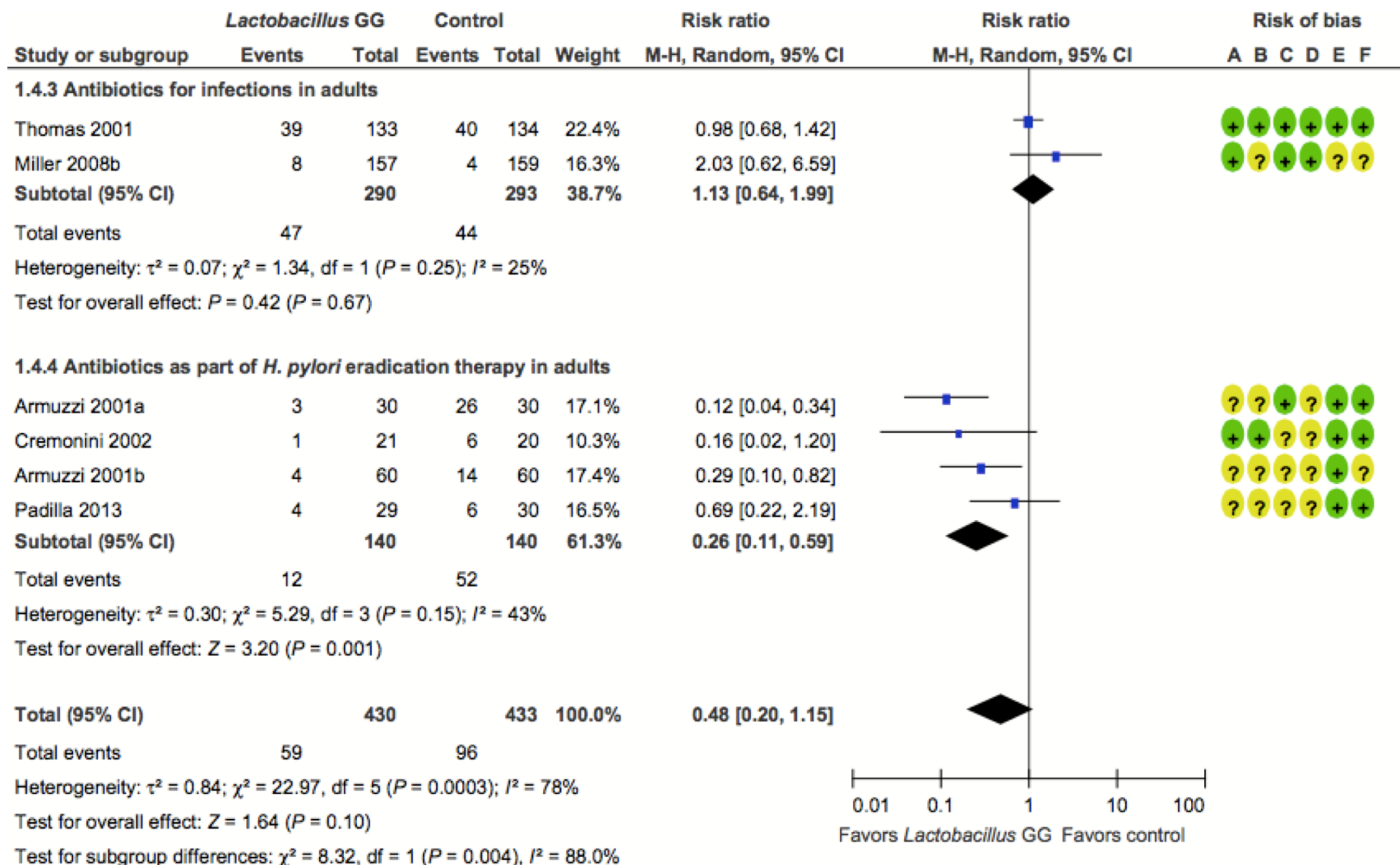
# L. GG Can Decline Occurrence of AAD (1)



# L. GG Can Decline Occurrence of AAD (2)



# L. GG Can Decline Occurrence of AAD (3)



## ***II. Effect of Probiotics in NEC***



# Prevention of Necrotizing Enterocolitis (I)

- Lin et al:
  - Very low birth weight (<1500 g), n=367
  - **Infloran (*L acidophilus* and *B infantis*)**, twice daily with breast milk
  - Decreased risk of NEC (9 in 180 vs 24 in 187)

Lin et al. Pediatrics 2005;115:1-4.

- Bin-Nun et al:
  - ***B infantis*, *Sthermophilus*, *B bifidus*** at  $10^9$  cfu/day
  - Reduced incidence: 16.4% in 73 control infants, 4% in 72 supplemented infants

Bin-Nun A, et al. J Pediatr 2005;147:192-6.

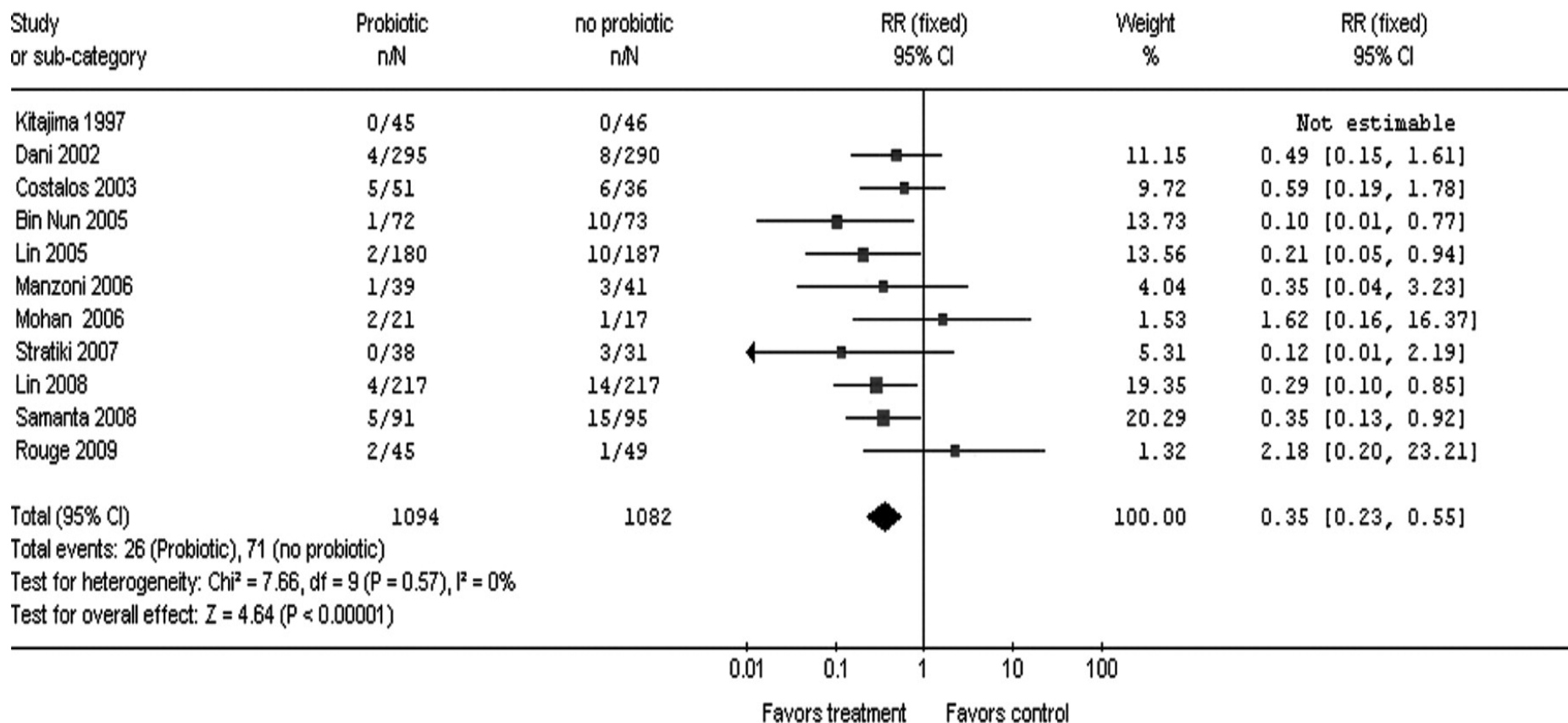
# Prevention of Necrotizing Enterocolitis (2)

- A meta-analysis by Deshpande
  - II RCT, n=2176
  - 30% reduction in the incidence of NEC
  - The dramatic effect sizes, tight confidence intervals, extremely low P values, and overall evidence indicate that additional placebo-controlled trials are unnecessary.

Deshpande et al. Pediatrics 2010;125:921-30.

# Effect of probiotics on NEC-Meta-analysis

Review: Probiotics for prevention of necrotizing enterocolitis  
 Comparison: 01 NEC  
 Outcome: 01 Definite NEC



Deshpande, G. et al. Pediatrics 2010;125:921-930

PEDIATRICS®

### ***III. Effect of Probiotics in Constipation***

# Effect in Constipation (I)

- A double-blinded RCT study by Coccorullo et al
  - N=44, at least 6 m/o infants
  - Probiotics: *L. reuteri*
  - Higher frequency of bowel movements at wk 2, wk 4, and wk 8
  - No improvement in stool consistency and episodes of inconsolable crying episodes

Coccorullo et al. J Pediatr 2010 Jun 12 epub

# Effect in Constipation (2)

- **A double-blinded RCT study by Banaszekiewicz et al:**
  - N=84, age 2-16
  - LGG ( $1 \times 10^9$  CFUs daily) versus placebo as an adjunct to lactulose for 12 weeks
  - No effect

Banaszekiewicz et al. J Pediatr 2005;146:364-9.

- Bu et al:
  - N=45
  - Lcr35 (Antibiophilus) for 4 weeks
  - Effective

Bu et al. Pediatr Int 2007;49:485-90.

# Constipation-RCT Studies

- Randomized, placebo-controlled trials of probiotics in patients with chronic constipation without irritable bowel syndrome, and in normal subjects with a tendency toward infrequent stools, suggest improvement in defecation frequency, stool consistency, and intestinal transit time with *Bifidobacterium lactis* DN-173 010, *B. lactis* BB12, *Lactobacillus casei* Shirota, *L. reuteri* DSM 19738 and *E. coli* Nissle 1917.<sup>1-2</sup>
  - However, these results using probiotics in the management of severe constipation should be interpreted with caution due to marked heterogeneity in study design and results, as well as publication bias.
- Limited heterogeneous studies do not support use of probiotics in children with functional constipation.<sup>3-4</sup>

1. Dimidi E, et al. Am J Clin Nutr 2014; 100:1075.
2. Miller LE, et al. Ann Gastroenterol 2017; 30:629.
3. Wojtyniak K, et al. Eur J Pediatr 2017; 176:1155.
4. Huang R, et al. Front Cell Infect Microbiol 2017; 7:153.

# Evidence

- Limited randomized controlled trials suggest improvement in defecation frequency and stool consistency in adult and older adult patients with chronic constipation, but limited benefit in children.
- However, larger studies are needed before probiotics can be routinely recommended in the management of severe chronic constipation.



## ***IV. Effect of Probiotics in IBS***

# IBS-RCT Studies (1)

- A meta-analysis of 16 randomized controlled trials found important methodologic limitations of most of the studies.
- There was some evidence of efficacy for *Bifidobacterium infantis* 35624 in two appropriately designed studies.<sup>1-2</sup>
  - The probiotics *B. infantis* was significantly more effective than placebo at 4 weeks in a controlled trial of 362 patients with IBS. However, the benefit was confined to only one of three doses tested and there was no clear dose-response relationship.<sup>1</sup>
  - A trial of 77 patients with IBS were randomly assigned to a malted milk drink containing *Lactobacillus salivarius* UCC4331 or *B. infantis* 35624 or to a malted milk drink alone. Symptoms were significantly improved at most time points in the group receiving *B. infantis*. There was a corresponding normalization in the ratio of serum IL-10/IL-12 suggesting that the probiotics may help reduce a proinflammatory state associated with IBS.<sup>2</sup>

1. Whorwell PJ, et al. Am J Gastroenterol 2006; 101:1581.

2. Brenner DM, et al. Gastroenterology 2005; 128:541.

# IBS-RCT Studies (2)

- In a 4-week trial, 60 patients with IBS were randomly assigned to *Lactobacillus plantarum* (DSM 9843) or placebo. Flatulence was significantly reduced in the probiotics group compared with placebo, while abdominal pain was reduced to a similar extent in both groups. Gastrointestinal function was maintained at 12 months in the probiotic group compared with placebo.<sup>1</sup>
- In a 4-week trial, 50 patients with IBS, according to Rome II criteria, were randomly assigned to a probiotics preparation containing the combination of *Lactobacillus plantarum* LPO 1 and *Bifidobacterium breve* BR or placebo. Pain and severity scores decreased significantly in the probiotics group after 14 days of treatment.<sup>2</sup>
- Improvement in abdominal pain and a trend towards normalization of stool frequency in constipated patients was found in the probiotics treated group in a placebo-controlled trial of 40 patients randomly assigned to *Lactobacillus plantarum* 299V or placebo.<sup>3</sup>
- No overall improvement was observed in a randomized, placebo-controlled trial involving 100 patients with IBS treated with a combination of four probiotic species.<sup>4</sup>

1. Nobaek S, et al. Am J Gastroenterol 2000; 95:1231.

2. Saggiaro A. J Clin Gastroenterol 2004; 38:S104.

3. Caroll IM, et al. Am J Physiol Gastrointest Liver Physiol 2011; 301:G799.

4. Drouault-Holowacz S, et al. Gastroenterol Clin Biol 2008; 32:147.

# Evidence

- Evidence remains unconvincing for benefits of probiotics for treating irritable bowel syndrome, probably due to marked heterogeneity in this disorder.
- Considerable disagreement as to which agent or group of probiotics is most beneficial and which patient subgroups should be targeted.
- A definitive therapeutic role remains unproven and needs to be further investigated in defined patient subsets.

## ***V. Effect of Probiotics in IBD***

# Ulcerative Colitis

- Various probiotic species have shown promise in the treatment of ulcerative colitis (mostly small number of patients in these studies)
  - *E. coli* Nissle 1917 shows promise in maintaining remission and could be considered as an alternative in patients intolerant or resistant to 5-ASA preparations.<sup>1-3</sup>
  - VSL#3 may have some efficacy in treating active disease as an adjunctive approach. No probiotic preparations have been validated for clinical use in ulcerative colitis.<sup>4-5</sup>
- Systematic reviews have reached variable conclusions regarding the use of probiotics for the induction and maintenance of remission of ulcerative colitis,<sup>6-9</sup> but publication bias may influence results.

1. Rembacken BJ, et al. Lancet 1999; 354:635.

2. Kruis W, et al. Gut 2004; 53:1617.

3. Henker J, et al. Z Gastroenterol 2008; 46:874.

4. Tursi A, et al. Med Sci Monit 2004; 10:PI126.

5. Miele E, et al. Am J Gastroenterol 2009; 104:437.

6. Derwa Y, et al. Aliment Pharmacol Ther 2017; 46:389.

7. Parker EA, et al. Nutrition 2018; 45:125.

8. Holubar SD, et al. Cochrane Database Syst Rev 2010; :CD001176.

9. Ganji-Arjenaki M, et al. J Cell Physiol 2018; 233:2091.

# Crohn Disease

- Clinical trials of probiotics in Crohn disease have shown **mixed results**.
- The reasons for the heterogeneity are unclear, but could be due to several factors such as the specific probiotics (and doses) used, differences in study duration, characteristics of the included patients (eg, location of disease), and endpoints that were measured. Likewise, use of probiotics in prevention of postoperative recurrence of Crohn disease has been unsuccessful.<sup>1</sup>
- The available data do **not** support clinical effectiveness of probiotic therapy for either induction or maintenance of remission in patients with Crohn disease.<sup>2-4</sup> Whether certain patient subgroups might benefit remains to be determined.
- A report of clinical improvement with combination of a **probiotic, *B. longum***, and a prebiotic suggested the possibility of using a symbiotic approach to treating Crohn disease, although previous reports with other agents were less positive.<sup>5</sup>

1. Doherty GA, et al. Aliment Pharmacol Ther 2010; 31:802.
2. Rolfe VE, et al, Cochrane Database Syst Rev 2006.
3. Whelan K, Quigley EM. Curr Opin Gastroenterol 2013; 29: 184.
4. Bourreille A, et al. Clin Gastroenterol Hepatol 2013; 11: 982
5. Steed H, et al. Aliment Pharmacol Ther 2010; 32:872.

## ***VI. Effect of Probiotics in H. Pylori Infection***



# *H. Pylori* Infection (1)

- Previous reports have suggested a role for probiotics in the treatment and prevention of *H. pylori* infection through both a probiotic-induced inhibition of *H. pylori* growth and adhesion to epithelial cells and an effect on the host immune system.
- In the presence of clarithromycin-resistant *H. pylori*, eradication is significantly attenuated. Ushiyama et al demonstrated that *Lactobacillus gasseri* inhibited both the in vitro growth of clarithromycin-resistant *H. pylori* and the release of interleukin-8 from epithelial cells.<sup>1,2</sup>
- In an in vivo mouse model, *H. pylori* colonization was significantly decreased by *L. gasseri*.<sup>3</sup>

1. Ushiyama A, et al. J Gastroenterol Hepatol 2003; 18 : 986 –991

2. Tamura a, et al. J Gastroenterol Hepatol 2006; 21 : 1399–1406

3. Uchida M, et al. J Pharmacol Sci 2004; 96: 84–90.

# *H. Pylori* Infection (2)

- Chatterjee et al also demonstrated an inhibitory effect of *Lactobacillus* (*L. acidophilus*) on *H. pylori* growth but only if the colonization ratio was 1:1 or higher.<sup>1</sup>
- In a double-masked, randomized, controlled clinical trial, 326 school children from a low socioeconomic area of Santiago, Chile, with *H. pylori* infection were treated with both live and heat-killed strains of *L. johnsonii*, *L. paracasei* once daily for 4 weeks. A <sup>13</sup>C-urea breath test demonstrated a significant decrease in *H. pylori* colonization in children receiving live *L. johnsonii* but not *L. paracasei*.<sup>2</sup>

1. Chatterjee A, et al. Mol Cell Biochem 2003; 243, 29–35.

2. 2. Cruchet S, et al. Nutrition 2003; 19 (9):716-721.

# *H. Pylori* Infection (3)

- In an attempt to identify why some strains of probiotics are effective in altering *H. pylori* colonization and others are not
- Mukai *et al* examined the binding of *Lactobacillus reuteri* and *H. pylori* to the putative *H. pylori* glycolipid receptor molecules.
  - Among the 9 *L. reuteri* strains tested, only 2 were shown to bind to the same glycolipid receptors as *H. pylori* and thereby inhibit *H. pylori* binding.<sup>1</sup>
  - The investigators suggested that the sharing of glycolipid specificity was required for the *Lactobacillus* strains to have a therapeutic effect on *H. pylori* eradication.

# *H. Pylori* Infection (4)

- Probiotics have been suggested to increase efficacy of eradication therapy by preventing antibiotic-associated side effects and thus increasing compliance.
- Cremonini *et al*/randomized 85 patients with *H. pylori* undergoing eradication with triple therapy to 1 of 4 *groups: L. casei subspecies ramnosus, Saccharomyces boulardii, L. acidophilus plus Bifidobacterium lactis, or placebo.*<sup>1</sup>
  - In all probiotic-supplemented groups, *there was a significantly lower* incidence of antibiotic-associated diarrhea and taste disturbance relative to placebo.
  - Nevertheless, there was no difference in *H. pylori* eradication or compliance rates between the various groups.

1. Cremonini F, et al. Am J Gastroenterol. 2002;97:2744–9.

## ***VII. Effect of Probiotics in Short Bowel Syndrome***

# Short Bowel Syndrome (1)

- Patients with short bowel syndrome have bacterial overgrowth and increased gut permeability.
  - In an animal model (32 adult Wistar rats) of short bowel syndrome (80% resection, from the duodeno-jejunal angle to 10 cm above the cecum ), *B. lactis* administration ( $7.8 \times 10^9$  CFU) reduced bacterial translocation (mesenteric lymph nodes (MLN), and peripheral and portal blood specimens) from 93% in the placebo-treated group (n =14) to 44% in the *B. lactis* group (n = 18).<sup>1</sup>
  - Same degree of success was not observed in human studies. McNaught et al studied patients undergoing elective abdominal surgery and found that there was no difference in bacterial translocation into mesenteric lymph nodes between patients pretreated for 1 week with *L. plantarum* or placebo.<sup>2</sup>

# Short Bowel Syndrome (2)

- Immunonutritional parameters before and after treatment with synbiotic (*Bifidobacterium breve*, *Lactobacillus casei*, galactooligosaccharides) in 4 children with SBS and 4 controls (normal, healthy, age-matched children).
  - Fecal samples were analysed for bacterial flora and organic acid (OA) contents. Levels of short chain fatty acids (SCFA), such as butyrate, propionate and acetate, increased in one patient, and SCFA/total OA levels increased in three patients.
  - Serum lymphocyte counts and pre-albumin levels increased after commencing synbiotic treatment, reaching a statistically significant level at the ninth month compared to the baseline level.
  - There was an increasing trend in height and weight gain velocity during the study *versus* the baseline period. The faecal bacterial flora improved in SBS patients after synbiotic therapy.

# Short Bowel Syndrome (3)

- Treatment of a 2-year-old SBS patient with with *Bifidobacterium breve* Yakult, *Lactobacillus casei* Shirota ( $>1 \times 10^9$  bacilli thrice a day) and galactooligosaccharides (3 gm/day) over a period of 2 years that resulted in dramatic improvement in intestinal motility and absorptive function.
  - Levels of *E. coli* and *Candida* and the ratio of facultative anaerobic bacteria to total bacteria in the fecal samples, which were very high, decreased after synbiotic therapy.
  - The episodes of fever and metabolic acidosis, thought to be related to Small bowel bacteria overgrowth, enterocolitis and catheter sepsis, which occurred prior to synbiotic therapy, ceased.
  - There was improvement in the composition of SCFA, with a decrease in the lactate/non-lactate SCFA ratio and an increase in total SCFAs.
  - Weight gain accelerated, and nutritional markers (serum prealbumin, transferrin, choline esterase) increased.



# Short Bowel Syndrome (4)

- A double-blind, placebo-controlled randomized crossover clinical trial to assess the effects of *Lactobacillus rhamnosus* (LGG) treatment on intestinal permeability (IP) in children [(4.5 (1.6–16.4) yrs] with SBS. IP was measured by the urinary lactose-mannitol ratio in 9 children with SBS (cases) and 12 healthy children (controls)
  - SBS patients received LGG or placebo for 4 weeks. IP, quantitative fecal cultures for *Lactobacillus* species and the hydrogen breath test (HBT) were performed during LGG and placebo phases of treatment.
  - IP (mean  $\pm$  SD) was comparable in SBS and healthy control:  $0.08 \pm 0.06$  vs.  $0.07 \pm 0.05$  ( $p = 1.0$ )
  - Fecal colonization with *Lactobacillus* species did not differ during LGG versus placebo treatment ( $1.4 \times 10^9$  ( $4.0 \times 10^5$  to  $4.0 \times 10^9$ ) cfu/g) vs. ( $6.0 \times 10^9$  ( $1.0 \times 10^3$  to  $1.0 \times 10^{10}$ ) CFU/g), respectively; ( $p = 0.83$ ).
  - LGG treatment had no consistent effects on IP ( $p = 0.58$ ) or its relationship with age ( $r = -0.40$ ,  $p = 0.29$ ) and was associated with conversion to positive HBT results in one subject.

# Strength of Efficacy for Probiotics with Identified Strain at least two Randomized, Controlled Trials with Significant Findings

Disease indication	Net $\geq 2$ significant randomized clinical trials (RCTs) (number of significant RCTs/non-significant RCTs)	At least two RCTs with significant efficacy (number of significant RCTs/non-significant RCTs)
<b>Prevention</b>		
Adult AAD	<i>Saccharomyces boulardii</i> I-745 (11+/6–) <i>Lactobacillus acidophilus</i> CL1285+ <i>Lactobacillus casei</i> LBC80R+ <i>Lactobacillus rhamnosus</i> CLR2 (4+/0) <sup>a</sup> <i>L. casei</i> DN114001 (2+/0–)	<i>Enterococcus faecalis</i> SF68 (2+/1–) <i>L. rhamnosus</i> GG (2+/4–)  <i>Lactobacillus reuteri</i> 55730 (2+/1–)
Pediatric AAD	<i>S. boulardii</i> I-745 (7+/3–)	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (2+/1–)
CDI-primary	None	<i>L. acidophilus</i> CL1285 + <i>L. casei</i> LBC80R + <i>L. rhamnosus</i> CLR2 (2+/2–) <sup>a</sup>
Nosocomial infections	None	<i>L. rhamnosus</i> GG (2+/2–)
Travelers' diarrhea	<i>S. boulardii</i> I-745 (2+/0–)	

# Strength of Efficacy for Probiotics with Identified Strain at least two Randomized, Controlled Trials with Significant Findings

## Treatment

Pediatric acute diarrhea	<i>S. boulardii</i> I-745 (25+/4–) <i>L. rhamnosus</i> GG (12+/3–) <i>L. reuteri</i> DSN 17938 (3+/0–) <i>L. acidophilus</i> LB (3+/1–) <i>L. casei</i> DN114001 (3+/0–) VSL#3 <sup>b</sup> (2+/0–) <i>Bac. clausii</i> OC/SN/R (3+/1–)	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (2+/1–)
Irritable bowel syndrome	<i>B. infantis</i> 35624 (2+/0–) <i>L. plantarum</i> 299v (4+/1–) <i>L. rhamnosus</i> GG + <i>L. rhamnosus</i> LC705 + <i>B. breve</i> Bb99 + <i>Prop. freudenreichii shermanii</i> Jc (2+/0–)	<i>L. rhamnosus</i> GG (2+/2–) <i>S. boulardii</i> I-745 (2+/2–) VSL#3 <sup>b</sup> (2+/2–)
<i>Helicobacter pylori</i> eradication	<i>L. helveticus</i> R52 + <i>L. rhamnosus</i> R11 (4+/1–)	<i>S. boulardii</i> I-745 (5+/11–) <i>L. reuteri</i> 55730 (2+/2–) <i>L. acidophilus</i> La5 + <i>B. animalis</i> spp. <i>lactis</i> Bb12 (3+/2–)
Inflammatory bowel disease	VSL#3 <sup>b</sup> (8+/2–)	<i>S. boulardii</i> I-745 (2+/1–)
CDI-recurrences	<i>S. boulardii</i> I-745 (2+/0–)	

# ***Summary-Probiotics in GI Diseases***

- Acute infectious diarrhea-EBM (specific strains)
- Antibiotics associated diarrhea (AAD)-EBM (specific strains)
- Pseudomembraneous colitis (PPC)- probiotics (primary prevention), fecal microbiota transplant (treatment)
- Necrotizing enterocolitis (NEC)-specific strains with EBM (specific strains)
- Constipation- specific strains for mild constipation
- Irritable bowel syndrome-EBM (Specific strains)
- Inflammatory bowel diseases-UC (specific strain), CD (controversial)
- *H. Pylori*-peptic ulcer disease- help to eradicate *H. Pylori* (specific strains)
- Short bowel syndrome- EBM (Specific strains, multiple strains or synbiotics) for abdominal discomfort and stool frequency
- Lactose intolerance-specific strains? need further studies

***Thank You for Your Attention!***

