



-Biotics- The Wisdom of Grandma

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Disclosures



OVERVIEW

- **Case presentation**
- **Introduction**
- **Gut microbiota and mechanism of action**
- **Definitions**
- **History**
- **Clinical implications**
 - **Preventive power of probiotics**
 - **Therapeutic power of probiotics**
 - **Clinical effect of prebiotics**
 - **Safety issues of probiotics**



Case presentation:

14-month-old boy, who is having persistent vomiting and profuse diarrhea over the last 2 days, was brought for evaluation and management





After her EXAM



This boy is having stomach cold





Objective of the talk:

To understand the evidence
behind her management



Gut Health

Bischoff introduced the concept of (Gut Health) as:

a state of physical and mental well-being in the absence of gastrointestinal complaints that require the consultation of a doctor, in the absence of indications or risks of bowel disease and in the absence of confirmed bowel disease.

BMC medicine,2011



Gut health covers multiple aspects:

- A. Effective digestion and absorption of food nutrients
- B. Absence of gastrointestinal illness
- C. Effective immune function
- D. Wellbeing
- E. Normal and stable microbiota



Gut microbiota

An assortment of microorganisms inhabiting the mammalian gastrointestinal tract

Roughly 100 trillion bacteria reside in the gut

Luckey 1974 popularized the idea that the G.I tract and organisms within its lumen **constitute** an ecologic unit



Brain

Probiotics

Liver



3 lbs.

3.5 lbs.

4 lbs.



The composition of this microbial community is host specific, evolving throughout an individual's lifetime and susceptible to both exogenous and endogenous modifications

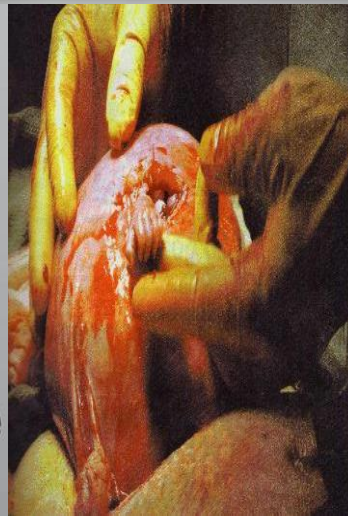
1000 different species of bacteria known to populate the gut

In each individual; a group of 160 species can be found



Initial colonization

- Transfer of maternal vaginal, colonic and skin microbiota
- Mode of delivery
- Antibiotic exposure
- Environment



Developing factors

- Host genetics
- Maternal diet
- Breast vs. formula feeding
- Antibiotics exposure
- Environmental exposure
- Developing immune system



Birth

Infancy



Early microbiota

Baby's gut microbiota



Stable microbiota, acquired by 2-4 years



The cell population of this “organ” outnumbered the cells in a human body

Research suggests that the relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather a symbiotic relationship

Recent researches illuminated its central position in health and disease

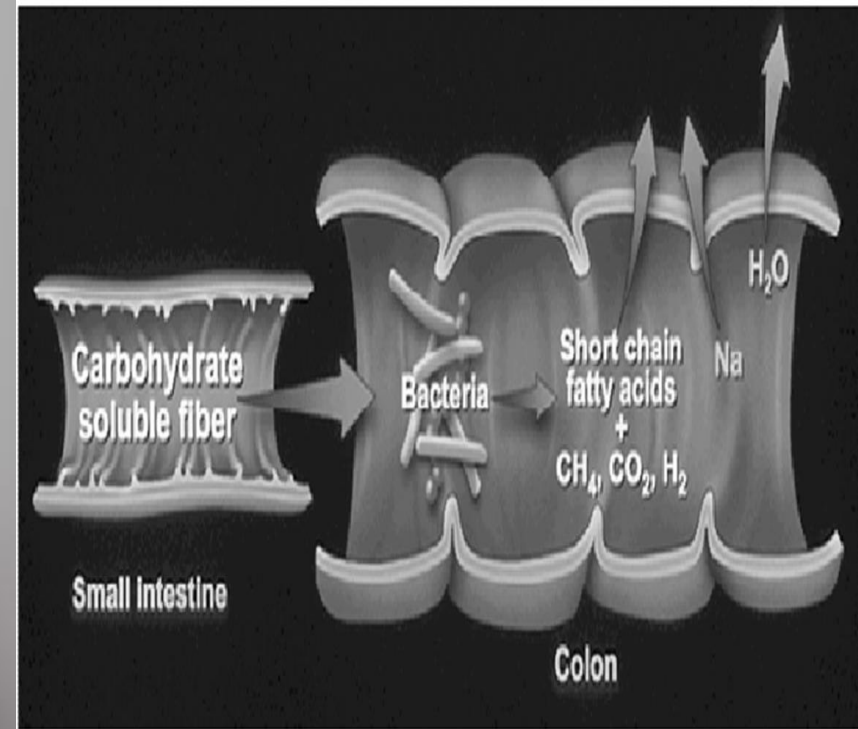


The microbiota is intimately involved in numerous aspects of normal host physiology, from nutritional status to behavior and stress response

Physiol Rev,2010

Functions of Gut microbiota:

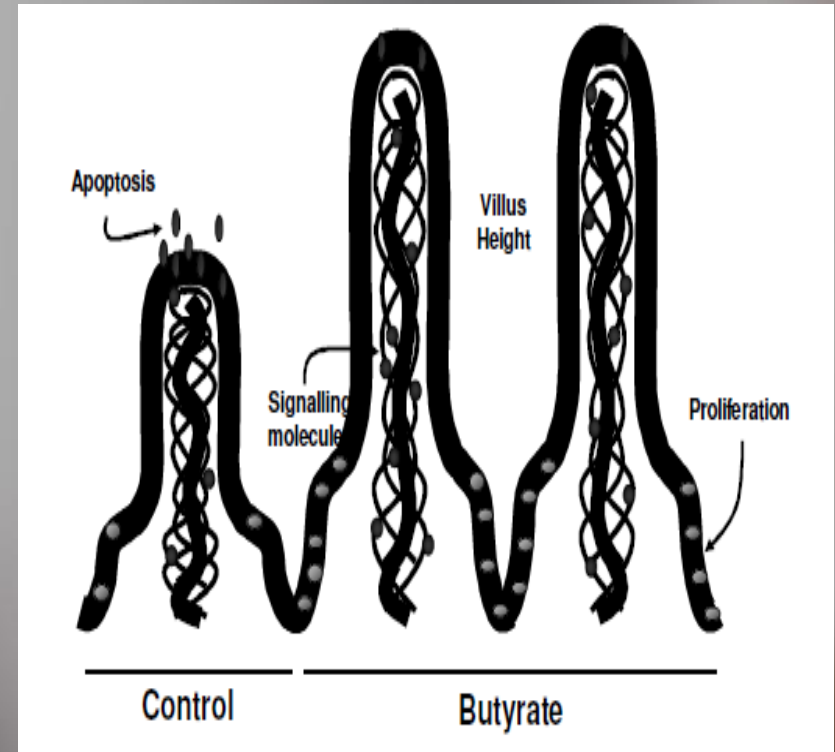
- Nutritional:
 - Nutrient bioavailability and digestion
 - Production of SCFAs
 - Production of essential nutrients; Vitamin B12, Vitamin K and Folic acid
 - Metabolizing bile acids





■ Physiologic

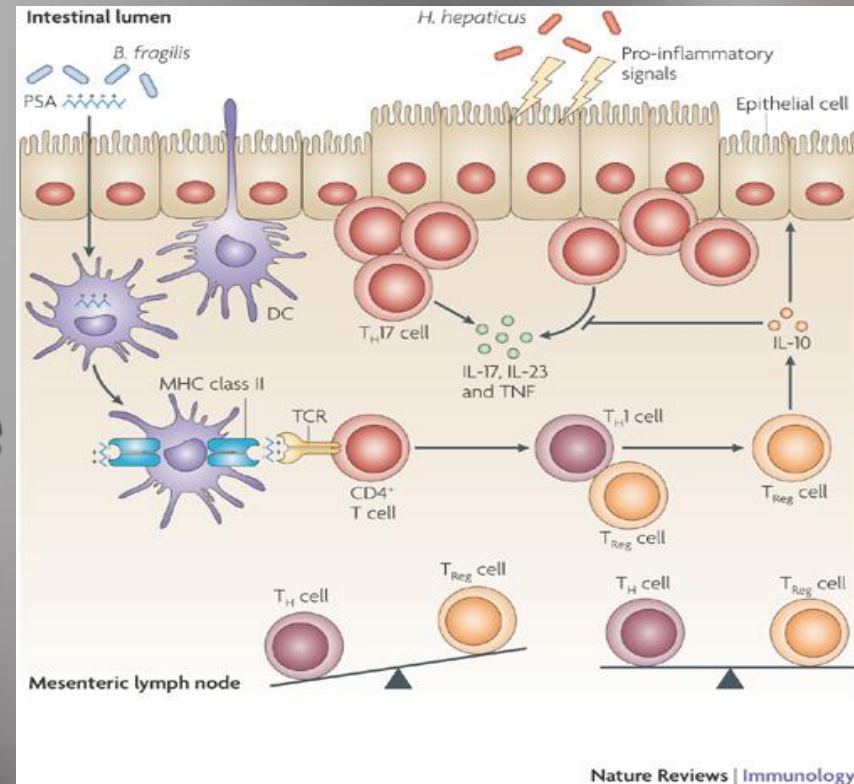
- Influence gut development
- Provides defense against pathogen colonization (competitive inhibition, antimicrobial production)
- Influences development and function of intestinal mucosal / epithelial barrier



JPEN ,2004



- Immunologic:
 - Guides development of infant immune system
 - Contributes to development of appropriate oral tolerance
 - Protects against development of inflammatory, atopic, and autoimmune diseases

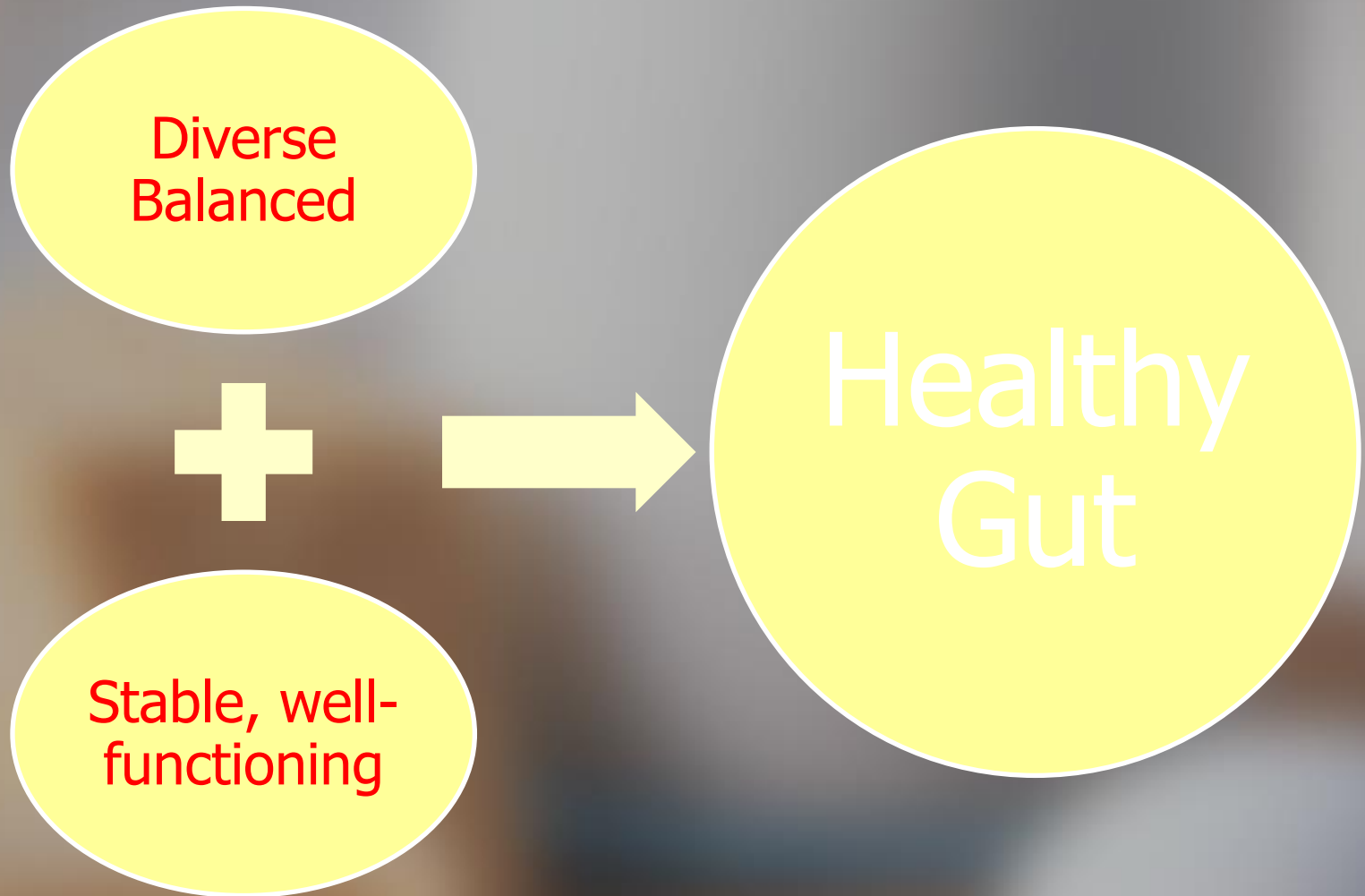




- Metabolic and others:
 - Helps regulate energy homeostasis
 - Production of metabolites
 - Contributes to development and maintenance of gut sensory and motor function
 - Contributes to feelings of general wellbeing



Role of gut microbiota in health and wellbeing





Healthy, or 'Balanced' Microbiota

predominantly saccharolytic and comprises significant numbers of bifidobacteria and lactobacilli

Eur J Nutr ,2004

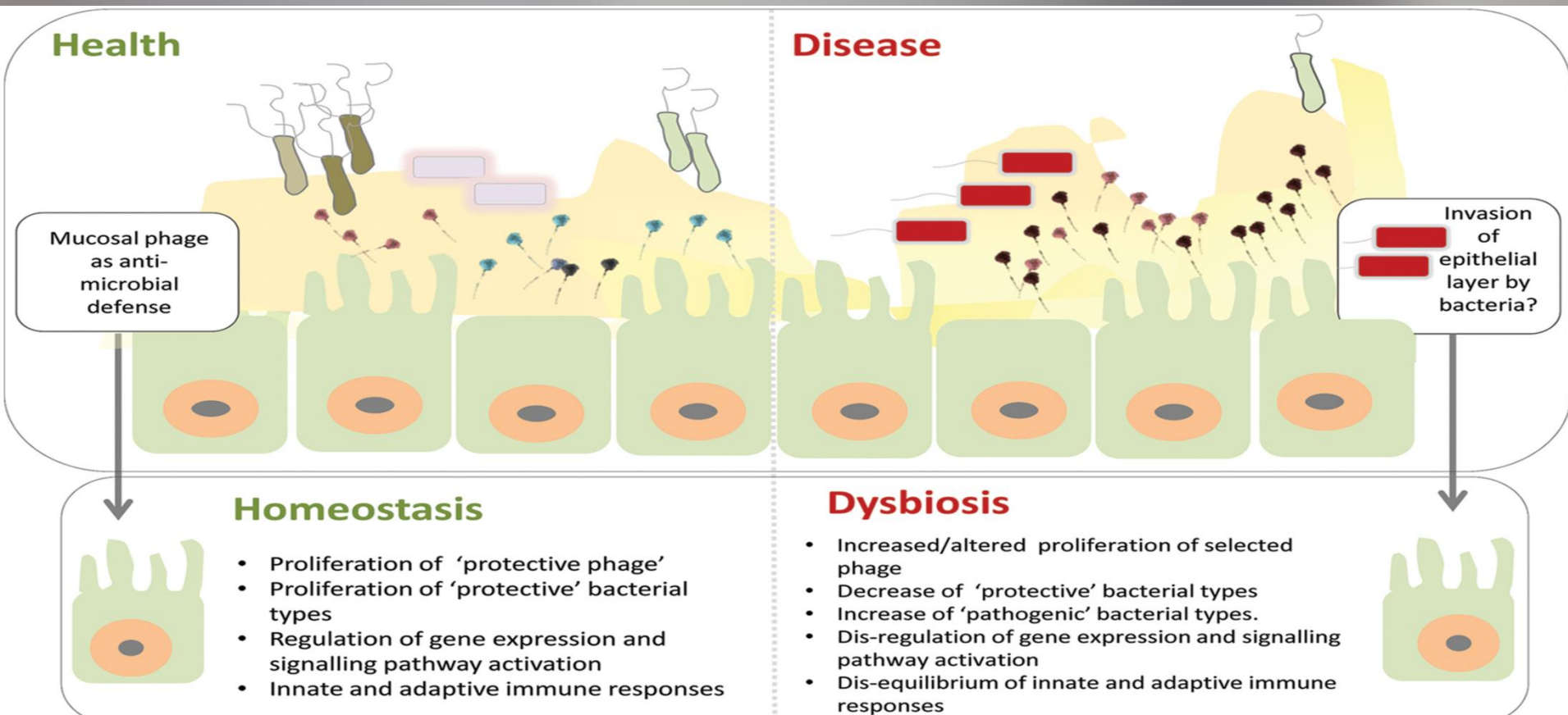
- ❖ B. & L. do not contain pathogens
- ❖ CHO fermenting bacteria
- ❖ The products of CHO fermentation, principally SCFA are beneficial to host health, while those of protein breakdown and amino acid fermentation, which include ammonia, phenols, indoles, thiols, amines and sulphides are not

J Appl Bacteriol ,1991



Dysbiosis

Disturbances or imbalances in gut microorganisms community





Patho-biont

- Bacteria that coexist in very low abundance, with the commensal bacteria in a healthy individual
- These microbes bloom and exhibit **pathogenic properties**, in many cases causing immune activation and inflammation.
 - Some **Dietary components** (excessive amounts of dietary L-carnitine from red meat) can promote the emergence of pathobionts from the commensal microbiota, causing dysbiosis and disease.



There is significant body of literature associated dysbiosis with many diseases:

- During infancy:
 1. Colic
 2. GI infections
 3. Constipation
 4. Diarrhea
 5. Allergic disorders



- Later in life
 1. Atopic disorders
 2. Celiac disease
 3. Obesity
 4. Diabetes
 5. Autoimmune disorders
 6. Irritable bowel syndrome
 7. Behavioral and mood disorders



Therapeutic Approaches

With the understanding of the role of gut microbiota in health and disease, modulating the composition of the gut microbiota offers a rational therapeutic target



The symbiotic relationship between gut microbiota and host can be optimized by :

1. Nutritional modifications
2. - Biotics
3. Antimicrobials
4. Fecal transplant



Functional Foods

A *food* similar in appearance to, or may be, a conventional food that is consumed as part of a usual diet, and is demonstrated to have ***physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions, i.e. they contain bioactive compound***



Probiotics

Live microorganisms, which when administered in adequate amounts, colonize the gut and exert beneficial biological effects on host

Nat Rev Gastroenterol Hepatol, 2014

- Non-pathogenic
- Resistant to technological processing, storage and delivery
- Resistant to gastric acidity and lysis by bile
- Viable in the gastrointestinal environment
- May adhere to the epithelium
- Produces antimicrobial substances



A Brief History of Probiotics



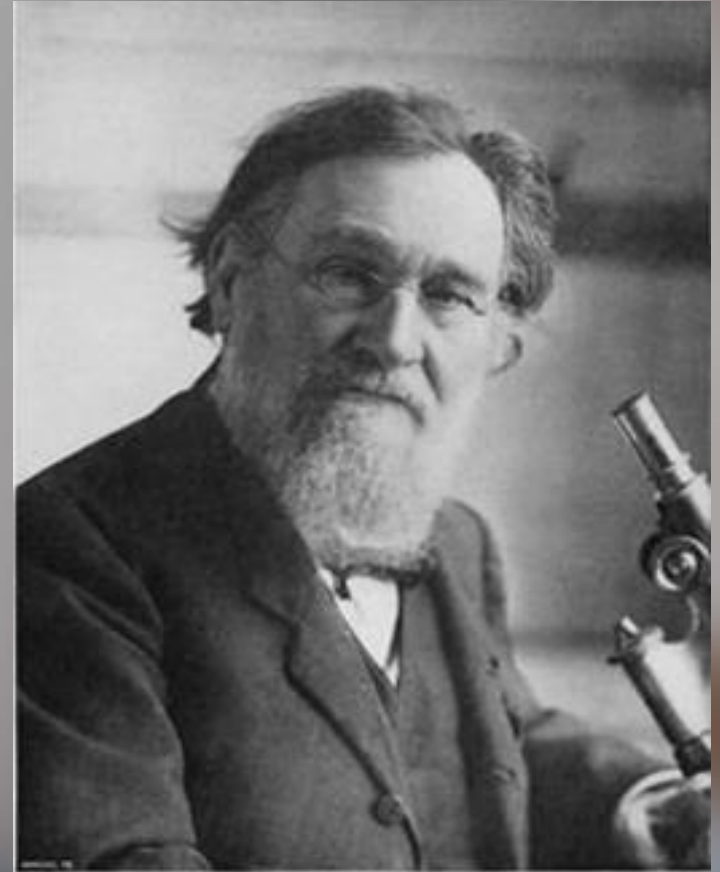


Elie Metchnikoff

(Russian scientist, Nobel laureate,
and professor at the Pasteur Institute in Paris)

Postulated ingesting
yogurt with
Lactobacilli reduces
toxic bacteria of the
gut and prolongs life

He developed a diet of
milk fermented with
the bacterium he
called "Bulgarian
bacillus"





- Kipeloff – 1926 – stressed importance of *Lactobacillus acidophilus* for good health
- Rettger – 1930's – early clinical application of *Lactobacillus*
- Parker – 1974 – 1st to use the term probiotics
- Fuller – 1989 – defined probiotics



Probiotics and gastrointestinal health effects

Numerous clinical studies have reported positive effects of probiotics in the prevention and/or treatment of several GI diseases

Nobaek et al. 2000
Wullt et al. 2003
Yamano et al. 2006





Do you use Prebiotics / Probiotics in your daily practice?





The preventive power of Probiotics

- Acute Gastroenteritis
- Nosocomial diarrhea
- Antibiotic associated diarrhea
- Clostridium difficile
- NEC
- URI
- Allergy
- Pouchitis





Acute Gastroenteritis

3-5 billion cases of acute gastroenteritis and nearly 2 million deaths occur each year in children under 5 years

The cost of gastroenteritis to the community is huge but often underestimated if costs to the family, including lost time at work, are not considered

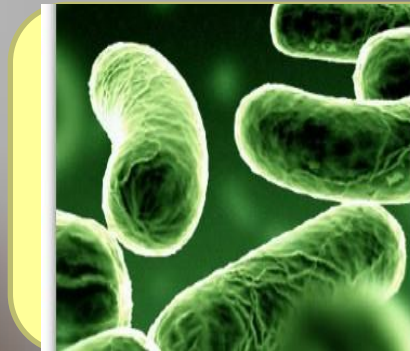
Children with poor nutrition are at increased risk of complications and longer hospital stay



A placebo-controlled trial of *Lactobacillus* GG to prevent diarrhea in undernourished Peruvian children

204 undernourished children 6 to 24 months old

Placebo



L. GG Daily
6 days/week
15 months

Fewer episodes of diarrhea
Formula fed patients

(J Pediatr, 1999)



Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents

201 healthy infants
4-10 mo.

Placebo
n = 60



B.lactis
n= 73



L.reuteri
n=68

Child care infants fed a formula supplemented with L reuteri or B lactis had fewer and shorter episodes of diarrhea



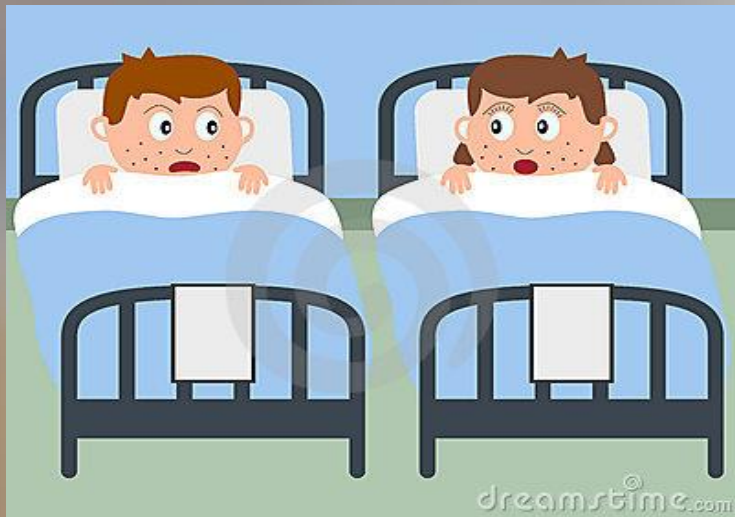
Nosocomial Gastroenteritis



Rota virus is the leading cause for hospital acquired gastroenteritis in children



Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants



N=45

Placebo (n = 36)

Prophylactic use L.GG significantly reduced the risk of nosocomial diarrhea in infants, particularly nosocomial Rota gastroenteritis



Antibiotic associated Diarrhea

- 1- Result of the disruption of the normal micro flora of the gut
- 2- Overgrowth of the microorganisms that induce diarrhea
- 3- Decrease in metabolism of carbohydrate and bile acids



A Randomized Formula Controlled Trial of Bifidobacterium lactis and Streptococcus thermophilus for Prevention of Antibiotic-Associated Diarrhea in Infants



Oral treatment with daily dose of B. lactis and S. thermophilus could prevent antibiotic associated diarrhea.



Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)

Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC

COLLABORATIVE

23 studies with 4213 patients

Moderate quality evidence suggests that probiotics are both safe and protective against C. difficile

Necrotizing Enterocolitis



An inflammatory gastrointestinal disease, occurs in 1%–5% of infants in neonatal intensive care units with a reported mortality rate of 25%–66%.





Do you give Probiotics to premature infants
in your NICU to prevent NEC?





Probiotics for prevention of necrotizing enterocolitis in preterm infants (Review)

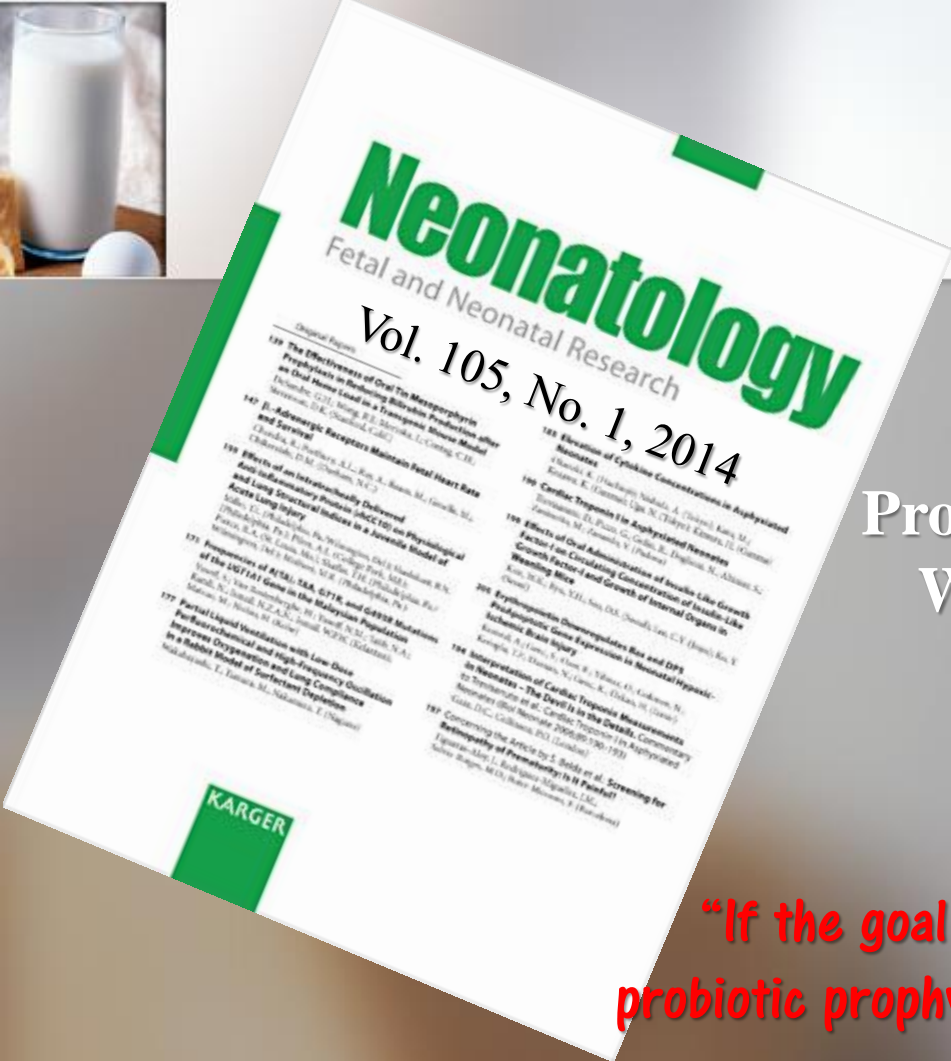
AlFaleh K, Anabrees J, Bassler D, Al-Kharfi T



**THE COCHRANE
COLLABORATION®**

16 trials randomizing 2842 infants

Enteral supplementation of probiotics prevents severe NEC and all cause mortality in preterm infants



Probiotics for Preterm Neonates: What Will It Take to Change Clinical Practice?

“If the goal is to have zero tolerance for NEC, then probiotic prophylaxis must be adopted as soon as possible”

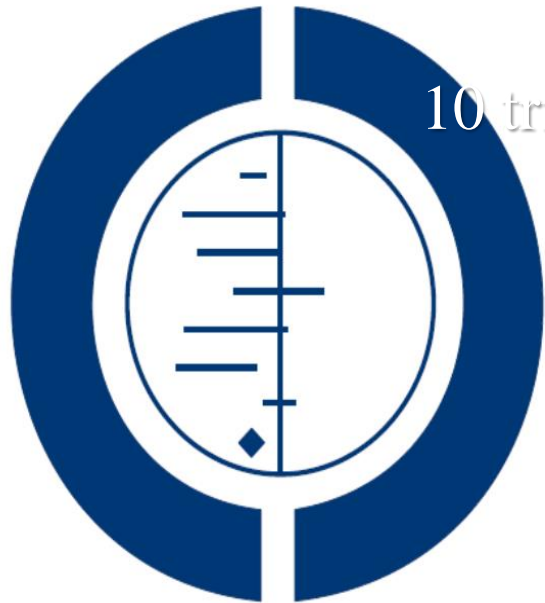
“Currently we are at trial number 25; how many more trials do we need to change clinical practice? At what potential cost?”

Upper respiratory tract infection in children



Probiotics for preventing acute upper respiratory tract infections (Review)

Hao Q, Lu Z, Dong BR, Huang CQ, Wu T



THE COCHRANE
COLLABORATION®

10 trials which involved 3451 participants

The results have some heterogeneity, but probiotics decreased the chance of having URI and reduced the rate of using antibiotics.

Allergy



"I started out with a little scratching on the couch, then I totally lost control."

Probiotics in infants for prevention of allergic disease and food hypersensitivity (Review)

Osborn DA, Sinn JKH



- There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity
- Although there was a reduction in clinical eczema in infants, this effect was not consistent between studies and caution is advised in view of methodological concerns regarding included studies. Further studies are required to determine whether the findings are reproducible

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

There is a likely net benefit from using probiotics in infancy, particularly with regard to prevention of eczema, and suggests the use of probiotics in pregnant women at high risk of giving birth to an allergic child, or who are breastfeeding infants at high risk of allergy



Pouchitis

inflammation of the intestinal mucosa of the small intestine after restorative proctocolectomy

Clinical Study BioMed Research International January 2014

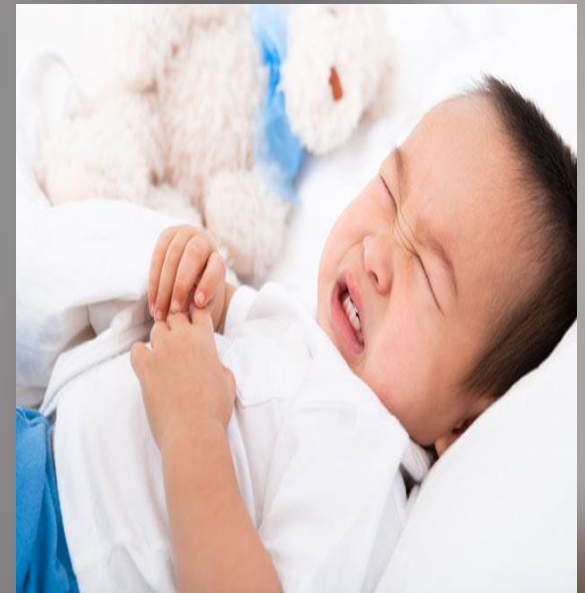
Long-Term Use of Probiotics *Lactobacillus* and *Bifidobacterium* Has a Prophylactic Effect on the Occurrence and Severity of Pouchitis: A Randomized Prospective Study

Patients	Placebo group before treatment	Placebo group after treatment	Probiotic group before treatment	Probiotic group after treatment
Number of patients	22	21	21	19
Number of patients with pouchitis (PDAI \geq 7 pts)	7	8	7	3
Age of patients (years)	41.2	41.5	38.6	38.4
Time from operation (years)	9.2	9.1	8.9	8.9
PDAI	5.97	5.72	6.28*	4.43*
<i>P</i> value		<i>P</i> = 0.115861		<i>P</i> = 0.000342
M2-PK (U/mL)	87.4	90.1	92.3*	45.5*
<i>P</i> value		<i>P</i> = 0.877654		<i>P</i> = 0.000322
Calprotectin (mg/L)	57.5	55.8	65.8*	30.1*
<i>P</i> value		<i>P</i> = 0.107476		<i>P</i> = 0.000236



Treatment Power of Probiotics

- Acute Gastroenteritis
- *C. difficile*
- Atopy
- Infantile colic
- *H. pylori*
- Irritable bowel syndrome
- IBD





JPGN

Journal of Pediatric
Gastroenterology
and Nutrition

MEDICAL POSITION PAPER

Use of Probiotics for Management of Acute Gastroenteritis: A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics

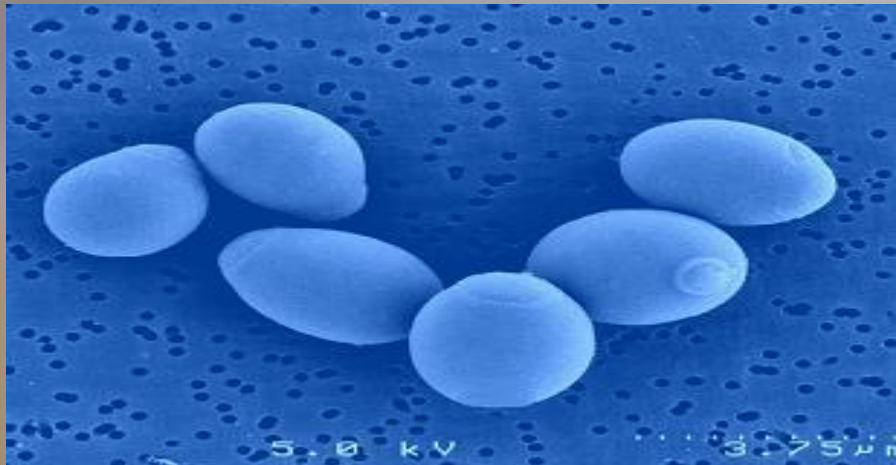
**Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek,
||Raanan Shamir, ¶Yvan Vandenplas, and #Zvi Weizman,
on Behalf of the ESPGHAN Working Group for Probiotics and Prebiotics*



ALTHOUGH OF WEAK EVIDENCE THE WG STRONGLY RECOMMEND:

Recommendation. The use of *S. boulardii* may be considered in the management of children with AGE as an adjunct to rehydration therapy.

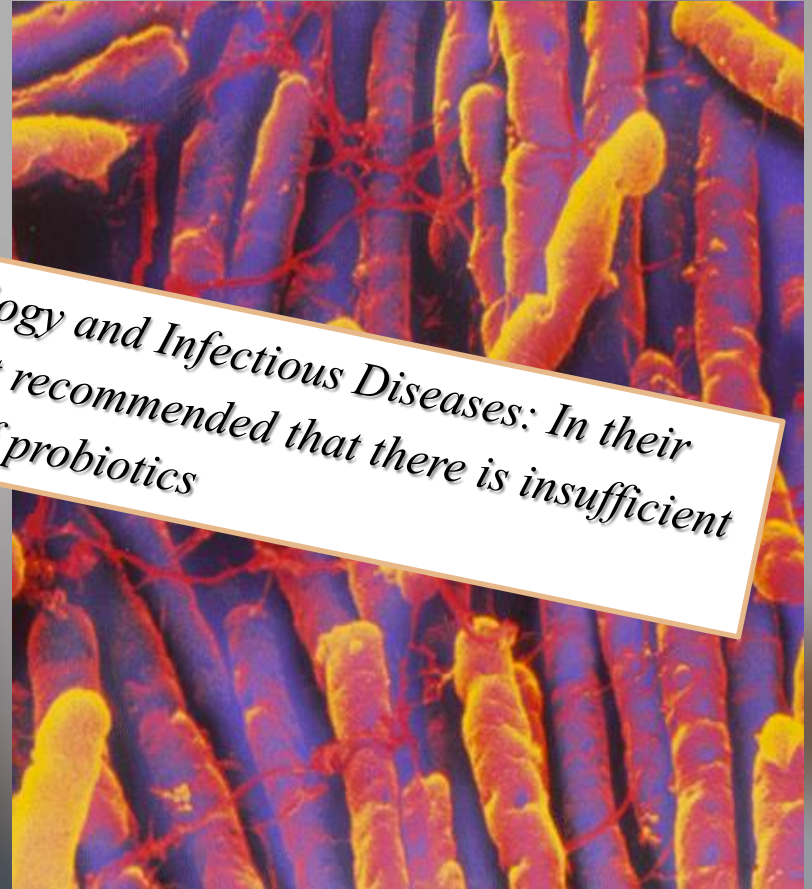
Recommendation. The use of *Lactobacillus* GG may be considered in the management of children with AGE as an adjunct to rehydration therapy.



Probiotics reduced the duration of diarrhea by approximately one day



C. diff



European Society of Clinical Microbiology and Infectious Diseases: In their updated guidance for C. Difficile treatment recommended that there is insufficient data to usage of probiotics



Probiotics for treating eczema (Review)

Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang MLK



The evidence suggests that probiotics are not an effective treatment for eczema, and probiotic treatment carries a small risk of adverse events.



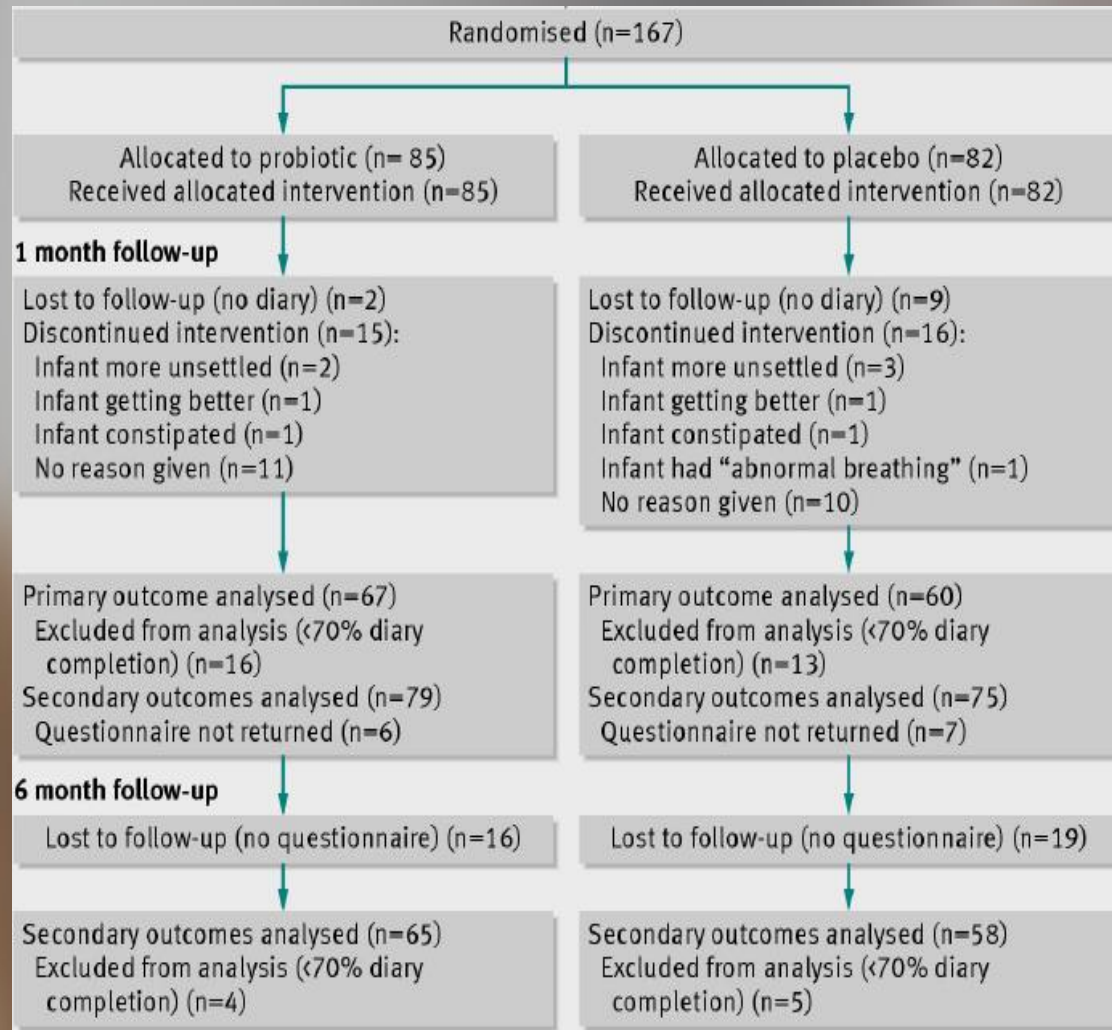
THE CO
COLLABORATION[®]

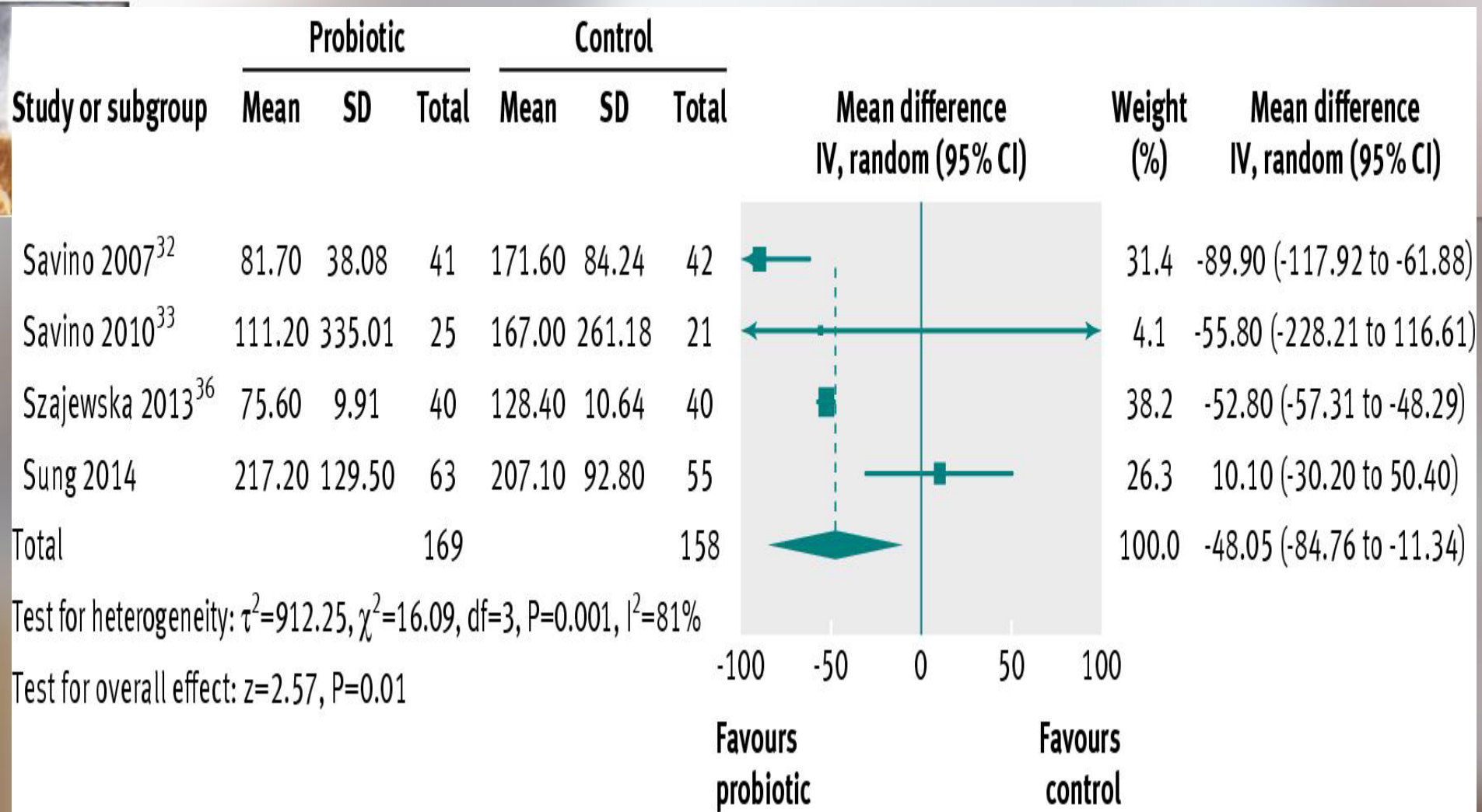
some case reports of infections and
bowel ischemia

Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial



BMJ 2014;348:g2107





Adding this study to previous meta-analysis still in favor of positive effect of probiotics

Helicobacter pylori (H. pylori)



Helicobacter pylori

©iStock.com/iLexx

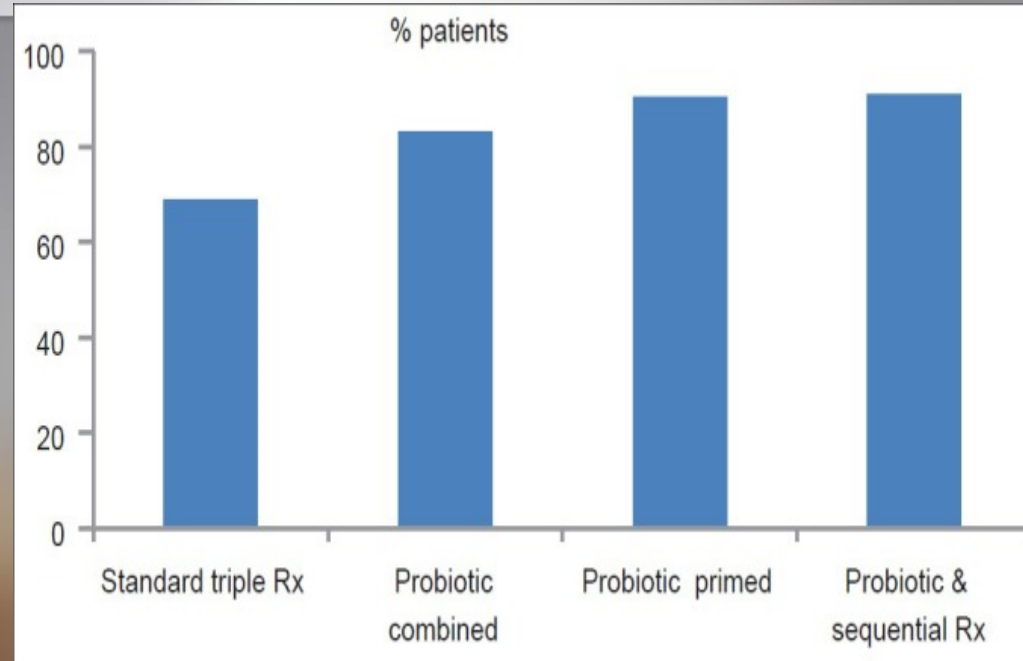
Highly prevalent, serious and chronic infection

H. Pylori has been associated causally with a diverse spectrum of gastrointestinal disorders including:

- chronic gastritis
- peptic ulcer disease
- gastric adenocarcinoma
- gastric mucosa-associated lymphoid tissue lymphoma



Do probiotics improve eradication response to *Helicobacter pylori* on standard triple or sequential therapy?



Adding *B. infantis* as an adjuvant to several therapeutic regimens commonly used for the eradication of *H. pylori* infection significantly improves the cure rates

WJG

World Journal of
Gastroenterology

2014 January 21; 20(3): 673-683

Probiotics for the treatment of *Helicobacter pylori* infection in children

Reduce *H. pylori* therapy associated side effects and indirectly may help to improve the eradication rate; however it seems that the beneficial effects are strain specific

The effect is temporary and lost when administration of the inhibiting factors are interrupted

No convincing evidence on the beneficial effect of supplementation of probiotics to triple therapy for eradicating *H. pylori* infection in children



Irritable Bowel Syndrome

Characterized by abdominal discomfort, bloating, and disturbed defecation in the absence of organic gastrointestinal disease

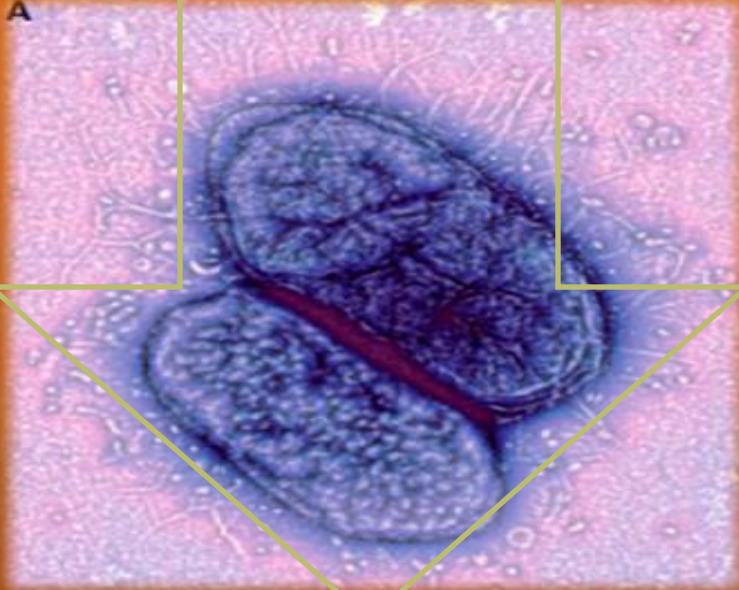
Multifactorial disorder, and its underlying pathophysiology is unclear

Intestinal microbiota is altered in some Irritable bowel syndrome (IBS) patients, and the symptoms of IBS can be alleviated by treatments that target the microbiota



IBS balance

A



Bacteroides

B



Firmicutes

Kelly et al. Immunological Review, 2012



JPGN

Journal of Pediatric
Gastroenterology
and Nutrition

ORIGINAL ARTICLE: GASTROENTEROLOGY

(*JPGN* 2010;51: 24–30)

VSL#3 Improves Symptoms in Children With Irritable Bowel Syndrome: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Crossover Study

**Stefano Guandalini, †Giuseppe Magazzù, †Andrea Chiaro, ‡Valeria La Balestra,
‡Giovanni Di Nardo, §Sarath Gopalan, §A. Sibal, ||Claudio Romano,
¶Roberto Berni Canani, #Paolo Lionetti, and *Mala Setty*

Effective in improving the overall perception of symptoms, the severity and the frequency of the abdominal pain, abdominal bloating, and caregivers' assessment of "life's disruption" due to IBS; a non-significant trend was found for number and characteristics of the stool



L. plantarum

L. casei,

B. infantis,

B. longum

Bifidobacterium breve

Streptococcus thermophilus

Lactobacillus acidophilus

L. bulgaris,





Inflammatory Bowel Disease

Chronic inflammatory diseases of the gastrointestinal tract that occur in genetically susceptible individuals

An altered balance between microbiota and its host (*dysbiosis*) would appear to contribute to the development of Inflammatory Bowel Disease

Vast potential exists for manipulating the gut microbiota for therapeutic effect, such as use of probiotics and fecal microbiota transplantation

Effect of a Probiotic Preparation (VSL#3) on Induction and Maintenance of Remission in Children With Ulcerative Colitis

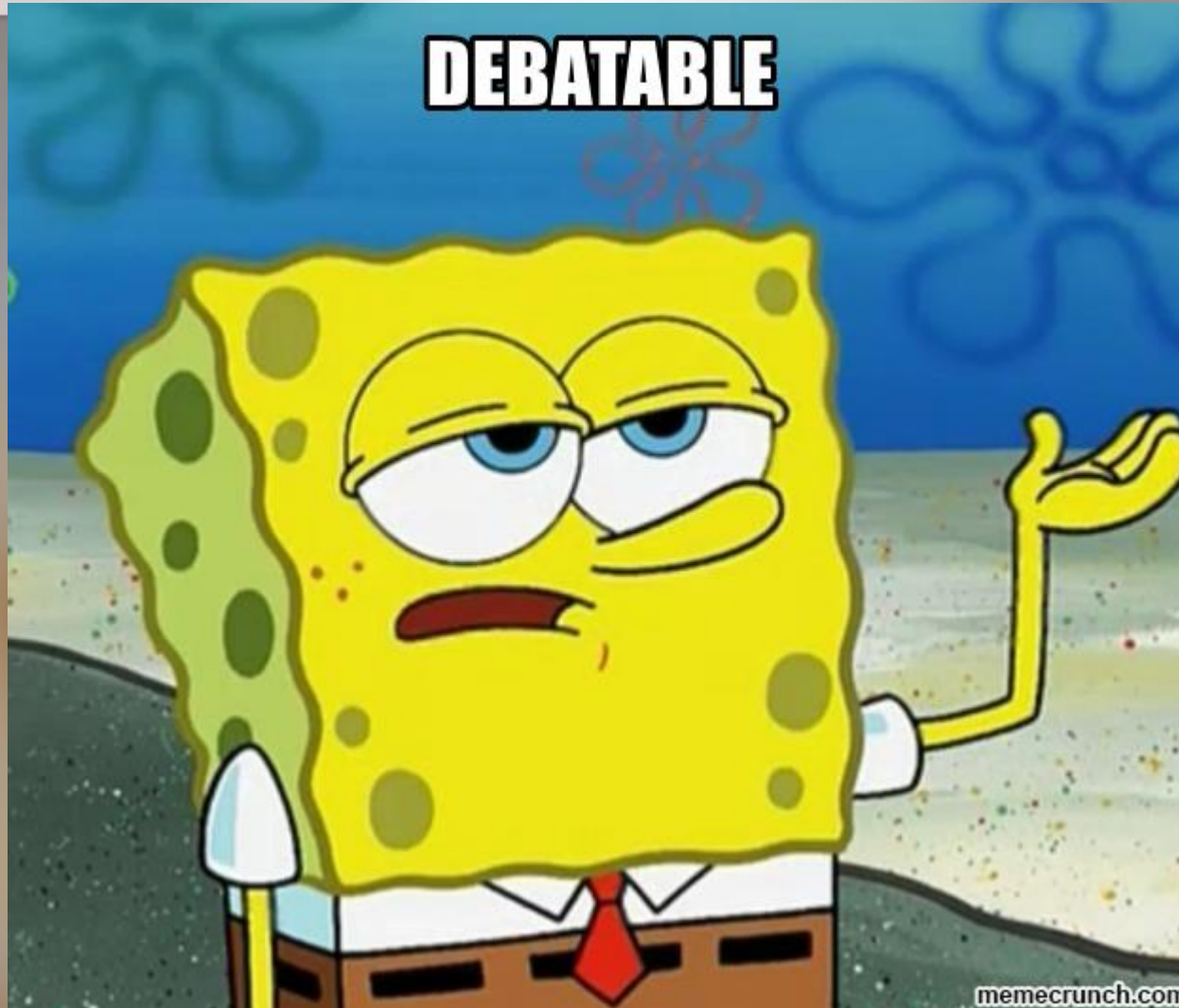
Erasmus Miele, MD, PhD¹, Filomena Pascarella, MD¹, Eleonora Giannetti, MD¹, Lucia Quaglietta, MD¹, Robert N. Baldassano, MD² and Annamaria Staiano, MD¹

In children with ulcerative colitis, administration of VSL#3 resulted in the induction and maintenance of remission of the disease (92.8%), compared with the results of the placebo group

Am J Gastroenterol, 2009



Probiotics in Crohn`s Disease





An alternative approach to probiotics for intestinal flora modulation is the use of ***prebiotics***

Selectively fermented ingredient that results in specific changes , in the composition and or activity of the gut microbiota, thus conferring benefit(s) upon host health



For a food ingredient to be classified as a prebiotic, it must:

- (1) Be resistant to digestion- neither being hydrolysed nor absorbed
- (2) Be fermented by the large intestinal microbiota
- (3) Have a selective effect on the microbiota that has associated health promoting effects



Commonly known prebiotics are:

- HMOS
- **Oligofructose:** found naturally in many foods, such as wheat, onions, bananas, honey, garlic
- **Inulin**
- **Galacto -oligosaccharides**
- **Lactulose:** synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy



Role of prebiotics OGs mixture

Prebiotics OGs pass undigested
to the large colon

B. & L. metabolize prebiotics producing
SCFA in the large intestine

Low pH (acidic) intestine

Softer stool

Increase growth of
Beneficial bacteria

Support the function of the immune system

SCFA promotes a thicker
mucous layer

Reduce risk of infection
And diarrhea



Prebiotics Power

- Prevention of Allergy
- Prevention of Antibiotic associated diarrhea
- Infant formula supplementation

Prebiotics in infants for prevention of allergy (Review)

Osborn DA, Sinn JKH



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*There is some evidence that a prebiotic supplement added to infant feeds may prevent eczema.
Further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula fed infants*

Cochrane Library, 2013



JPGN

Journal of Pediatric
Gastroenterology
and Nutrition

JPGN 2012; 54:828-829

Inulin and Fructo-oligosaccharides for
the Prevention of Antibiotic-associated
Diarrhea in Children: Report by the
ESPGHAN Working Group on
Probiotics and Prebiotics

The administration of the 2 prebiotics (inulin and FOS) was not effective for preventing diarrhea and AAD. The overall frequency of diarrhea was low, and the study was **underpowered**



JPGN

Journal of Pediatric
Gastroenterology
and Nutrition

(JPGN 2011;52: 238–250)

POSITION PAPER

Supplementation of Infant Formula With Probiotics and/or Prebiotics: A Systematic Review and Comment by the ESPGHAN Committee on Nutrition

The administration of currently evaluated probiotic and/ or prebiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects



Infant formula supplementation with pre- & pro-



NUTRITION
JOURNAL

Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review

Nutrition Journal, 2012

Probiotics, prebiotics infant formula use in preterm or low birth weight infants: a systematic review

Nutrition Journal, 2012



Postbiotics(Active ferments)

Products made by or involving beneficial microorganisms, such as products of fermentation, but containing no live bacteria

Thought to exhibit immunomodulatory properties

Using postbiotics to modify gut flora is gaining popularity



it's not workingggggggg



1. Using varying compositions, different doses for variable diseases
2. Variable host response (genetic & personal microbiota fingerprint)



Probiotics

**THE
OTHER
SIDE**



Potential Mechanisms of Harm

1. Infective dissemination
2. Transfer of antibiotic resistance
3. Transfer of genetic material



U MEAN THERE'RE

NO

**REAL FRIENDS OR
ENEMIES?**

memegenerator.net





Infective dissemination

Proven in severely ill patients

Multiple case reports of bacteremia with:

- *S. Boulardii* & *cerevisiae*
- *Lactobacillus*
- *Bacillus cereus*
- *Bifidobacterium*

Transfer of antibiotic resistance



Gut Pathogens



Prevalence of antibiotic resistance in lactic acid bacteria isolated from the faeces of broiler chicken in Malaysia



Transfer of genetic material

***In Silico* Assigned Resistance Genes Confer *Bifidobacterium* with Partial Resistance to Aminoglycosides but Not to B-Lactams**



Conclusion

- FDA grants GRAS status to Bidifobacteria & Lactobacillus
- Current evidence does not indicate increased risk in not severely sick
- Probiotics could be very useful in sick patients (prevention of CD infection) but special caution is required

Back to our Granmma...



ieGEEK



Synbiotics

A further possibility in microflora management is the use of Synbiotics, the combination of probiotics and prebiotics

A synbiotic has been defined as 'a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GI tract, by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare'

Gibson & Roberfroid, 1995

A synbiotic product exerts both a prebiotic and probiotic effect



Thank you

*Wish you a healthy and happy
microbiota*