



Il ruolo del Lactobacillus GG in pediatria: tra vecchie certezze e nuovi orizzonti:

Alfredo Guarino has participated as a clinical investigator, and /or advisory board member, and/or consultant, and/or speaker from Biocodex, Dicofarm, the Menarini Group, Malesci, Angelini, Ferring, His Institution received research grants from Mead Johnson USA, Dicofarm Italy, Ippsen France



Alfredo Guarino

**Dipartimento di Scienze Mediche Translazionali
"Federico II", Napoli**

Outline

- Il successo dei probiotici in pediatria
- Tra mercato ed EBM
- Probiotici e Linee guida
- LGG: certezze e prospettive
- Barriere contro l'uso dei probiotici
- Verso una stewardship dell'uso dei probiotici



ROME - SEPTEMBER 10/12, 2017
UNIVERSITÀ URBANIANA

9TH

PROBIOTICS, PREBIOTICS
& NEW FOODS, NUTRACEUTICALS AND BOTANICALS
for NUTRITION & HUMAN and MICROBIOTA HEALTH

A guided use of probiotics in children

MONDAY, SEPTEMBER 11

AULA ELIE METCHNIKOFF

PEDIATRIC DAY

09.00-09.30 a.m.

LECTURE

Stewardship in clinical practice... lessons from the antibiotic world
L. Balli (Italy)

09.30-11.00 a.m.

PROBIOTICS STEWARDSHIP IN PEDIATRICS

Chair: Y. Yamashiro (Japan)

Evaluation tools for probiotics in clinical practice
H. Szajewska (Poland)

Quality of probiotics
S. Kolacek (Croatia)

Implementation: sciences applied to probiotics
A. Guackuo (Italy)

11.00-11.30 a.m.

Break

11.30-01.00 p.m.

PROBIOTICS IN CLINICAL PRACTICE: CONSOLIDATED INDICATIONS

Chair: H. Szajewska (Poland)

Acute gastroenteritis
A. La Vecchia (Italy)

Antibiotic associated diarrhea
V. Vandecasteele (Belgium)

Neonocomial infections
L. Hajsak (Croatia)

Infantile colic
E. Indrio (Italy)

01.00-02.00 p.m.

Lunch

02.00-03.30 p.m.

PROBIOTICS IN PAEDIATRIC GASTROENTEROLOGY: EMERGING INDICATIONS

Chair: S. Kolacek (Croatia)

IBDs
E. Scarpato (Italy)

Functional intestinal disorders
M. M. Tabbers (The Netherlands)

NEC
J. B. van Goudoever (The Netherlands)

NAFLD/NASH
V. Nobili (Italy)

03.30-04.00 p.m.

Break

04.00-05.30 p.m.

PROBIOTICS FOR PAEDIATRIC EXTRAINTESTINAL DISORDERS: WHERE WE ARE NOW

Chair: J. A. Vandemoortel (USA)

Respiratory tract infections
E. Bruzzese (Italy)

Allergy
R. Berni Canani (Italy)

Obesity
E. Isolauri (Finland)

05.30-05.00 p.m.

Conclusions

Stewardship

Antimicrobial stewardship

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.

Gut microbiota and diseases: the concept of “signature”

Table 2. Major changes in the composition of gut microbiome in the intestinal and extraintestinal childhood diseases

Disease	Changes in gut microflora composition
Celiac disease	Lack of bacteria of the phylum Bacteroidetes along with an abundance of Firmicutes
Inflammatory bowel disease	Low concentrations of <i>Faecalibacterium prausnitzii</i> and <i>Bifidobacteria</i> Increased levels of <i>Escherichia coli</i> Reduced diversity of gut microbiota
Inflammatory bowel syndrome	Significantly greater percentage of the class Gammaproteobacteria Presence of unusual Ruminococcus-like microbes
Necrotizing enterocolitis	Predominance of Gammaproteobacteria Reduced diversity of gut microbiota
Atopy	Lower counts of Lactobacilli, Bifidobacteria, and Bacteroides Increased counts of <i>Clostridium difficile</i> Reduced diversity of gut microbiota
Obesity	Increased Firmicutes at expenses of the Bacteroidetes group
Cystic fibrosis	Lower species richness Lower counts of lactic acid bacteria, clostridia, <i>Bifidobacterium</i> spp., <i>Veillonella</i> spp., and <i>Bacteroides-Prevotella</i> spp.

DETERMINANTI DEL SUCCESSO DEI PROBIOTICI IN PEDIATRIA

- **Trend culturale verso la naturalità**
- **Assenza di effetti collaterali**
- **Palatabilità**
- **L'effetto clinico in alcune condizioni**
- **Mancanza di alternative terapeutiche valide**
- **Costi ragionevoli**

Probiotici: un successo di mercato

Numero totale di pezzi venduti = 33.000.000 in 12 mesi

Azienda	Prodotto	Ceppo	Numero di pezzi venduti	Quota di mercato
Sanofi	Enterogermina	Bacillus clausii	7.600.000	23%
Sofar	Enterolactis	L. paracasei	3.400.000	10%
	Bifidolactis	Bifidobacterium-BB12	19.000	
Montefarmaco OTC	Lactoflorene	mix	2.500.000	7,5%
Zeta	Prolife	mix	1.600.000	5%
Zambon	Codex	S.boulardii	1.500.000	4,5%
Bromatech	Multibrand (enterelle, bifiselle, femelle ecc..)	L bulgaricus, altri	1.400.000	4,3%
Italchimici	Reuflor	Lactobacillus reuteri	1.120.000	3,4%
Unifarco	LFP	mix	930.000	2,8%
Dicofarm	Dicoflor	L.GG	840.000	2,5%
SigmaTau	Yovis	mix	740.000	2,4%
AgPharma	Dicoflor	L.GG	620.000	1,9%
Ferring	VSL3	mix	560.000	1,7%
Noos	Reuterin	<i>Lactobacillus reuteri</i> DSM 17938 e <i>Lactobacillus reuteri</i> ATCC PTA 5289	470.000	1,4%

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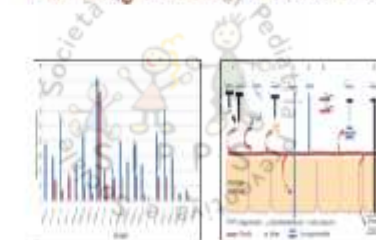
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- 1. [Reclamation of Chinese herb residues using probiotics and evaluation of their beneficial effect on pathogen infection.](#)
Meng F, Yang S, Wang X, Chen T, Wang X, Tang X, Zhang R, Shen L.
J Infect: Public Health. 2017 Feb 8; pii: S1876-0341(17)30025-4. doi: 10.1016/j.jiph.2016.11.013. [Epub ahead of print]
PMID: 28189536
- 2. [\[Irritable bowel syndrome with constipation and functional constipation in adults: Treatment \(Part 2 of 2\)\].](#)
Mearin F, Ciriza C, Minguez M, Rey E, Mascort JJ, Peña E, Cañones P, Júdez J, en nombre de la SEPD, la semFYC, la SEMERGEN y la SEMG.
Semergen. 2017 Feb 8; pii: S1138-3593(17)30039-6. doi: 10.1016/j.semerg.2017.01.001. [Epub ahead of print]
Spanish
PMID: 28189436
- 3. [Antivirulence Properties of Probiotics in Combating Microbial Pathogenesis.](#)
Surenran Nair M, Amalaradjou MA, Venkatanarayanan K.

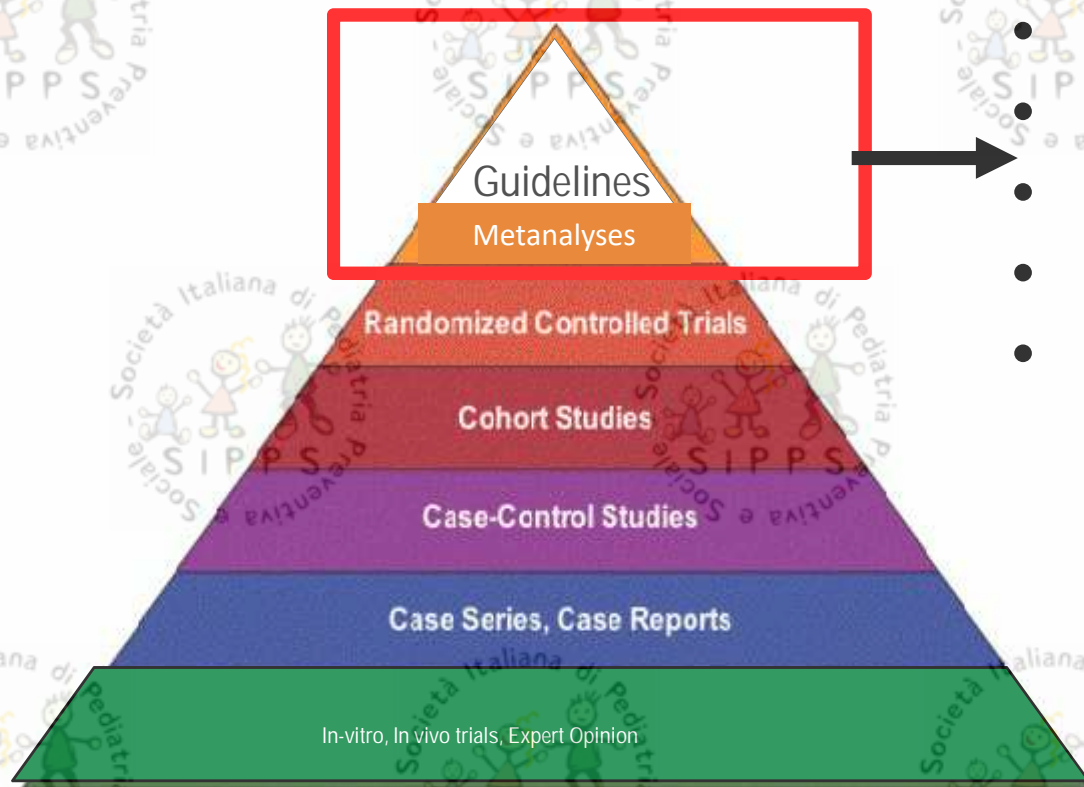
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- probiotics review
- probiotics preiotics
- probiotics antibiotic
- probiotics prevention
- probiotics diarrhea

PMC Images search for probiotics



La piramide delle evidenze



- Gastroenterite acuta
- Diarrea nosocomiale
- Diarrea associata ad antibiotici
- Enterocolite necrotizzante
- Infezioni respiratorie

Gastroenterite acuta

J Pediatr Gastroenterol Nutr 1997 Nov;25(5):516-9.

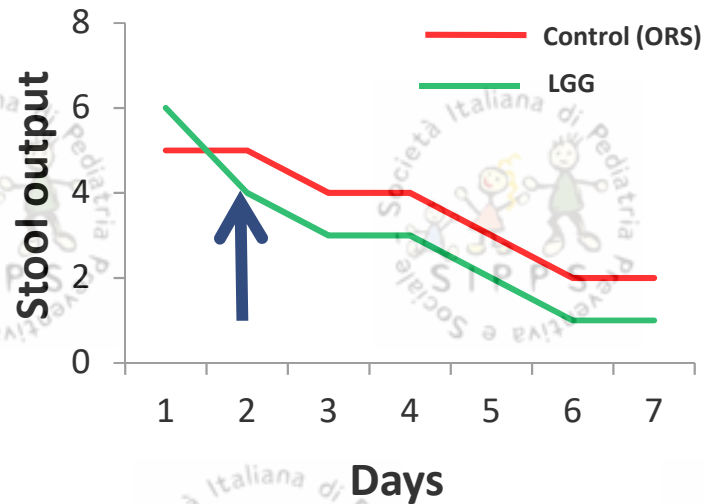
Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea.

Guarino A, Canani RB, Spagnuolo M, Albaro E, Di Benedetto L.

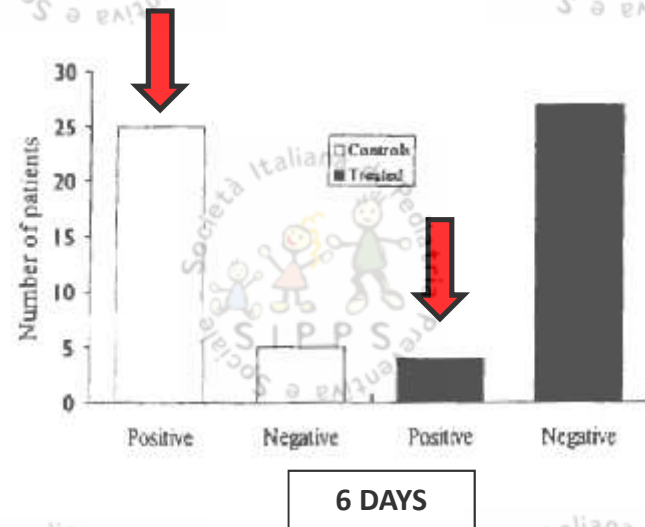
> 200 citations

Clinical effect

Daily stool outputs from the first day of probiotic administration



Microbiological effect



Gastroenterite acuta

Recommended strains

PROBIOTIC STRAIN	STUDIES IN SUPPORT	QUALITY OF EVIDENCE	GRADE OF RECOMMENDATION	RECOMMENDATION
LGG	15 RCTs	Low	Strong	May be considered + ORS
S. boulardii	13 RCTs	Low	Strong	May be considered + ORS
L. reuteri (DSM 17938)	1 RCT	Very low	Weak	May be considered + ORS
Heat-killed L. acidophilus LB	4 RCTs	Very low	Weak	May be considered + ORS

Other strains

Gastroenterite acuta

PROBIOTIC STRAIN	STUDIES IN SUPPORT	QUALITY OF EVIDENCE	GRADE OF RECOMMENDATION	RECOMMENDATION
L. rhamnosus (573/L1-2-3)	1 RCT	Moderate	Weak	Insufficient data
L. acidophilus	1 RCT	Very low	Weak	Insufficient data
L. paracasei ST11	1 RCT	Moderate	Weak	Insufficient data
L. helveticus 0052 L. rhamnosus 0011	None	-	-	Insufficient data
L. rhamnosus L. acidophilus B. longum S. boulardii	1 RCT	Moderate	Weak	Insufficient data
B. mesentericus C. butyricum E. faecalis	1 RCT	Very low	Weak	Insufficient data
L. delbrueckii L. acidophilus Str. termophilus B. bifidum	1 RCT	Very low	Weak	Insufficient data
B. lactis Bb12	None	-	-	Insufficient data
B. lactis B12 Str. termophilus	1 RCT	Very low	Weak	Insufficient data
B. clausii	1 RCT	Very low	Weak	Insufficient data

Gastroenterite acuta

Journal of Parent Science, Nutrition, and Gastroenterology and Nutrition
46:S1-S11 (2008) European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe

Expert Working Group: *Alfredo Guarino (Coordinator), *Fabio Albano, †Shai Ashkenazi, ‡Dominique Gendrel, §J. Hans Hoekstra, ¶Raanan Shamir, and ||Hania Szajewska

Probiotics

Probiotics may be an effective adjunct to the management of diarrhea. However, because there is no evidence of efficacy for many preparations, we suggest the use of probiotic strains with *proven efficacy* and in appropriate doses for the management of children with AGE as an adjunct to rehydration therapy (II, B).

The following probiotics showed benefit in meta-analyses of RCTs: *Lactobacillus GG* (I, A) and *Saccharomyces boulardii* (II, B).

Evidence of lack of risk of antibiotic resistance transfer is required for probiotics proposed for clinical use (Vb, D).

I,A (Muir-Gray)

Gastroenterite acuta

TREATMENT

European Society for Pediatric Gastroenterology,
Hepatology, and Nutrition/European Society for Pediatric
Infectious Diseases Evidence-Based Guidelines for the
Management of Acute Gastroenteritis in Children in
Europe: **Update 2014**

¹Alfredo Guarino (Coordinator), ¹Shai Ashkenazi, ¹Dominique Gendrel,
²Andrew Lo Vecchio, ²Raouf Shamir, and ³Hania Szajewska



Active treatment with
probiotics, in adjunct to
ORS, is effective in reducing
the **duration and intensity**
of symptoms of
gastroenteritis. *Lactobacillus*
GG and *Saccharomyces*
boulardii **have the**
strongest proof of efficacy.

**Strong
recommendation**

Comparison of Recommendations in Clinical Practice Guidelines for Acute Gastroenteritis in Children

*Andrea Lo Vecchio,¹ Jorge Amil Dias,⁴ James A. Berkley,⁹ Chris Boey,¹¹ Mitchell B. Cohen,¹ Sylvia Cruchet,¹ Ilaria Liguoro,⁴ Eduardo Salazar-Lindo,¹ Bhupinder Sandhu,¹¹ Philip Sherman,¹¹ Toshiaki Shimizu,¹¹ and Alfredo Guarino

JPGN 2016
Journal of Pediatric Gastroenterology and Nutrition

Table 1. Guidelines reporting the recommendations of probiotics in the treatment of acute infectious diarrhea

Guidelines	Country	Conclusion	Evidence in support	Strain	Dose/time
ESPGHAN 2014 [7]	France	Strongly recommended	++	LGG	10 ¹¹ CFU/day, (typical) ~7 days
		Weakly recommended	+	S. boulardii L. reuteri Lactobacillus P	250-750 mg/day (typically 5-7 days)
Salazar-Lindo 2014 [20]	Peru	Strongly recommended	++	LGG S. boulardii L. reuteri	-
Ministry of Health-Kenya 2013 [23]	Kenya	Not recommended	+	-	-
Wittenberg 2012 [22]	South Africa	Can be considered in specific situations	+	-	-
Cincinnati Children's Hospital Medical Center 2011 [13]	USA	Recommended	++	LGG	10 ¹¹ CFU/day, (typical) ~7 days
College of Paediatrics, Academy of Medicine of Malaysia - Malaysian Paediatric Association 2011 [19]	Malaysia	Can be considered	+	LGG S. boulardii L. acidophilus	-
NICE 2009 [24]	UK	Not recommended	+	-	-
Harris 2008 [21]	Australia	Can be considered	+	LGG	-
DeWazir, IAP 2005 [25]	India	Insufficient evidence to recommend probiotics	+	-	-
CDC 2009 [26]	USA	Not recommended	+	-	-

Note: WHO 2005 guidelines were not included in this table because probiotics were not discussed

PROBIOTICS FOR THE PREVENTION OF NOSOCOMIAL DIARRHEA IN CHILDREN

Iva Hojsak,²Hania Szajewska^{1*},Roberto Berni Canani^{3,4}, Alfredo Guarino,³ Flavia Indrio⁵, Sanja Kolacek², Rok Orel⁶,Raanan Shamir⁷,Yvan Vandenplas⁸, Johannes B. van Goudoever⁹, Zvi Weizman¹⁰

on behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

*Contributed equally

Probiotic strains with recommendation

Lactobacillus rhamnosus GG (LGG)

RECOMMENDATION. If the use of probiotics for preventing nosocomial diarrhea in children is considered, the WG recommends using *L. rhamnosus* GG.

QUALITY OF EVIDENCE: Moderate

STRENGTH OF RECOMMENDATION: Strong

No new studies were identified after 2011 systematic review and meta-analysis (12) which included 3 RCTs (2, 19, 21). LGG dose used in the included studies varied from 10⁹CFU/day (2) through 2x10¹⁰ CFU/day (19) to 12x10⁹ CFU/day (21).

Commento [P1]: A question.. do we limit to diarrhea? Or do we go broader and look for infections? There are studies that looked also at respiratory infections..

Commento [P16]: Same question as in beginning.. only diarrhea? Or also infections?

Commento [r17]: I will accept the majority vote but prefer conditional recommendation for "considering treatment with moderate quality of evidence)

Yvan: I agree with raanan

Commento [SK18]: Agree with the current version because the statement is "if probiotics are considered.." It is not suggesting that every hospitalized child should receive probiotic, but if it does then LGG is recommended. However, accept the majority vote

PROBIOTICS FOR THE PREVENTION OF NOSOCOMIAL DIARRHEA IN CHILDREN

Diarrea nosocomiale

Iva Hojsak^{1*}, Hanna Szajewska^{2*}, Roberto Berni Canani^{3,4}, Alfredo Guarino⁵, Flavia Indrio⁵, Sanja Kolacek², Rok Oreš⁶, Raanan Shamir⁷, Yvan Vandenplas⁸, Johannes B. van Goudoever⁹, Zvi Weizman¹⁰

on behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

Probiotic strains with recommendation

***Lactobacillus rhamnosus* GG (LGG)**

RECOMMENDATION. If probiotics for preventing nosocomial diarrhea in children are considered, the WG recommends using *L. rhamnosus* GG (at least 10⁹ CFU/day, for the duration of hospital stay).

QUALITY OF EVIDENCE: Moderate

STRENGTH OF RECOMMENDATION: Strong

Randomised clinical trial: a Lactobacillus GG and micronutrient-containing mixture is effective in reducing nosocomial infections in children, vs. placebo

E. Bruzzese*, M. C. Fedele*, D. Bruzzese†, S. Viscovo*, A. Giannattasio*, C. Mandato‡, P. Siani‡ & A. Guarino*

Aliment Pharmacol Ther, 2016

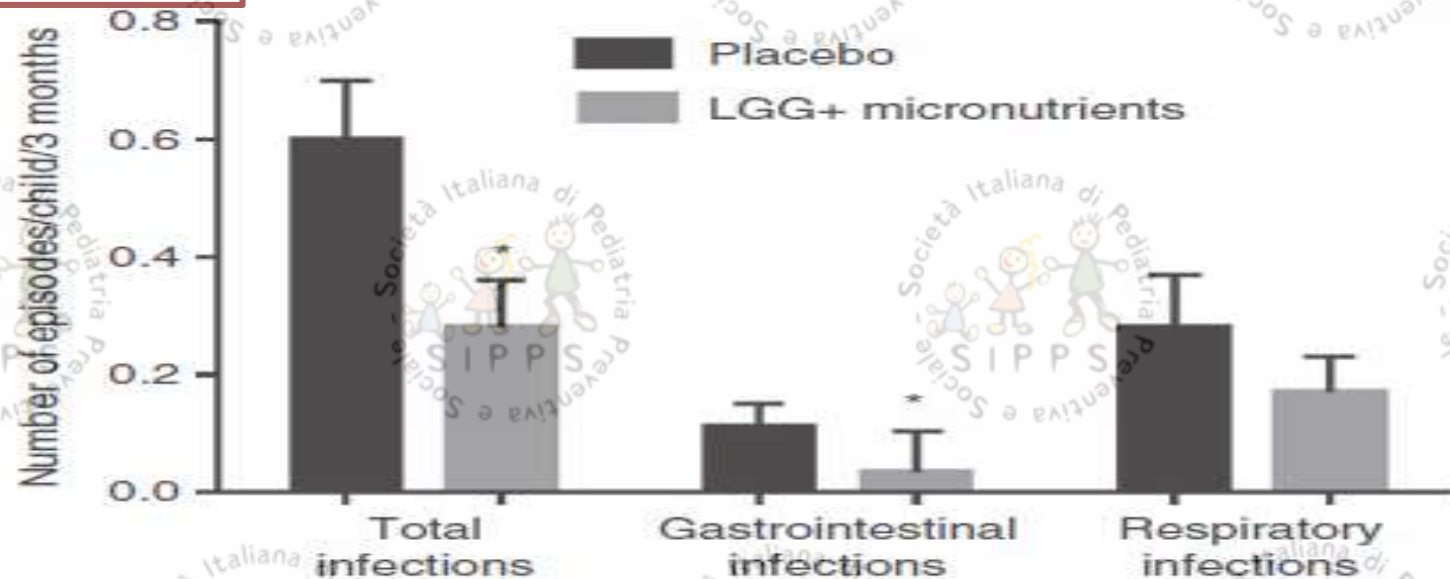


Figure 1 | During a 3-month follow-up period the incidence of infections in children supplemented with LGG and micronutrients was significantly reduced compared to placebo group ($P = 0.02$). The main effect was observed in the incidence of gastrointestinal infections ($P = 0.016$) whereas no difference was observed in the incidence of respiratory infections. * $P < 0.05$.

Variable	LGG/Vitamin DCB Group (n= 45)	Placebo Group (n= 45)	O.R. [95% C.I.]	p	NNT [95% C.I.]
Nosocomial infections	15 (33.3)	4 (8.8)	0.2 [0.06 ; 0.65]	0,008	5 [3 ; 17]
Nosocomial gastrointestinal tract infections	11 (24.4)	2 (4.4)	0.14 [0.03 ; 0.69]	0,016	5 [3 ; 17]
Nosocomial respiratory tract infections	4 (8.8)	2 (4.4)	0.48 [0.08 ; 2.75]	0,407	-

1.7 vs 1.2 ± 4.9; p = 0.003). During the follow-up period, a total of 11/45 (24.4%) children in the treatment group had at least one episode of infection compared to 22/45 (48.9%) in the placebo group (p=0.016). **Conclusions.** A mixture containing LGG and micronutrients may reduce the incidence of nosocomial infections. This data support the hypothesis that this may represent a valid strategy to prevent nosocomial infections.

Bruzzese E. et al, Aliment Pharmacol Ther, 2016

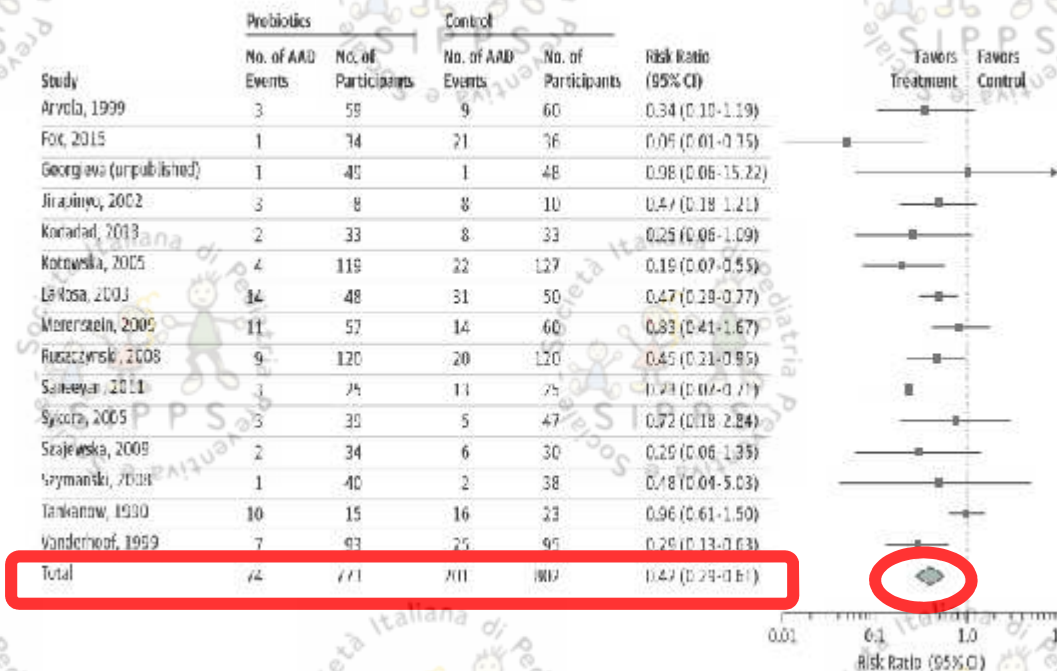
Diarrea associata ad antibiotici

JAMA Clinical Evidence Synopsis

Probiotics and the Prevention of Antibiotic-Associated Diarrhea in Infants and Children

Bradley C. Johnston, PhD, Joshua Z. Goldenberg, ND, Patricia C. Parkin, MD

Figure. Probiotics for Antibiotic-Associated Diarrhea (AAD) Prevention in 15 Placebo-Controlled Trials



Evidence Profile

No. of randomized clinical trials: 23
 Study years: Conducted, 1989-2012; published, 1990-2015
 Last search date: November 2, 2015
 No. of patients: 3938
 Boys: 53% Girls: 47%
 Race/ethnicity: Not reported
 Age, mean (range): 5.6 years (1 month to 18 years)
 Clinical settings: Inpatient, outpatient, and mixed (inpatient and outpatient)
 Countries: Australia, Brazil, Bulgaria, China, Czech Republic, England, Finland, France, Iran, Italy, Philippines, Poland, Thailand, Turkey, United States

Comparison: Children receiving antibiotics were randomized to single-strain or multistrain probiotics (typically for a predefined period [eg, 5-12 days]) vs control (placebo, no treatment, active treatment) and followed up for 1 to 12 weeks. Probiotic genus administered included *Bacillus*, *Bifidobacterium*, *Clostridium*, *Lactobacilli*, *Lactococcus*, *Leuconostoc*, *Saccharomyces*, *Streptococcus*.

Primary outcome measures: Incidence of diarrhea and number and type of adverse events.

Secondary outcome measures: Mean duration of diarrhea and mean stool frequency.

Diarrea associata ad antibiotici

Probiotics for the prevention of pediatric antibiotic-associated diarrhea (Review)

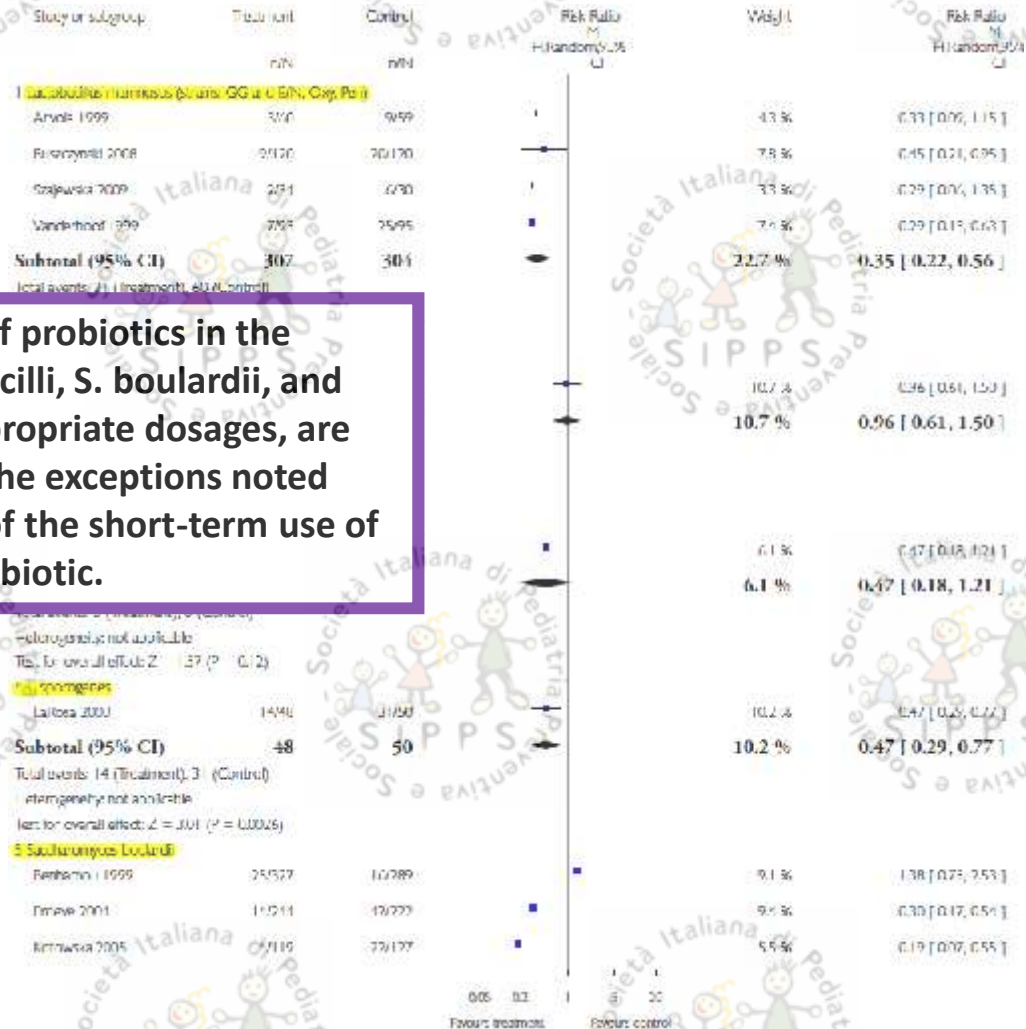
Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC

LGG



Clearly, current evidence favors the use of probiotics in the prevention of symptoms of AAD. Lactobacilli, *S. boulardii*, and selected multistrain combinations, in appropriate dosages, are clinically useful. The safety profile, with the exceptions noted earlier, is acceptable particularly in view of the short-term use of an antibiotic when accompanied by a probiotic.

Saccharomyces boulardii





CLINICAL GUIDELINE



Diarrea associata ad antibiotici

Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

Ilana Szajewska, Roberto Berni Canani, Alfredo Guarino, Iva Hojsak, Flavia Indrio, Sanja Kolacek, Rok Orel, Raanan Shamir, Yvan Vandeplass, Johannes B. van Goudoever, and Zvi Weizman, on Behalf of the ESPGHAN Working Group for Probiotic Treatments
JPGN • Volume 62, Number 3, March 2016

Recommendations:

L rhamnosus GG (LGG)

RECOMMENDATION. If the use of probiotics for preventing AAD in children is considered, the WG recommends using *L rhamnosus* GG.
QUALITY OF EVIDENCE: Moderate.
STRENGTH OF RECOMMENDATION: Strong

NNT
8

Saccharomyces boulardii

RECOMMENDATION. If the use of probiotics for preventing AAD in children is considered, the WG recommends using *S boulardii* for preventing AAD in children.
QUALITY OF EVIDENCE: Moderate.
STRENGTH OF RECOMMENDATION: Strong.

NNT
9

La somministrazione precoce di antibiotici altera il microbiota e condiziona il futuro

[JAMA Pediatr.](#) 2016 Aug 1;170(8):750-7. doi:
10.1001/jamapediatrics.2016.0585.

[Pediatrics.](#) 2015 Apr;135(4):617-26. doi:

La somministrazione di LGG ripristina l'eubiosi e riduce in rischi della terapia antibiotica

[PLoS One.](#) 2016 Apr 25;11(4):e0154012. doi: 10.1371/journal.pone.0154012. eCollection 2016.

Lactobacillus rhamnosus GG Intake Modifies Preschool Children's Intestinal Microbiota, Alleviates Penicillin-Associated Changes, and Reduces Antibiotic Use

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Infezioni respiratorie

Systematic Review and Meta-Analysis

Medicine

OPEN

Probiotics for prevention and treatment of respiratory tract infections in children

A systematic review and meta-analysis of randomized controlled trials

Yizhong Wang, PhD¹, Xiaolu Li, MD², Ting Ge, MD², Yongmei Xie, MD², Yang Liao, MD², Yun Qiu, MD², Yucui Zhang, MD, PhD², Wenzhe Ho, MD, MPH², Guangjun Yu, PhD², Ting Zhang, MD, PhD²

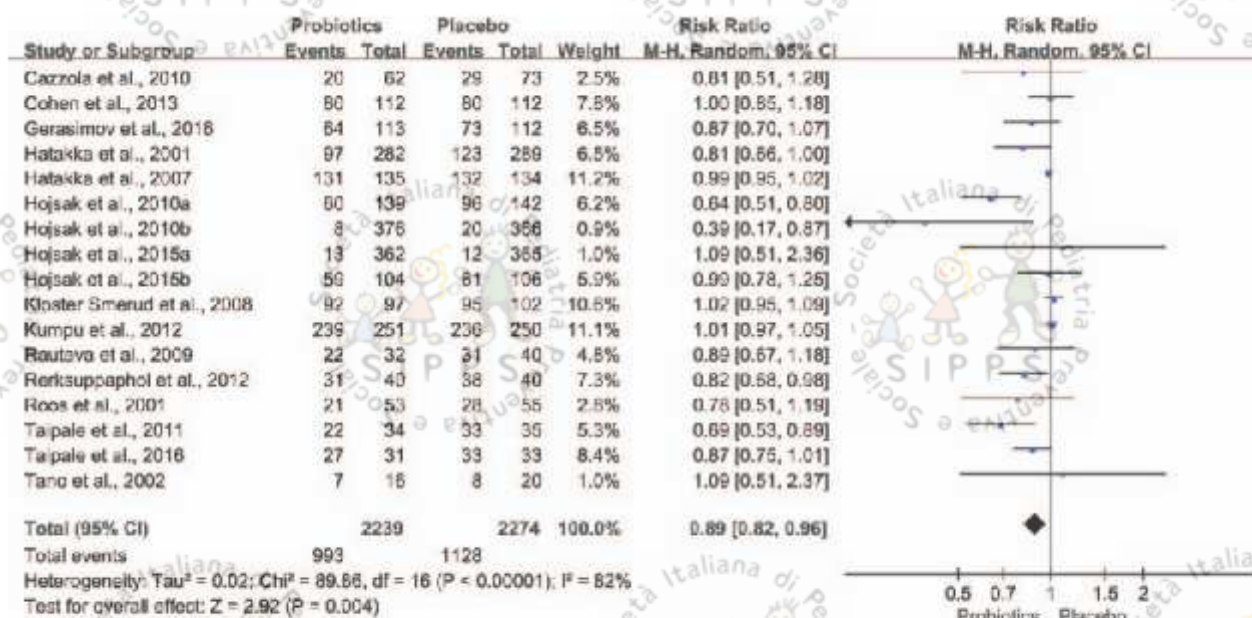


Figure 2. Effect of probiotics on the number of subjects who had at least 1 RTI episode. The "total" is the number of subjects included in the analysis in probiotics and placebo group. CI = confidence interval, M-H = Mantel-Haenszel, RTI = respiratory tract infection.

Infezioni respiratorie



Hao Q et al
2015

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who experienced URTI episodes; at least 1 event	7	1927	Odds Ratio (IV, Random, 95% CI)	0.53 [0.37, 0.76]
1.1 Adults	1	318	Odds Ratio (IV, Random, 95% CI)	0.68 [0.44, 1.06]
1.2 Children	5	1457	Odds Ratio (IV, Random, 95% CI)	0.43 [0.29, 0.63]
1.3 Elderly	1	152	Odds Ratio (IV, Random, 95% CI)	0.95 [0.50, 1.81]
2 The number of participants who experienced URTI episodes: at least 3 events	3	650	Odds Ratio (IV, Random, 95% CI)	0.53 [0.36, 0.80]
2.1 Adults	1	318	Odds Ratio (IV, Random, 95% CI)	0.47 [0.21, 1.03]
2.2 Children	2	332	Odds Ratio (IV, Random, 95% CI)	0.56 [0.35, 0.89]
3 The rate ratio of episodes of acute URTI	5	1608	Rate Ratio (Random, 95% CI)	0.83 [0.66, 1.05]
3.1 Adults	1	318	Rate Ratio (Random, 95% CI)	0.71 [0.56, 0.90]
3.2 Children	3	1136	Rate Ratio (Random, 95% CI)	0.77 [0.57, 1.05]
3.3 Elderly	1	154	Rate Ratio (Random, 95% CI)	1.37 [0.94, 1.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The number of participants who used antibiotics	4	1184	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.45, 0.94]

Infezioni respiratorie

Probiotics for preventing acute upper respiratory tract infections (Review)

ABSTRACT

Main results

We included 13 RCTs, although we could only extract data to meta-analyse 12 trials, which involved 3720 participants including children, adults (aged around 40 years) and older people. We found that probiotics were better than placebo when measuring the number of participants experiencing episodes of acute URTI (at least one episode: odds ratio (OR) 0.53; 95% confidence interval (CI) 0.37 to 0.76, P value < 0.001, low quality evidence; at least three episodes: OR 0.53; 95% CI 0.36 to 0.80, P value = 0.002, low quality evidence); the mean duration of an episode of acute URTI (mean difference (MD) -1.89; 95% CI -2.03 to -1.75, P value < 0.001, low quality evidence); reduced antibiotic prescription rates for acute URTIs (OR 0.65; 95% CI 0.45 to 0.94, moderate quality evidence) and cold-related school absence (OR 0.10; 95% CI 0.02 to 0.47, very low quality evidence). Probiotics and placebo were similar when measuring the rate ratio of episodes of acute URTI (rate ratio 0.83; 95% CI 0.66 to 1.05, P value = 0.12, very low quality evidence) and adverse events (OR 0.88; 95% CI 0.65 to 1.19, P value = 0.40, low quality evidence). Side effects of probiotics were minor and gastrointestinal symptoms were the most common. We found that some subgroups had a high level of heterogeneity when we conducted pooled analyses and the evidence level was low or very low quality.

Authors' conclusions

Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTI, the duration of an episode of acute URTI, antibiotic use and cold-related school absence. This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs. However, the quality of the evidence was low or very low.

Study or Subgroup	Experimental		Control		Weight	Risk Ratio		Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Overall respiratory infections								
Hatakka 2001	97	252	123	261	25.1%	0.82	[0.67, 1.00]	
Hojsak 2010	60	139	96	142	24.2%	0.64	[0.51, 0.80]	
Kukkonen 2008	309	468	302	471	29.7%	1.03	[0.94, 1.13]	
Rautava 2009	22	32	31	40	21.0%	0.89	[0.67, 1.18]	
Total (95% CI)		891		914	100.0%	0.84	[0.67, 1.05]	
Total events	488		552					
Heterogeneity: Tau ² = 0.04; Chi ² = 17.69, df = 3 (P = 0.0005); I ² = 83%								
Test for overall effect: Z = 1.51 (P = 0.13)								
Acute otitis media								
Hatakka 2001	79	252	101	261	45.4%	0.81	[0.64, 1.03]	
Hojsak 2010	8	139	13	142	5.9%	0.63	[0.27, 1.47]	
Kukkonen 2008	70	468	69	471	40.6%	0.79	[0.59, 1.05]	
Rautava 2009	7	32	20	40	8.1%	0.44	[0.21, 0.90]	
Total (95% CI)		891		914	100.0%	0.76	[0.64, 0.91]	
Total events	164		223					
Heterogeneity: Chi ² = 2.77, df = 3 (P = 0.43); I ² = 0%								
Test for overall effect: Z = 3.06 (P = 0.002)								
Upper respiratory infections								
Hojsak 2010	58	139	95	142	100.0%	0.62	[0.50, 0.78]	
Total (95% CI)		139		142	100.0%	0.62	[0.50, 0.78]	
Total events	58		95					
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.06 (P < 0.0001)								
Lower respiratory infections								
Hojsak 2010	4	139	5	142	100.0%	0.82	[0.22, 2.98]	
Total (95% CI)		139		142	100.0%	0.82	[0.22, 2.98]	
Total events	4		5					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.31 (P = 0.76)								
Antibiotic treatments								
Hatakka 2001	119	252	144	261	43.1%	0.86	[0.72, 1.01]	
Hojsak 2010	23	139	34	142	10.3%	0.69	[0.43, 1.11]	
Kukkonen 2008	108	468	132	471	40.1%	0.82	[0.66, 1.03]	
Rautava 2009	10	32	24	40	6.5%	0.52	[0.29, 0.92]	
Total (95% CI)		891		914	100.0%	0.80	[0.71, 0.91]	
Total events	260		334					
Heterogeneity: Chi ² = 3.16, df = 3 (P = 0.37); I ² = 5%								
Test for overall effect: Z = 3.31 (P = 0.0009)								

0.1 0.2 0.5 1 2 5 10
Favours LGG Favours Placebo

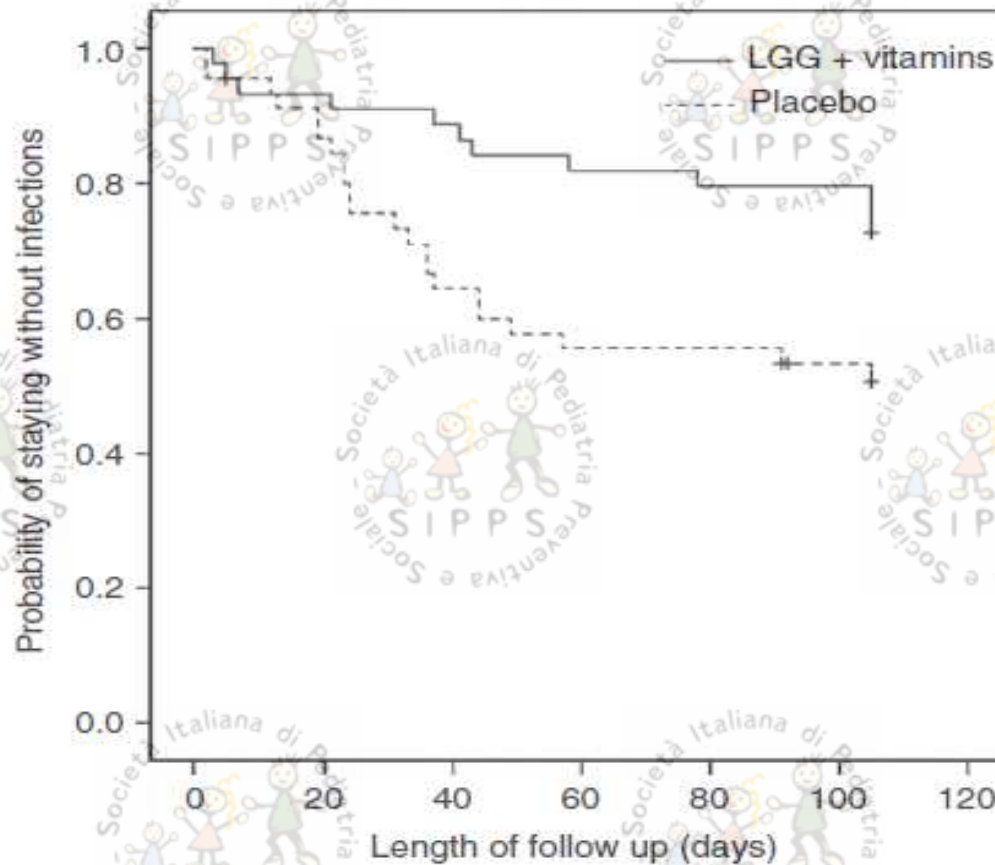
The effect of probiotics
in preventing URTI
is species-related

LGG

- Reduced incidence of acute otitis media.
- Reduced risk of upper respiratory infections and antibiotic treatments.
- No significant difference in the risk of overall respiratory infections and the incidence of lower respiratory infections.

Randomised clinical trial: a Lactobacillus GG and micronutrient-containing mixture is effective in reducing nosocomial infections in children, vs. placebo

E. Bruzzese*, M. C. Fedele*, D. Bruzzese†, S. Viscovo*, A. Giannattasio*, C. Mandato†, P. Siani† & A. Guarino*



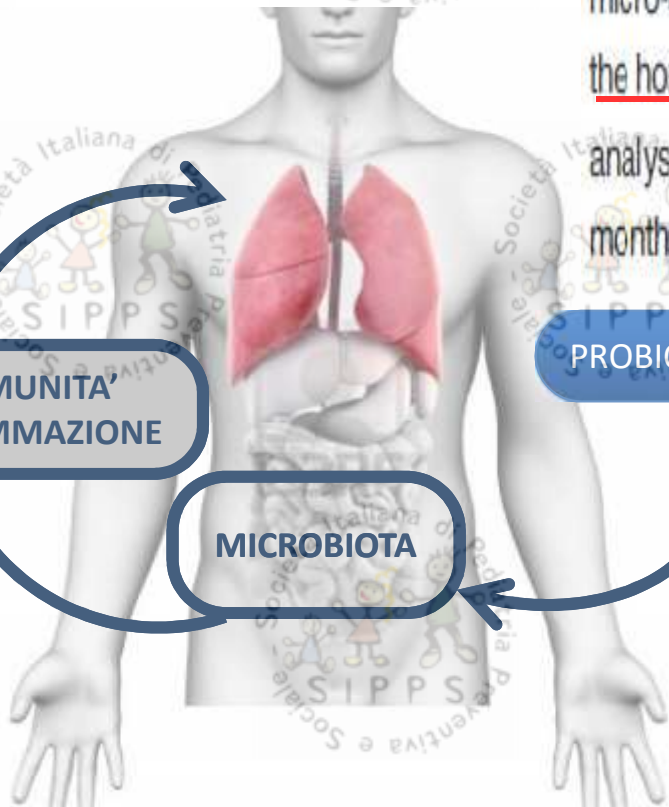
Aliment Pharmacol Ther, 2016

Infezioni respiratorie

The Clinical and Economic Impact of Probiotics Consumption on Respiratory Tract Infections: Projections for Canada

Irene Lenoir-Wijnkoop^{1,2*}, Laetitia Gerlier³, Denis Roy⁴, Gregor Reid⁵

There is accumulating evidence supporting the use of probiotics, which are defined as “live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host”, as a preventive measure against respiratory tract infections (RTI). Two recent meta-analyses showed probiotic consumption (daily intake of 10^7 to 10^{10} CFU in any form for up to 3 months) significantly reduced RTI duration, frequency, antibiotic use and work absenteeism.



IMMUNITÀ
INFIAMMAZIONE

MICROBIOTA

PROBIOTICI

The Clinical and Economic Impact of Probiotics Consumption on Respiratory Tract Infections: Projections for Canada

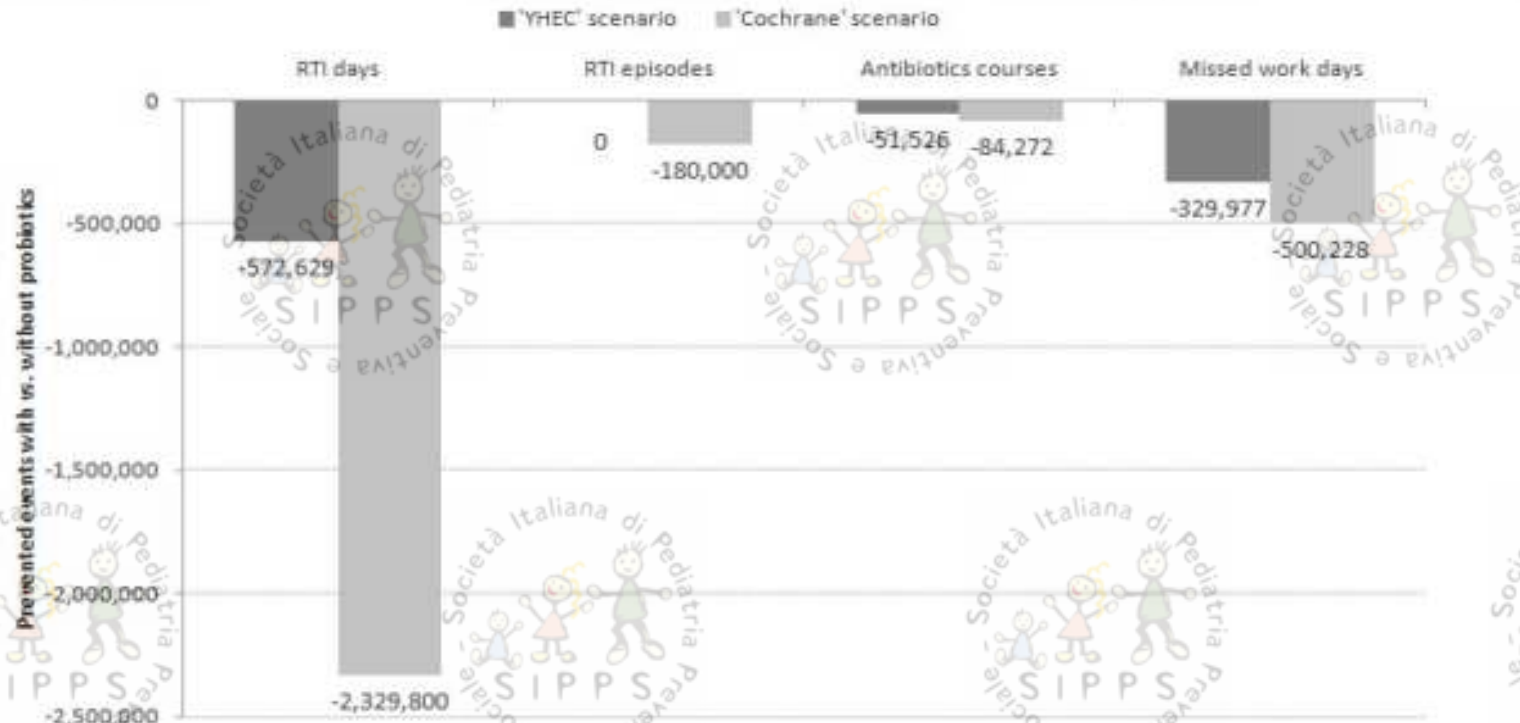


Fig 3. Prevented RTI-related events with vs. without probiotics according to two scenarios.

The results indicate that probiotic use saved 573 000–2.3 million RTI-days, according to the YHEC–Cochrane scenarios respectively. These reductions were associated with an avoidance of 52 000–84 000 antibiotic courses and 330 000–500 000 sick-leave days.

NEC

Prematuri e probiotici: una questione di vita o di morte



NEC

- “NEC is a **devastating disease** in neonates characterized by **inflammatory changes** in the intestines and **microbial disruption** leading to gastrointestinal dysfunction that **can quickly progress** from feeding intolerance to intestinal perforation, shock, and death in severe cases.”
- “There is **high associated morbidity and mortality, health care burden**, and **long-term poor developmental outcomes** for those affected by NEC.”
- “The pathogenesis of NEC has been extensively studied yet still remains incompletely understood. It is **multifactorial**, including **prematurity** with intestinal immaturity and excessive inflammatory response to intestinal stimuli, **genetic predisposition**, and **abnormal microbial colonization** of the intestine”.

[Hourigan SK et al
Clin Ther 2016](#)

NEC

Pediatrics. 2010 May;125(5):921-30. Epub 2010 Apr 19.

Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates.

Deshpande G, Rao S, Patole S, Bulsara M.

Department of Neonatal Paediatrics, King Edward Pediatrics. 2010 Sep;126(3):e740-1; author reply e743-5.

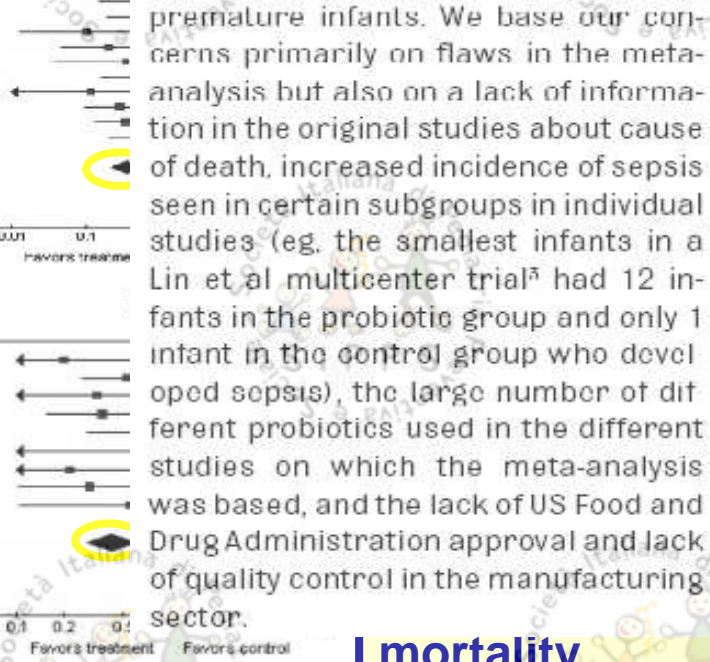
Nonadministration of routine probiotics unethical--really?

Nou J, Shuster J.

Study or sub-category	Probiotic n/N	Control n/N
Hilajnia 1997	0/45	2/290
Dani 2002	4/295	4/28
Cordasco 2003	2/51	1/28
Bin Nk 2005	1/72	10/73
Lin 2005	2/180	15/187
Meyer 2006	1/28	1/28
Nou		
Strat		
Lin 2		
Sam		
Roug		
Total		
Total		
Test		
Test		

a reduced risk for LOS. The significant effect size, precision, consistency of the results across all trials, extremely low P values almost ruling out the role of chance alone, low risk for publication bias, no statistical heterogeneity, critical areas of benefit, and the TSA conclusive of at least 30% reduction in the incidence of NEC all indicate that **withholding probiotics from high-risk neonates is now almost unethical.**⁵³

Total 0
 Total e
 Test for heterogeneity: Chi² = 4.01, df = 8 (P = 0.86), I² = 0%
 Test for overall effect: Z = 4.49 (P < 0.00001)



mortality

Probiotics for Prevention and Treatment of Diarrhea.

Guarino A¹, Guandalini S, Lo Vecchio A.

NEC

Recommendations for use of probiotics in preterms in available guidelines

Guidelines	Country	Conclusion	Evidence in Support
ASPEN ⁵⁶	USA	There are insufficient data to recommend the use of probiotics in infants at risk for NEC.	+ +
APSA ⁵⁷	USA	No formal recommendations regarding the formulation, timing or duration of supplementation could be determined, but at least one probiotic formulation initiated in the first week of life and continued for at least 2 wk appears appropriate.	+ +
ESPGHAN ⁵⁸	Europe	There is not enough available evidence to recommend the routine use of probiotics in preterm infants.	+ +
Cincinnati ⁵⁹	USA	There may be a preventive role of probiotics.	+

Guarino A et al. J Clin Gastroenterol 2015

REVIEW ARTICLE

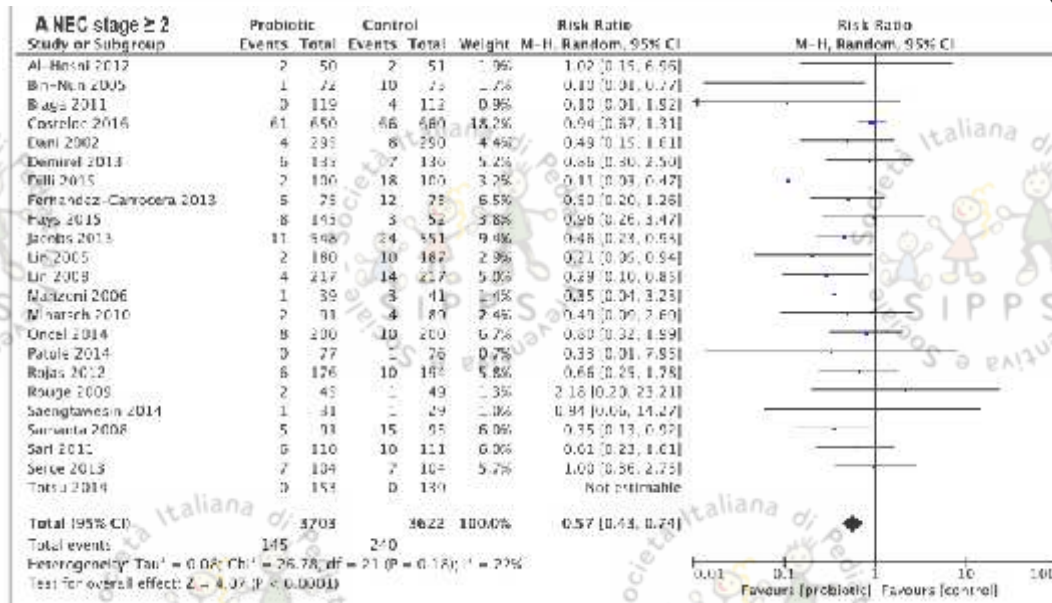
Probiotics for the prevention of necrotising enterocolitis in very low-birth-weight infants: a meta-analysis and systematic review

John P. Thomas (drjohnpthomas@gmail.com)¹, Tim Raine², Sanath Reddy³, Guslay Belleki⁴

¹Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich, UK
²Division of Gastroenterology, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
³Department of Paediatrics, Princess Alexandra Hospital, Harlow, UK
⁴Department of Neonatology, Cambridge University Hospitals NHS Trust, Cambridge, UK

GUIDELINES IN PREPARATION

Probiotics and NEC events in VLBW infants (RR of 0.57 p < 0.0001)





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Items: 1 to 20 of 403 of 21

[Curr Opin Infect Dis.](#) 2016 Jun;29(3):256-61. doi: 10.1097/QCO.0000000000000269

Probiotics for prevention of necrotizing enterocolitis and sepsis in preterm infants.

[Lambleton NU¹](#), [Zalewski S](#), [Berrington JL](#).

Author Information

Abstract

PURPOSE OF REVIEW: Few areas in neonatal medicine have generated as much discussion and controversy as the use of prophylactic probiotics for the prevention of necrotizing enterocolitis. We summarize recent studies from the last 1-2 years.

RECENT FINDINGS: Systematic reviews show that probiotics reduce the risk of necrotizing enterocolitis but there are methodological limitations to all the published trials, and the largest trial to date is at odds with the conclusions of the meta-analyses. Trials have used a range of commercially available products with differing species, and administered these at different times to heterogeneous populations of preterm babies. Although there is strong evidence to show that 'probiotics' are likely to represent a major advance for neonatal care, it is increasingly clear that not all species have beneficial effects in preterm infants. This makes interpretation of meta-analyses complex, and the determination of a single 'risk reduction' potentially flawed.

SUMMARY: Despite current uncertainties, it is difficult for clinicians to ignore the current data, and increasing numbers now use commercially available products. It remains a matter of concern that many products lack the robust quality control most clinicians and parents would consider important for use in vulnerable populations. Head-to-head trials are needed.

SCHEMA: Efficacia di specifici probiotici in bambini basata su prove scientifiche

DISEASE	EVIDENCE	EFFECT	STRAINS
GASTROENTERITIS	Multiple RCT, multiple guidelines	Reduces duration and severity by 30% (1 day on average)	LGG, S. boulardii
ANTIBIOTIC-ASSOCIATED DIARRHEA (and Clostridium difficile)	Multiple RCT, multiple guidelines	Reduces the risk of diarrhea by 25-30%	LGG, S. boulardii
NOSOCOMIAL INFECTIONS	Multiple RCT, few guidelines	Reduces intestinal and respiratory infections	LGG
URTI	Multiple RCT, metanalyses	Reduces incidence	LGG, Bifidobacteria
NEC/DEATH IN PRETERMS	Multiple RCT, guidelines in preparation	Significantly reduces risks of NEC and all cause mortality	Various



Guidelines
production



For many health conditions, there is a **GAP** between what medical science has shown to be effective practice and what is actually done

*NICU study:
best practices are not always followed.
Healthcare Benchmarks Qual Improv. 2003*



FINAL TARGET

Prescrizione di probiotici in bambini con gastroenterite acuta

IN-PATIENTS

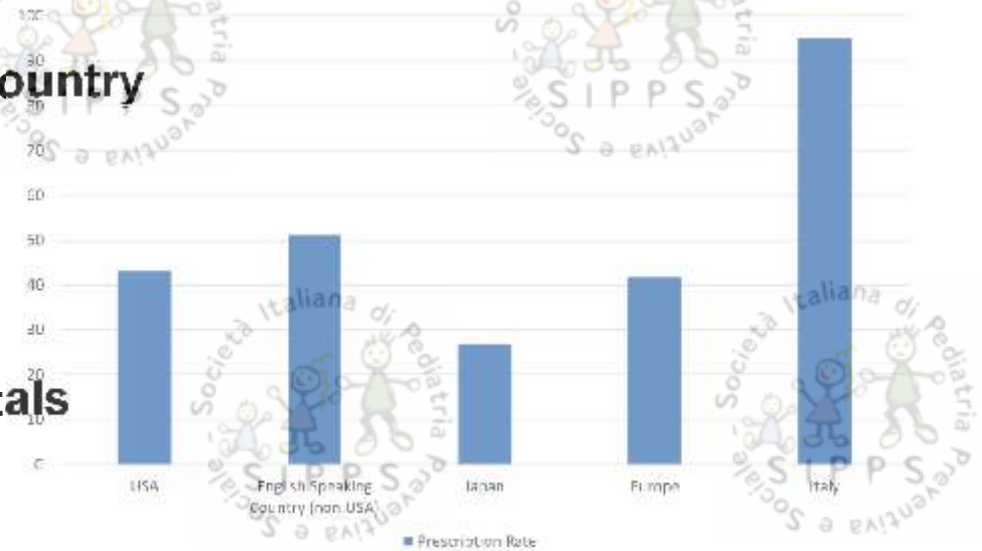
- Implementation study in **11 European country**
(Nicastro PLOS One 2015)

Use of probiotics **9,4%** (33/351)

- Observational study in **31 Italian Hospitals**
(Lo Vecchio PIDJ 2014)

Use of probiotics **38%** (193/502)

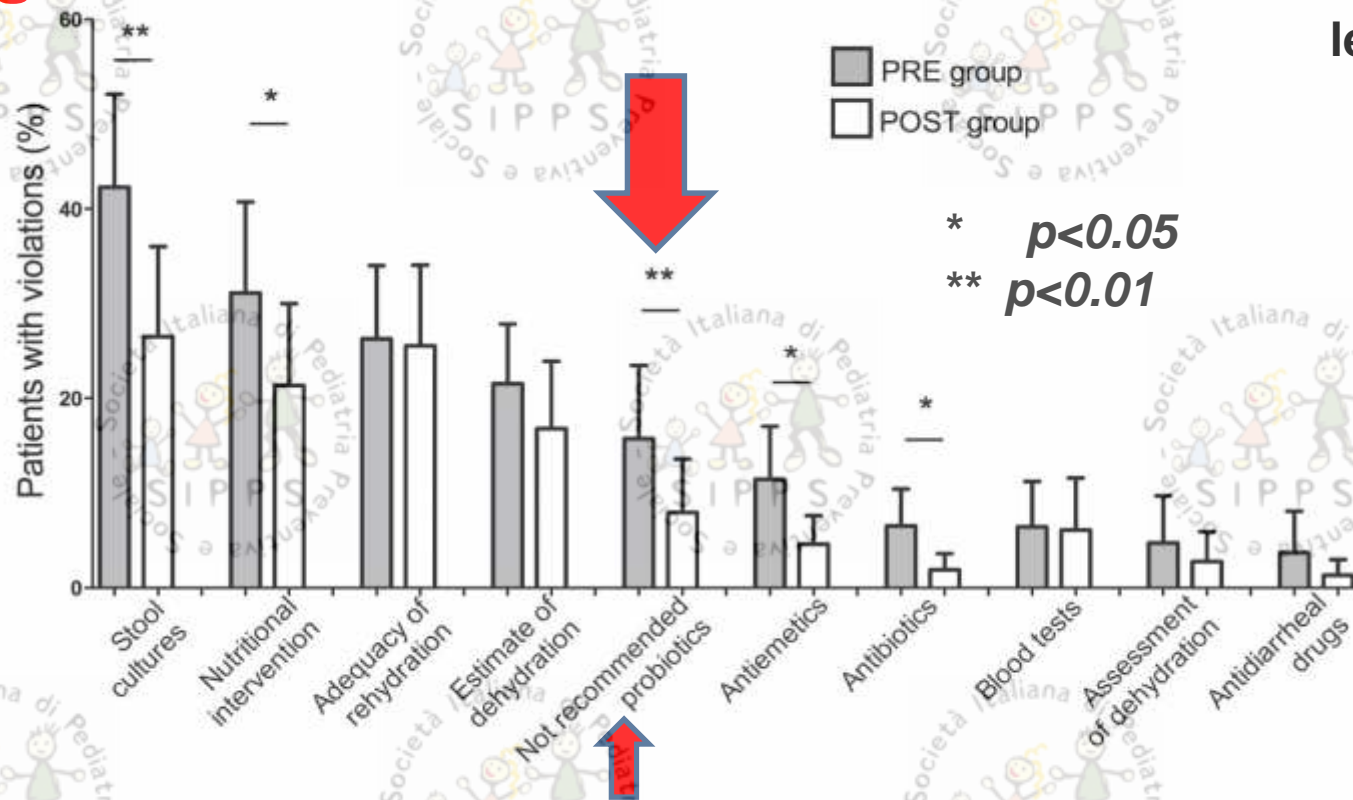
OUT-PATIENTS



Albano – J Pediatrics 2010
Kita – J Clin Phar Ther 2010
Weizman – J Clin Gastroenterol 2011

Uso di ceppi difformi da quelli indicati nelle linee guida

Violations to guidelines for gastroenteritis before and after an e-learning course



Adherence to guidelines for management of children hospitalized for acute diarrhea.

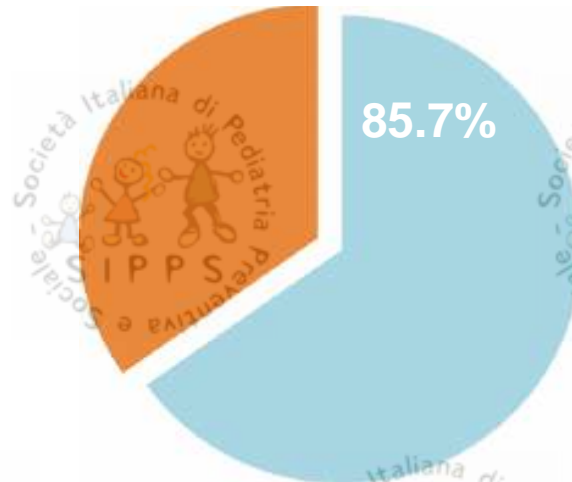
Lo Vecchio A¹, Liquoro I, Bruzzese D, Scotto R, Parola L, Gargantini G, Guarino A; Accreditation and Quality Improvement Working Group of Italian Society of Pediatrics.

Prescrizione di probiotici in bambini ospedalizzati per gastroenterite acuta

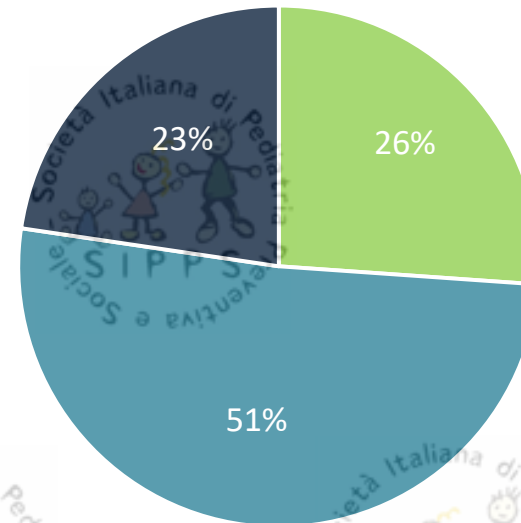
In-patients

N= 612

■ Yes ■ No



$p < 0.0001$



■ Strongly recommended

■ Weakly recommended

■ Not recommended

Barriere



- Non conoscenza
- Disponibilità dei ceppi (ospedale)
- Delega della scelta ad altre figure (farmacia)
- Terapie alternative
- Costi (per cicli lunghi)
- Sottovalutazione dell'efficacia
- Fake news

venerdì 08/09/2017 04:32

DottNet - Panorama Medico <noreply@newsletter.mercurio.net>

Obbligo di bancomat: ecco i costi per il Pos

A: alfguari@unina.it

Mario Melazzini

Il valore etico delle aziende del farmaco

Medicina Generale

Dolore legato all'herpes zoster: il vaccino può prevenire

Ma tre persone su quattro non sanno che esiste questa possibilità...

Antonella Cerano

Le richieste delle Associazioni dei pazienti alle industrie del farmaco

Nutrizione

Probiotici, per la diarrea efficaci solo in un caso su tredici

Pediatra, sbagliato pensare che siano un farmaco importante...

Probiotici, per la diarrea efficaci solo in un caso su tredici



Nutrizione | Redazione DottNet | 06/09/2017 19:17

Pediatra, sbagliato pensare che siano un farmaco importante

I probiotici, tanto di moda e spesso prescritti ai bambini quando si dà l'antibiotico per evitare la diarrea, sono nella maggior parte dei casi "un'operazione commerciale dai pochi benefici". Secondo le prove scientifiche di efficacia infatti, c'è 1 probabilità su 13 che si rivelino efficaci nel ridurre la diarrea.

Lo spiega il pediatra Costantino Panza, dell'Associazione culturale pediatri (Acp), in una revisione pubblicata sui QuaderniAcp. La continua "messa in vendita di nuove formulazioni e l'informazione data direttamente ai medici e, attraverso campagne pubblicitarie, alla popolazione, ne fanno tra i più venduti alimenti funzionali, con stime di oltre 15 miliardi di dollari l'anno nel mondo, e in Italia di oltre 360 milioni di euro l'anno", scrive Panza. Ma pur essendoci centinaia di prodotti, quelli per cui è stato "dimostrato questo tipo di beneficio, sono solo tre", continua Panza. Tra l'altro, perchè i probiotici siano efficaci, ne servono elevate quantità, dai 5 fino a 40 miliardi di CFU (unità formanti colonie) al giorno di *Lactobacillus rhamnosus* o *Saccharomyces boulardii*.

"Ma quando si comprano l'indicazione di solito è di 1-3 miliardi. E' scorretto pensare che siano un farmaco importante. Si fanno spendere soldi inutilmente. Spesso è una questione di ignoranza e mancanza di corretta informazione", rileva Panza. **Quando il bambino ha la gastroenterite la terapia fondamentale è la reidratazione, ricorda il pediatra.** "La cosa più importante è prescrivere l'antibiotico in modo motivato, cosa che in Italia spesso non si fa. E poi dare al bambino una dieta ricca di fibre, frutta, verdura e vitamina B, già dopo le prime 6 ore dall'inizio della diarrea. Niente dieta in bianco invece, perchè fa aumentare le scariche", conclude Panza.

FAKE NEWS



PROBIOTIC USE IN ACUTE GASTROENTERITIS: Does one day matter?

- Two billion episodes of diarrheal disease per year (WHO)
- Therefore probiotics could prevent 2 billion days of diarrhoea.
- At an estimate of 1 liter of stool per day of diarrhea, this volume would take:

12 days to flow past in the Seine



Ganges – 3 minutes. Yangtze 1.5 minutes

Courtesy of Don Cameron

14 minutes to flow over the Niagara Falls



Courtesy of Don
Cameron

Metà del contenuto del Canal Grande



Stewardship

ANTIBIOTICS: Strategies to optimize and control the use of antibiotics to prevent the unnecessary use of antibiotics and decrease the resistance of bacterial pathogens

PROBIOTICS: A strategy to optimize and promote the use of probiotics to fully exploit their benefits in children based on evidence (and also to eventually limit the use of antibiotics...)



LGG is the strain for which solid proof of evidence is available and should be considered as standard of care

A guided use of probiotics in children

MONDAY, SEPTEMBER 11

AULA ELIE METCHNIKOFF

PEDIATRIC DAY

09.00-09.30 a.m.

LECTURE

Stewardship in clinical practice... lessons from the antibiotic world
L. Balli (Italy)

09.30-11.00 a.m.

PROBIOTICS STEWARDSHIP IN PEDIATRICS

Chair: Y. Yamashiro (Japan)

Evaluation tools for probiotics in clinical practice
H. Szajewska (Poland)

Quality of probiotics
S. Kolacek (Croatia)

Implementation: sciences applied to probiotics
A. Guacko (Italy)

11.00-11.30 a.m.

Break

11.30-01.00 p.m.

PROBIOTICS IN CLINICAL PRACTICE: CONSOLIDATED INDICATIONS

Chair: H. Szajewska (Poland)

Acute gastroenteritis
A. La Vecchia (Italy)

Antibiotic associated diarrhea
V. Vandecasteele (Belgium)

Neonocomial infections
L. Hajsek (Croatia)

Infantile colic
E. Indrio (Italy)

01.00-02.00 p.m.

Lunch

02.00-03.30 p.m.

PROBIOTICS IN PAEDIATRIC GASTROENTEROLOGY: EMERGING INDICATIONS

Chair: S. Kolacek (Croatia)

IBDs
E. Scarpato (Italy)

Functional intestinal disorders
M. M. Tabbers (The Netherlands)

NEC
J. B. van Goudoever (The Netherlands)

NAFLD/NASH
V. Nobili (Italy)

03.30-04.00 p.m.

Break

04.00-05.30 p.m.

PROBIOTICS FOR PAEDIATRIC EXTRAINTESTINAL DISORDERS: WHERE WE ARE NOW

Chair: J. A. Vandemoortel (USA)

Respiratory tract infections
E. Bruzzese (Italy)

Allergy
R. Berni Canani (Italy)

Obesity
E. Isolauri (Finland)

05.30-05.00 p.m.

Conclusions

Stewardship

Specifici ceppi di probiotici sono oggi lo standard di cura o di prevenzione di:

- Gastroenterite
- Diarrea da antibiotici (in particolari categorie/condizioni)
- Infezioni nosocomiali
- Enterocolite necrotizzante (in attesa di linee guida)
- Prevenzione di infezioni respiratorie in particolari categorie (in attesa di linee guida)

J Pediatr Gastroenterol Nutr. 2017 Jul;65(1):117-124. doi: 10.1097/MPG.0000000000001603.

Commercial Probiotic Products: A Call for Improved Quality Control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics.

Kolaček S¹, Hoisak I, Berni Canani R, Guarino A, Indrio F, Orel R, Pot B, Shamir R, Szajewska H, Vandenplas Y, van Goudoever J, Weizman Z: ESPGHAN Working Group for Probiotics and Prebiotics.

Author information

Abstract

Probiotics have been proposed for a number of indications ranging from the hypothetical long-term immunomodulatory effects to proven benefits in the management of different clinical conditions. An increasing number of commercial products containing probiotics are available. In those products, irrespective if it is food, food supplement, medical food, or drug, the probiotic microorganisms have to be present in a sufficient number by the end of the shelf-life, to pass through the gastrointestinal tract resisting acid and bile, to colonize the gut, and to retain functional properties required to obtain the suggested beneficial effect. Finally, it should be contamination-free. Studies organized worldwide and summarized in this article have shown that inconsistencies and deviations from the information provided on the product label are surprisingly common. Frequently strains are misidentified and misclassified, products are occasionally contaminated, sometimes with even facultative or obligatory pathogens, strains are not viable, the labeled number of colonies cannot be verified, or the functional properties are diminished to the extent that preclude the proposed health benefit. As the probiotic preparations are commonly used for a wide range of conditions, the aim of the Working Group was to summarize results of the studies looking into the quality of the probiotic products and to raise the awareness of the important issue of their quality control. Based on the results obtained, we strongly suggest a more stringent quality control process. This process should ensure that the probiotic content as mentioned on the label meets the actual content throughout the shelf life of the product, while no contamination is present.

Uso di probiotici nelle linee guida internazionali

Condizione	Effetto dei probiotici	Ceppo consigliato
Gastroenterite acuta	Riduzione della durata e intensità dei sintomi	LGG, S. boulardii
Prevenzione infezioni respiratorie	Riduzione del rischio	LGG, altri
Disordini funzionali gastrointestinali-correlati al dolore addominale	Alcuni probiotici riducono intensità del dolore (specialmente in sindrome del colon irritabile)	LGG VSL3
Mantenimento della remissione in colite ulcerativa	Evidenze limitate che i probiotici aggiunti alla terapia standard possano apportare modesti benefici	VSL3, E. coli Nissle1917
Diarrea da antibiotici	Riduzione del rischio	LGG, S. boulardii
Infezioni nosocomiali	Riduzione del rischio di diarrea e potenzialità di infezioni respiratorie	LGG
M. Crohn	I probiotici non hanno effetto nella terapia né nel mantenimento.	
Stipsi funzionale	Fino a quando non saranno disponibili ulteriori dati, l'uso dei probiotici dovrebbe essere considerato sperimentale	
NEC	Riduzione del rischio di NEC e della mortalità sia da NEC che da altre cause	Vari
Clostridium difficile	Raccomandato in specifiche	Saccharomyces boulardii

