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REVIEW

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Using probiotics in clinical practice: Where are we now? A review of existing meta-analyses

Mariangela Rondanelli [a], Milena Anna Faliva[a], Simone Perna [a], Attilio Giacosa[b], Gabriella Peroni[a], and Anna Maria Castellazzi[c]

[a]Department of Applied Health Sciences, Azienda di Servizi alla Persona (ASP) di Pavia, University of Pavia, Pavia, Italy; [b]Department of Gastroenterology, Policlinico di Monza, Monza, Italy and Centro Diagnostico Italiano, Milan, Italy; [c]Castellazzi Department of Clinical Surgical Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

ABSTRACT

The scientific literature has demonstrated that probiotics have a broad spectrum of activity, although often the results are contradictory. This study provides a critical overview of the current meta-analyses that have evaluated the efficacy of probiotics in physiologic and pathological conditions, such as metabolic disease, antibiotic-associated and Clostridium difficile-associated diarrhea, IBS, constipation, IBD, chemotherapy-associated diarrhea, respiratory tract infection, ventilator-associated pneumonia, NAFLD, liver encephalopathy, periodontitis, depression, vaginosis, urinary tract infections, pancreatitis, incidence of ventilator-associated pneumonia, hospital infection and stay in ICU, mortality of post-trauma patients, necrotising enterocolitis in premature infants.

Only for antibiotic- and Clostridium difficile-associated diarrhea, and respiratory tract infections the effects of probiotics are considered "evidence-based." Concerning other fields, meta-analyses lacks to define type and biologic effect of probiotic strains, as well as the outcome in a disease state. Therefore, the results presented should be a stimulus for further studies which will provide clinical recommendations.

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Introduction

The scientific literature related to the favorable effects of probiotics on human health has continued to accumulate in recent years,[1] and meta-analyses that have collectively evaluated the effects of probiotics in specific physiologic and pathological conditions are now numerous.

The fields of study in which meta-analysis and systematic reviews have been published concerning the assessment of effectiveness of taking probiotics are given in Table 1, and cover certain categories of patients (premature infants and trauma patients) and specific diseases, such as metabolic disorders (diabetes, dyslipidemia, hypertension, obesity), gastrointestinal disorders (inflammatory bowel disease, constipation, antibiotic-associated diarrhea, diarrhea secondary to treatment of eradication Clostridium difficile, Helicobacter Pylori, diarrhea secondary to chemotherapy), atopic diseases (atopic syndrome and food hypersensitivity, allergic rhinitis), liver disease (cirrhosis, non-alcoholic fatty liver disease, hepatic encephalopathy), pancreatic disorders (acute pancreatitis), infections of the respiratory tract, urinary tract infections, bacterial vaginosis, periodontitis, and depressive disorder.

The purpose of this study was to perform a review considering all the meta-analysis published in the literature on the effectiveness of the use of probiotics in clinical practice.

Materials and methods

The present systematic review was performed following the steps by Egger et al.[2] as follows: 1. configuration of a working group: 2 operators skilled in clinical nutrition, one skilled in gastroenterology, and one skilled in pediatric, of whom 2 are acting as a methodological operator and 2 participating as clinical operators. 2. Formulation of the revision question on the basis of considerations made in the abstract: "use of probiotics: meta-analysis."

CONTACT Simone Perna simoneperna@hotmail.it Department of Public Health, Experimental and Forensic Medicine, School of Medicine, University of Pavia, Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona di Pavia, Pavia, Italy.

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Table 1. Fields of study in which there are meta-analysis concerning the evaluation of efficacy of the consumption of probiotics.

Diseases	Main results
	METABOLIC DISEASES
Type II diabetes	Reduction of glucose and glycated hemoglobin
Dyslipidemia	Reduction of total cholesterol and LDL cholesterol
Hypertension	Improvement in blood pressure, especially if the basal blood pressure is high
Overweight and Obesity	Different effects on body weight changes
	GASTRO INTESTINAL TRACT DISEASES
Helicobacter Pylori	Significant improvement of the eradication rate of bacteria
Cronic Inflammatory Bowel Diseases	Practical option in ulcerative colitis both as induction therapy that maintenance
Irritable bowel syndrome	Reduction of the pain and the severity of related-symptoms
Costipation	Improve in whole gut transit time, stool frequency and stool consistency
Antibiotic-associated diarrhea	Prevention of diarrhea
Diarrhea associated with chemotherapy	Prevention of diarrhea, specially of second degree
Diarrhea associated with Clostridium Difficile	Risk reduction of 64 %
	ALLERGIC DISEASES
Atopic syndrome and hypersensitivity to food	Reduction in eczema infant, improvement of atopic syndrome
Allergic riniti	Improvement of the quality of life and nasal symptom
	RESPIRATORY TRACT INFECTIONS
Respiratory tract infections	Reduction in the incidence of symptoms of respiratory tract infections
ventilator-associated pneumonia	There are insufficiency evidence to recommend probiotics as a routine therapy
	LIVER DISEASES
Non alcholic fatty liver disease (NAFLD)	NAFLD: decrease in liver aminotransferase levels and improving insulin resistance
Encephalopathy	Probiotics decrease overt hepatic encephalopathy in patients with liver cirrhosis
	OTHER DISEASES
Acute pancreatitis	No significant effect
Bacterial vaginosis	No significant evidence
Urinary tract infections	No significant evidence
Periodontitis	Use as an adjunct to non-surgical periodontal treatment of chronic periodontitis
Depression	Decrease in the score on the depression scale
Children born prematurely	Reduction of sepsis, both bacterial and fungal origin, that reduced incidence of severe necrotizing enterocolitis
Post-trauma patients	Reduction in the incidence of hospital infections, Ventilatory-associated pneumonia and length of intensive care

3. Identification of relevant studies: a research strategy was planned, on PubMed [Public MedIine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bethesda (USA)], as follows: a) definition of the keywords (probiotics use, meta-analysis), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas ("…") and used separately or in combination; b) use of: the Boolean AND operator, that allows the establishments of logical relations among concepts; c) research modalities: advanced search; d) limits: time limits: papers published in the last 10 years; humans; languages: English; e) manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on nutrition and body composition published in journals qualified in the Index Medicus. 4. Analysis and presentation of the outcomes: the data extrapolated from the meta-analysis were collocated in tables; in particular, for each meta-analysis we specified: the author, the name of the journal where the study was published and year of publication, study characteristics and results 5. The analysis was performed in the form of a narrative review of the reports.

Moreover, since all of the meta-analysis considered in this study included randomized clinical trials, then all studies are with a level of evidence I and II.[3,4]

Results

Metabolic diseases

Diabetes

As for the effectiveness of probiotics in patients with type 2 diabetes, all 5 meta-analysis published to date, 4 involving adult subjects[5-8] and 1 on both adults and children,[9] shown in Table 2, agree on a significant reduction in fasting plasma glucose and glycosylated hemoglobin. However, there is no agreement in the demonstration of reduction in blood insulin levels.

The meta-analysis does not specify whether there are more effective strains in blood glucose control, but all stress the need for an intervention that lasts at least 8 weeks to get a significant result.

Table 2. Metabolic pathologies.

Authors and study partecipants	Results	Conclusions
	DIABETES	
	ADULT	
Zhang et al., Medicina (Kaunas) 2016[5] 7 trials with 497 subjects in total	Probiotic consumption significantly changed fasting plasma glucose (FPG) by −15.92 mg/dL (95% confidence interval [CI], −29.75 to −2.09) and glycosylated hemoglobin (HbA1c) by −0.54% (95% CI, −0.82 to −0.25) compared with control groups. Meta-analysis of trials with multiple species of probiotics found a significant reduction in FPG (weighted mean difference [WMD]: −35.41 mg/dL, 95% CI: −51.98 to −18.89). The duration of intervention for ≥ 8 weeks resulted in a significant reduction in FPG (WMD: −20.34 mg/dL, 95% CI: −35.92 to −4.76). Furthermore, the duration of intervention <8 weeks did not result in a significant reduction in FPG. The results also showed that probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: −1.08, 95% CI: −1.88 to −0.28; and WMD: −1.35 mIU/L, 95% CI: −2.38 to −0.31, respectively).	Consuming probiotics may improve glucose metabolism by a modest degree, with a potentially greater effect when the duration of intervention is ≥ 8 weeks, or multiple species of probiotics are consumed.
Samah et al., Diabetes Res Clin Pract 2016[6] 6 randomized controlled trials included in the systematic review (n = 317), whereas only 5 included in meta-analysis	When compared with placebo, fasting blood glucose (FBG) was significantly lower with probiotic consumption (MD=−0.98 mmol/L; 95% CI: −1.17, 0.78, p<0.00001), with moderate but insignificant heterogeneity noted. Insignificant changes between the groups were also noted for glycosylated hemoglobin (HbA1c) and other secondary outcomes.	A moderate hypoglycaemic effect of probiotics, with a significantly lower FBG was noted. Findings on HbA1c, anti-inflammatory and anti-oxidative effects of probiotics in the clinical setting, however, remain inconsistent.
Kasińska et al., Pol Arch Med Wewn 2015[7] 8 trials with 438 individuals	The meta-analysis showed a significant effect of probiotics on reducing glycosylated hemoglobin (HbA1c) levels (standardized mean difference [SMD], −0.81; confidence interval [CI], −1.33 to −0.29, P = 0.0023; I2 = 68.44%; P = 0.0421 for heterogeneity) and HOMA-IR (SMD, −2.10; CI −3.00 to −1.20, P <0.001; I2 = 82.91%; P = 0.0029 for heterogeneity). Supplementation with probiotics did not have a significant effect on FPG, insulin, and C-reactive protein (CRP) levels as well as the lipid profile.	Probiotic supplementation might improve, at least to some extent, metabolic control in subjects with type 2 diabetes. However, larger well-designed, long-term RCTs are needed to confirm any potentially beneficial relationship between the use of probiotics and modifiable cardio-metabolic risk factors in patients with type 2 diabetes
Ruan et al., PLoS One 2015[8] 17 randomized controlled trials, with 17 fasting blood glucose (n = 1105), 11 fasting plasma insulin (n = 788), 8 homeostasis model assessment of insulin resistance comparisons (n = 635)	Probiotic consumption, compared with placebo, significantly reduced fasting glucose (MD = −0.31 mmol/L; 95% CI 0.56, 0.06; p = 0.02), fasting plasma insulin (MD = −1.29 μU/mL; 95% CI −2.17, −0.41; p = 0.004), and HOMA-IR (MD = 0.48; 95% CI −0.83, −0.13; p = 0.007).	Probiotic consumption may improve glycemic control modestly. Modification of gut microbiota by probiotic supplementation may be a method for preventing and control hyperglycemia in clinical practice.
	ADULT + PEDIATRIC	
Sun et al., Br J Nutr 2016[9] 11 studies with 614 subjects in total	There are statistically significant pooled mean differences between the probiotics and the placebo-controlled groups on the reduction of glucose (−0·52 mmol/l, 95% CI −0·92, −0·11 mmol/l; P = 0·01) and glycosylated hemoglobin (HbA1c) (−0·32%, 95% CI −0·57, −0·07%; P = 0·01). There was no statistically significant pooled mean difference between the probiotics and the placebo-controlled groups on the reduction of insulin (−0·48 μIU/ml, 95% CI −1·34, 0·38 μIU/ml; P = 0·27) and HOMA-IR (pooled effect of −0·44, 95% CI −1·57, 0·70; P = 0·45). Meta-regression analysis identified that probiotics had significant effects on reduction of glucose, HbA1c, insulin and HOMA-IR in participants with diabetes, but not in participants with other risk factors.	Probiotics may be used as an important dietary supplement in reducing the glucose metabolic factors associated with diabetes

(*continued on next page*)

Table 2. (*Continued*)

Authors and study partecipants	Results	Conclusions
	DYSLIPIDEMIA	
	ADULT	
Shimizu et al., PLoS One 2015[10] 11 randomized clinical trials with 574 partecipants in total	Probiotic interventions (including fermented milk products and probiotics) produced changes in total cholesterol (TC) (mean difference −0.17 mmol/L, 95% CI: −0.27 to −0.07 mmol/L) and low-density lipoprotein cholesterol (LDL-C) (mean difference −0.22 mmol/L, 95% CI: −0.30 to −0.13 mmol/L). High-density lipoprotein cholesterol and triglyceride levels did not differ significantly between probiotic and control groups. In subanalysis, long-term (> 4-week) probiotic intervention was statistically more effective in decreasing TC and LDL-C than short-term (≤ 4-week) intervention. The decreases in TC and LDL-C levels with probiotic intervention were greater in mildly hypercholesterolemic than in normocholesterolemic individuals. Both fermented milk product and probiotic preparations decreased TC and LDL-C levels. Gaio and the Lactobacillus acidophilus strain reduced TC and LDL-C levels to a greater extent than other bacterial strains. *L. reuteri* NCIMB also markedly reduced TC and LDL-C levels, although it was only included in a single study.	Gaio and the Lactobacillus acidophilus strain reduced TC and LDL-C levels to a greater extent than other bacterial strains.
Sun J et al., Ann Med 2015[11] 15 studies with 788 subjects	Statistically significant pooled effects of probiotics were found on reduction of total cholesterol, low-density lipoprotein (LDL), body mass index (BMI), waist circumference, and inflammatory markers. Subgroup analysis revealed statistically significant effects of probiotics on total cholesterol and LDL when the medium was fermented milk or yogurt ($P < 0.001$) compared with capsule form, consumption was at least 8 weeks in duration ($P < 0.001$), and the probiotics consisted of multiple strains ($P < 0.001$) rather than a single strain. A significant reduction was found in LDL in trials which contained Lactobacillus Acidophilus strain ($P < 0.001$) compared with other types of strains.	Probiotic supplementation use is effective in lowering the lipid level and coexisting factors associated with cardiovascular disease. *Lactobacillus Acidophilus* strain is more effective for reduction of LDL.
Guo et al., Nutr Metab Cardiovasc Dis 2011[12] 13 trials, which included 485 participants with high, borderline high and normal cholesterol levels	The pooled mean net change in total cholesterol for those treated with probiotics compared with controls was −6.40 mg dl(−1) (95% confidence interval (CI), −9.93 to −2.87), mean net change in low-density lipoprotein (LDL) cholesterol was −4.90 mg dl(−1) (95% CI, −7.91 to −1.90), mean net change in high-density lipoprotein (HDL) cholesterol was −0.11 mg dl(−1) (95% CI, −1.90–1.69) and mean net change in triglycerides was −3.95 mg dl(−1) (95% CI, −10.32–2.42).	A diet rich in probiotics decreases total cholesterol and LDL cholesterol concentration in plasma for participants with high, borderline high and normal cholesterol levels.
	ADULT + PEDIATRIC	
Cho et al., Medicine (Baltimore) 2015[13] 30 randomized controlled trials with 1624 participants (828 in intervention groups and 796 in placebo groups)	Subjects treated with probiotics demonstrated reduced total cholesterol and LDL cholesterol compared with control subjects by 7.8 mg/dL (95% CI: −10.4, −5.2) and 7.3 mg/dL (95% CI: −10.1, −4.4), respectively. There was no significant effect of probiotics on HDL cholesterol or triglycerides. The significant effects were greater for higher baseline total cholesterol levels, longer treatment durations, and certain probiotic strains. In addition, these associations seem stronger in studies supported by probiotics companies.	Use of probiotics may improve lipid metabolism by decreasing total and LDL cholesterol. However, both the efficacy of probiotics for cholesterol lowering and safety should be investigated further in well-designed clinical trials.

	OVERWEIGHT AND OBESITY	
	ADULT	
Zhang et al., Int J Food Sci Nutr 2015[15] 25 trials (1931 participants with age over 18 years)	Probiotic consumption significantly reduced body weight by 0.59 kg (95% CI, 0.30–0.87) and BMI by 0.49 kg/m(2) (95% CI, 0.24–0.74). A greater reduction in BMI was found with multiple species of probiotics. Subgroup analysis of trials with intervention duration $\geq$ 8 weeks found a more significant reduction in BMI. Limiting analysis to trials with a baseline BMI $\geq$ 25 kg/m(2) showed a greater	Consuming probiotics could reduce body weight and BMI, with a potentially greater effect when multiple species of probiotics were consumed, the duration of intervention was $\geq$ 8 weeks, or the objects were overweight.
Park et al., Nutr Res 2015[16] 4 randomized controlled trials that compared the therapeutic efficacy of probiotics with placebo as a treatment of weight loss (n = 449)	There was no significant effect of probiotics on body weight and BMI (body weight, n = 196; mean difference, −1.77; 95% confidence interval, −4.84 to 1.29; P = .26; BMI, n = 154; mean difference, 0.77; 95% confidence interval, −0.24 to 1.78; P = .14).	Probiotics have limited efficacy in terms of decreasing body weight and BMI and were not effective for weight loss. However, the total number of randomized controlled trials included in the analysis, the total sample size, and the methodological quality of the primary studies were too low to draw definitive conclusions.
	BLOOD PRESSURE	
	ADULT	
Khalesi et al., Hypertension 2014[14] 9 parallel randomized, controlled trials, with 7 studies reporting a double-blind design. 543 participants in total	Probiotic consumption significantly changed systolic BP by −3.56 mmHg (95% confidence interval, −6.46 to −0.66) and diastolic BP by −2.38 mmHg (95% confidence interval, −2.38 to −0.93) compared with control groups. A greater reduction was found with multiple as compared with single species of probiotics, for both systolic and diastolic BP. Subgroup analysis of trials with baseline BP $\geq$ 130/85 mmHg compared with <130/85 mmHg found a more significant improvement in diastolic BP. Duration of intervention <8 weeks did not result in a significant reduction in systolic or diastolic BP. Furthermore, subgroup analysis of trials with daily dose of probiotics <10(11) colony-forming units did not result in a significant meta-analysis effect.	Consuming probiotics may improve BP by a modest degree, with a potentially greater effect when baseline BP is elevated, multiple species of probiotics are consumed, the duration of intervention is $\geq$ 8 weeks, or daily consumption dose is $\geq$ 10(11) colony-forming units.

Dyslipidemia

Concerning the effectiveness of probiotic intake in patients with dyslipidemia, the 4 meta-analyzes published to date, 3 on adults[10-12] and 1 on both adults and children[13] shown in Table 2, agree affirming that taking probiotics results in a significant reduction in total cholesterol and LDL cholesterol. As for HDL cholesterol, all studies show that intake of probiotics does not determine an increase.

As it regards the probiotic strains evaluated in these 4 meta-analysis, 2 of them[10,11] that there is a greater efficacy of *Lactobacillus Acidophilus* than the other species in the reduction of total and LDL cholesterol.

Hypertension

As for the effectiveness of probiotics intake in patients with hypertension, the unique meta-analysis,[14] reported in Table 2, noted that the intake of probiotics leads to an improvement in systolic and diastolic blood pressure, especially if the baseline blood pressure is $\geq$ 130/85 mmHg, with a treatment duration of at least 8 weeks, with the use of multiple strains and with a daily consumption of 10^{11} or more colony forming units.

Obesity

Regarding the effectiveness of probiotics in weight control, the 2 meta-analysis, both published in 2015, presented in Table 2, show conflicting results: one[15] shows that the intake of probiotics results in a significant reduction of body weight and of the body Mass Index (BMI) reporting that the weight loss is more consistent if the assumption is performed for a time greater than 8 weeks and when taken multiple strains. The other meta-analysis[16] instead shows that there is no efficiency in terms of weight and BMI reduction.

Disorders of the gastro-intestinal tract

Helicobacter pylori

As for the effectiveness of probiotic intake in both adult and pediatric patients, receiving treatment of the eradication of Helicobacter Pylori, 5[17-21] of the 6 meta-analysis published to date, shown in Table 3,[17-22] agree on a significant improvement of the eradication rate of bacteria when probiotics were used in combination with standard therapy for the eradication. With regard to the side effects of antibiotic therapy used for the eradication, the 5 meta-analysis also show that intake of probiotics helps in the control of these side effects and, in particular, the antibiotic-associated diarrhea.

The meta-analysis do not specify whether there are any more effective strains in treatment, although in 2 meta-analysis[17,20] combinations of probiotics containing *Acidophilus* and *Lactobacilus Bifidobactemium animalis* are taken into account, and then the authors conclude that association of these 2 strains is more effective than the single strain.

Inflammatory bowel diseases

With regard to the effectiveness of the probiotics intake in patients having inflammatory bowel diseases (IBD), 2 Cochrane were published, reported in Table 3: a 2011 Cochrane specific for ulcerative colitis in adult patient[23] and the other Cochrane in 2006 specifically for Crohn's disease in adult and pediatric patients.[24] Both Cochranes agree in reporting that there is insufficient evidence to demonstrate that the administration of probiotics can be helpful in maintaining remission in patients with IBD.

Conversely a more recent meta-analysis published in 2014,[25] presented in Table 3, however, shows that treatment with probiotics may be an useful therapeutic option for adult and pediatric patients with ulcerative colitis both in combination with specific therapy that in the maintenance phase. For both adult and pediatric patients having Crohn's disease, this meta-analysis confirms the results of the 2 previously mentioned Cochrane analyses, reporting that there is no evidence of effectiveness.

Irritable bowel syndrome

Concerning the effectiveness of probiotics in adult patients with irritable bowel syndrome, the only meta-analysis today published,[26] reported in Table 3, agrees on the effectiveness of the use of probiotics in reducing the pain and severity of symptoms related, thus demonstrating a beneficial effect of probiotics compared with placebo.

Constipation

As for the effectiveness of probiotics in adult patients with constipation, the only meta-analysis published today,[27] reported in Table 3, shows that their use may improve intestinal transit, the evacuation frequency and consistency of the faeces, with a subgroup

Table 3. Gastrointestinal pathologies.

Authors and study patecipants	Results	Conclusions
	HELICOBACTER PYLORI	
	ADULT	
Chao L et al., Sci Rep 2016[22] 21 randomized controlled trials (n = 3349) that investigated the effect of combining probiotics, with or without a placebo, with standard therapy	Probiotics with triple therapy plus a 14-day course of treatment did not improve the eradication of H. pylori infection (OR 1.44, 95% CI: 0.87, 2.39) compared with the placebo. Moreover, the placebo plus standard therapy did not improve eradication rates compared with standard therapy alone (P = 0.816). However, probiotics did improve the adverse effects of diarrhea and nausea.	The use of probiotics plus standard therapy does not improve the eradication rate of H. pylori infection compared with the placebo.
	ADULT + PEDIATRIC	
McFarland et al., United European Gastroenterol J 2016[17] 19 randomized controlled trials (20 treatment arms, n = 2730) assessing one of 6 mixtures of strains of probiotics.	Four multi strain probiotics significantly improved H. pylori eradication rates, 5 significantly prevented any adverse reactions and 3 significantly reduced antibiotic-associated diarrhea. Only 2 probiotic mixtures (*Lactobacillus Acidophilus/Bifidobacterium animalis* and an 8-strain mixture) had significant efficacy for all 3 outcomes.	There are adjunctive use of some multi-strain probiotics that may improve H. pylori eradication rates and prevent the development of adverse events and antibiotic-associated diarrhea, but not all mixtures were effective.
Zhang et al., World J Gastroenterol 2015[18] 6997 participants from 45 randomized, controlled trials investigating the effect of a combination of probiotics and standard therapy (probiotics group) with standard therapy alone (control group)	The use of probiotics plus standard therapy was associated with an increased eradication rate by per-protocol set analysis (RR = 1.11; 95%CI: 1.08–1.15; P < 0.001) or intention-to-treat analysis (RR = 1.13; 95%CI: 1.10–1.16; P < 0.001). Furthermore, the incidence of adverse events was 21.44% in the probiotics group and 36.27% in the control group, and it was found that the probiotics plus standard therapy significantly reduced the risk of adverse events (RR = 0.59; 95%CI: 0.48–0.71; P < 0.001), which demonstrated a favorable effect of probiotics in reducing adverse events associated with H. pylori eradication therapy. The specific reduction in adverse events ranged from 30% to 59%, and this reduction was statistically significant. Finally, probiotics plus standard therapy had little or no effect on patient compliance (RR = 0.98; 95%CI: 0.68–1.39; P = 0.889).	The use of probiotics plus standard therapy was associated with an increase in the H. pylori eradication rate, and a reduction in adverse events resulting from treatment in the general population. However, this therapy did not improve patient compliance
Zhu et al., World J Gastroenterol 2014[19] 14 randomized controlled trials with 2259 partecipants in total	The pooled ORs for the eradication rates in the probiotic group vs the control group were 1.67 (95%CI: 1.38–2.02) and 1.68 (95%CI: 1.35–2.08), respectively, using the fixed-effects model. The sensitivity of the Asian studies was greater than that of the Caucasian studies (Asian: OR = 1.78, 95%CI: 1.40–2.26; Caucasian: OR = 1.48, 95%CI: 1.06–2.05). The pooled OR for the incidence of total adverse effects was significantly lower in the probiotic group (OR = 0.49, 95%CI: 0.26–0.94), using the random effects model, with significant heterogeneity (I (2) = 85.7%). The incidence of diarrhea was significantly reduced in the probiotic group (OR = 0.21, 95%CI: 0.06–0.74), whereas the incidence of taste disorders, metallic taste, vomiting, nausea, and epigastric pain did not differ significantly between the probiotic group and the control group.	Supplementary probiotic preparations during standard triple H. pylori therapy may improve the eradication rate, particularly in Asian patients, and the incidence of total adverse effects.
Zheng et al., Rev Esp Enferm Dig 2013[20] 9 randomized controlled trials with 1163 patients	*Lactobacillus*-containing probiotics significantly increased the eradication rate compared with the control group based upon intention-to-treat analysis [RR = 1.14; 95%CI (1.06–1.22); number needed to treat (NNT) = 10] by the fixed effect model without significant publication bias, but no significant reduction associated with overall side effects was observed [RR = 0.88; 95%CI (0.73- 1.06)]. In the subgroup analysis, eradication rates raised significantly by 17% in lactobacillus administrated alone group [RR = 1.25; 95%CI (1.13–1.37); NNT = 6]. In multistrain probiotics group, eradication rates enhanced only 2.8% [RR = 1.04; 95%CI (0.94–1.14)]. It also showed that lactobacillus containing probiotics improved the	*Lactobacillus*-containing probiotic as an adjunct is effective to eradication therapy, while side effects caused by eradication treatment may not decrease. Furthermore, *Lactobacillus* administrated alone will distinctly benefit eradication therapy.

(*continued on next page*)

Table 3. (*Continued*)

Authors and study patecipants	Results	Conclusions
	eradication rates, respectively, both in adults [RR = 1.12; 95%CI (1.04–1.20); NNT = 12] and in children [RR = 1.25; 95%CI (1.01–1.53); NNT = 7].	
	PEDIATRIC	
Li et al., Eur J Pediatr 2014[21] 7 studies consisting of 508 pediatric patients comparing probiotics supplementation with placebo or no extra intervention in H. pylori eradication therapy	The pooled ORs of eradication rates by intention-to-treat and per-protocol analysis in the probiotics group versus the control group were 1.96 (95 % CI 1.28–3.02) and 2.25 (95 % CI 1.41–3.57), respectively. The pooled OR (studies n = 5) of incidence of total side effects was 0.32 (95 % CI 0.13–0.79), with significant heterogeneity observed (I (2) = 71.9 %).	Probiotics supplementation in triple therapy for H. pylori infection may have beneficial effects on eradication and therapy-related side effects, particularly diarrhea, in children.
	INFLAMMATORY BOWEL DISEASES	
	ADULT	
Naidoo et al., Cochrane Database Syst Rev 2011[23] 4 randomized controlled trials (587 subjects) that compared probiotics against placebo or any other intervention for the maintenance of remission in ulcerative colitis 3 trials compared probiotics to mesalazine and 1 trial compared probiotics with placebo	There was no statistically significant difference between probiotics and mesalazine for maintenance of remission in UC. Relapse was reported in 40.1% of patients in the probiotics group compared with 34.1% of patients in the mesalazine group (3 studies; 555 patients: OR 1.33; 95% CI 0.94 to 1.90 ; I(2) = 11%). Twenty-six per cent of patients in the probiotics group experienced at least one adverse event compared with 24% of patients in the mesalazine group (2 studies; 430 patients OR 1.21; 95% CI 0.80 to 1.84; I(2) =27%). Adverse events reported in the mesalazine-controlled studies include diarrhea, mucous secretion, bloody stools, abdominal pain, flatulence and distension, nausea and vomiting and headache. A small placebo controlled trial (n = 32) found no statistically significant difference in efficacy. Seventy-five per cent of probiotic patients relapsed at one year compared with 92% of placebo patients (OR 0.27; 95% CI 0.03 to 2.68). Adverse events reported in the placebo-controlled study include flatulence, abdominal bloating and pain, changes in faecal consistency, arthralgia, sacroiliitis, tiredness, incontinence, stress, oral blisters, eye dryness, headache, dizziness, influenza, gastroenteritis, cystitis and pneumonia.	There is insufficient evidence to make conclusions about the efficacy of probiotics for maintenance of remission in UC. There is a lack of well-designed RCTs in this area and further research is needed.
	ADULT + PEDIATRIC	
Fujiya et al., Clin J Gastroenterol 2014[25] 20 randomized controlled trials with a total of 1004 subjects, which investigated the therapeutic efficacy of probiotics on IBD.	Beneficial effects of probiotic treatments to improve the response rate and remission rate on the remission induction therapies [risk ratio (RR) 1.81; 95 % confidence interval (CI) 1.40–2.35 and RR 1.56; 95 % CI 0.95–2.56, respectively] were verified. Furthermore, probiotic treatments exhibited effects equal to mesalazine on the maintenance of remission in UC (RR 1.00; 95 % CI 0.79–1.26). In contrast, no significant effect of probiotic treatments was shown in either the induction or maintenance of remission in CD.	Probiotic treatment is a practical option for UC patients as both remission induction and maintenance therapy, but such treatment is not effective in CD patients.
Rolfe et al., Cochrane Database Syst Rev 2006[24] 7 randomized controlled trials (160 subjects) of probiotic therapy	There was no statistically significant benefit of E. coli Nissle for reducing the risk of relapse compared with placebo (RR 0.43, 95% CI 0.15 to 1.20), or Lactobacillus GG after surgically-induced remission (RR 1.58, 95% CI 0.30 to 8.40) or medically-induced remission (RR 0.83, 95% CI 0.25 to 2.80). There was no statistically significant benefit of probiotics for reducing the risk of relapse compared with maintenance therapy using aminosalicylates or azathioprine (RR 0.67, 95% CI 0.13 to 3.30), and in this study the probiotic Lactobacillus GG was associated with adverse events. In children, there was there was no statistically significant difference between Lactobacillus GG and placebo for reducing the risk of relapse (RR 1.85, 95% CI 0.77 to 4.40). A small study using the yeast Saccharomyces	There is no evidence to suggest that probiotics are beneficial for the maintenance of remission in CD. Larger trials are required to determine if probiotics are of benefit in Crohn's disease.

	boulardii demonstrated a difference that was not statistically significant in favor of probiotic combined with a reduced level of maintenance therapy over standard maintenance treatment alone (RR 0.17, 95% CI 0.02 to 1.23).	
	IRRITABLE BOWEL SINDROME	
	ADULT	
Didari et al., World J Gastroenterol 2015[26] 15 studies in patients with IBS that investigated the efficacy of probiotics in IBS improvement, eligible for meta-analysis and 9 reviewed systematically with a total of 1793 patients	The RR of responders to therapies based on abdominal pain score in IBS patients for 2 included trials comparing probiotics to placebo was 1.96 (95%CI: 1.14–3.36; P = 0.01). RR of responders to therapies based on a global symptom score in IBS patients for 2 included trials comparing probiotics with placebo was 2.43 (95%CI: 1.13–5.21; P = 0.02). For adequate improvement of general symptoms in IBS patients, the RR of 7 included trials (6 studies) comparing probiotics with placebo was 2.14 (95%CI: 1.08–4.26; P = 0.03). Distension, bloating, and flatulence were evaluated using an IBS severity scoring system in 3 trials (2 studies) to compare the effect of probiotic therapy in IBS patients with placebo, the standardized effect size of mean differences for probiotics therapy was −2.57 (95%CI: −13.05–7.92).	Probiotics reduce pain and symptom severity scores. The results demonstrate the beneficial effects of probiotics in IBS patients in comparison with placebo
	CONSTIPATION	
	ADULT	
Dimidi et al., Am J Clin Nutr 2014[27] 14 randomized controlled trials that reported administration of probiotics in adults with functional constipation (1182 patients)	Overall, probiotics significantly reduced whole gut transit time by 12.4 h (95% CI: −22.3, −2.5 h) and increased stool frequency by 1.3 bowel movements/wk (95% CI: 0.7, 1.9 bowel movements/wk), and this was significant for *Bifidobacterium lactis* (WMD: 1.5 bowel movements/wk; 95% CI: 0.7, 2.3 bowel movements/wk) but not for *Lactobacillus casei Shirota* (WMD: −0.2 bowel movements/wk; 95% CI: −0.8, 0.9 bowel movements/wk). Probiotics improved stool consistency (SMD: +0.55; 95% CI: 0.27, 0.82), and this was significant for *B. lactis* (SMD: +0.46; 95% CI: 0.08, 0.85) but not for *L. casei Shirota* (SMD: +0.26; 95% CI: −0.30, 0.82). No serious adverse events were reported. Attrition and reporting bias were high, whereas selection bias was unclear due to inadequate reporting.	Probiotics may improve whole gut transit time, stool frequency, and stool consistency, with subgroup analysis indicating beneficial effects of *B. lactis* in particular. Adequately powered RCTs are required to better determine the species or strains, doses, and duration of use of probiotics that are most efficacious.
	CHEMORADIOTHERAPY INDUCED DIARRHEA	
	ADULT	
Wang et al., Eur J Clin Nutr 2016[30] 11 trials with 1265 participants	Probiotic groups were compared with control groups with respect to the the incidence of diarrhea, OR = 0.47 (95% confidence interval 0.28–0.76; P = 0.002). Eleven studies, including 1612 people (873 consuming probiotics and 739 not consuming probiotics), were used for the analysis of safety of probiotics. Of the 11 studies, 7 studies had no adverse events (AEs) caused by probiotics, whereas 4 studies reported varying degrees of AEs in their treatment.	Probiotics may have a beneficial effect in prevention of chemoradiotherapy-induced diarrhea generally, especially for Grade 2 diarrhea. Probiotics may rarely cause AEs
	ANTIBIOTIC-ASSOCIATED DIARRHEA	
	ADULT + PEDIATRIC	
Goldenberg et al., Cochrane Database Syst Rev 2015[28] 23 studies (3938 participants)	The incidence of AAD in the probiotic group was 8% (163/1992) compared with 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35 to 0.61; I (2) = 55%, 3898 participants). A GRADE analysis indicated that the overall quality of the evidence for this outcome was moderate. This benefit remained statistically significant in an extreme plausible (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the	Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. The pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that

(*continued on next page*)

Table 3. (*Continued*)

Authors and study patecipants	Results	Conclusions
	control group had diarrhea) sensitivity analysis, where the incidence of AAD in the probiotic group was 14% (330/2294) compared with 19% (426/2235) in the control group (RR 0.69; 95% CI 0.54 to 0.89; I(2) = 63%, 4529 participants). None of the 16 trials (n = 2455) that reported on adverse events documented any serious adverse events attributable to probiotics. Meta-analysis excluded all but an extremely small non-significant difference in adverse events between treatment and control (RD 0.00; 95% CI −0.01 to 0.01). The majority of adverse events were in placebo, standard care or no treatment group. Adverse events reported in the studies include rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite.	adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Although no serious adverse events were observed among otherwise healthy children, serious adverse events have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events.
	CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA ADULT	
Goldenberg et al., Cochrane Database Syst Rev 2013[29] 31 randomized controlled (placebo, alternative prophylaxis, or no treatment control) trials investigating probiotics (any strain, any dose) for prevention of CDAD, or C. difficile infection (4492 participants). 23 trials with 4213 participants who completed the study.	The incidence of CDAD was 2.0% in the probiotic group compared with 5.5% in the placebo or no treatment control group (RR 0.36; 95% CI 0.26 to 0.51). Sixteen of 23 trials had missing CDAD data ranging from 5% to 45%. There were few events (154) and the calculated optimal information size (n = 8218) was more than the total sample size. With respect to the incidence of C. difficile infection, a secondary outcome, pooled complete case results from 13 trials (961 participants) did not show a statistically significant reduction. The incidence of C. difficile infection was 12.6% in the probiotics group compared with 12.7% in the placebo or no treatment control group (RR 0.89; 95% CI 0.64 to 1.24). The pooled complete case analysis indicates probiotics reduce the risk of adverse events by 20% (RR 0.80; 95% CI 0.68 to 0.95). In both treatment and control groups the most common adverse events included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. For the short-term use of probiotics in patients that are not immunocompromised or severely debilitated, the strength of this evidence is moderate.	

analyzed would indicate that the beneficial effects of *Bifidobacterium Lactis* in particular.

Antibiotic-associated diarrhea

Regarding the effectiveness of probiotics in pediatric patients with antibiotic-associated diarrhea, a 2015 Cochrane publication,[28] shown in Table 3, stressed that their use in pediatric patients may have a pivotal protective role in preventing antibiotic-associated diarrhea. Among the various strains evaluated, in particular *Lactobacillus rhamnosus* and *Saccharomyces boulardii* taken in quantity 50^{11} of colony forming units/day have proven useful, also given the low probability of the occurrence of adverse events.

Clostridium difficile-associated diarrhea

As for the effectiveness of probiotics in adult patients with diarrhea associated with Clostridium difficile (CDAD), a Cochrane analysis from 2013,[29] presented in table 10, was published, which showed that the use of probiotics represent a safe means and effective for the treatment of this disease, reducing the risk by 64%.

Diarrhea related to chemotherapy

With regard to the effectiveness of probiotics in adult patients with diarrhea associated with chemotherapy performed for the presence of abdominal or pelvic cancer, the only meta-analysis to date published,[30] reported in Table 3, stressed as their use could have a beneficial effect in the prevention of diarrhea, in particular grade 2 diarrhea, without causing adverse events.

Allergic diseases

Atopic and hypersensitivity syndrome to food in children

As for the effectiveness of probiotics in pediatric patients with atopic syndrome and hypersensitivity to food, 3 different meta-analyses,[31-33] shown in Table 4, have evaluated the effects of the intake of probiotics in the prevention of atopic syndrome, allergic disease and hypersensitivity related to food in children. According to 2007 Cochrane concerning the prevention of allergic disease and food hypersensitivity,[19] although there was a reduction in infant eczema, these data were not enough to recommend the supplementation of probiotics in infant. The other 2 most recent studies[20,21] have demonstrated that children treated with probiotics prenatally have lower levels of eczema, with no differences in terms of asthma, wheezing, and rhino-conjunctivitis. Even atopic syndrome and hypersensitivity to food shows a marked improvement in those who are treated with probiotics, as long as the duration of treatment covers the entire prenatal and postnatal periods

Allergic rhinitis

Concerning the effectiveness of probiotics in both adult and pediatric patients with allergic rhinitis, the 2 meta-analyses to date in the literature, shown in Table 4, have reported conflicting results: the 2015 study[34] has shown that there is not enough evidence to support the concept of the preventive role of probiotics in allergic rhinitis, even if probiotics improve the quality of life and nasal symptoms; conversely, the 2016 meta-analysis by Guvenc[35] which considered 22 double-blind randomized trials, has shown that probiotics, especially *L. paracasei*, have an important role in the treatment of allergic rhinitis.

Other diseases

Respiratory tract infections

As for the effectiveness of probiotics in patients both adults and children hospitalized in intensive care with ventilator-associated pneumonia, (VAP), the 2014 Cochrane[36] and a meta-analysis[37] presented in Table 5, are in agreement on the results: to date there is inadequate evidence to recommend probiotics as a routine therapy.

With regard to the effectiveness of probiotics for the prevention and therapy of respiratory tract infections in children, the only meta-analysis to date in the literature[38] has shown that the consumption of probiotics significantly reduces the number of subjects with at least 1 episode of respiratory tract infections; furthermore, children supplemented with probiotics showed the number of days with fever per person and number of days of absence from the nest/school lower than in children who were given a placebo. However, there was no statistically-significant difference in disease duration between the intervention group with probiotics and placebo.

Concerning the effectiveness of the probiotic intake for the prevention and therapy of respiratory tract infections, in children, in adults and in the elderly, the Cochrane analysis published in 2015[39] showed that

Table 4. Allergic diseases.

Authors and study partecipants	Results	Evidences
	ATOPIC DISEASES AND FOOD HYPERSENSITIVITY PEDIATRIC	
Zhang et al., Medicine (Baltimore) 2016[31] 17 trials involving 2947 infants	Probiotics administered prenatally and postnatally could reduce the risk of atopy (relative risk [RR] 0.78; 95% confidence interval [CI] 0.66–0.92; I = 0%), especially when administered prenatally to pregnant mother and postnatally to child (RR 0.71; 95% CI 0.57–0.89; I = 0%), and the risk of food hypersensitivity (RR 0.77; 95% CI 0.61–0.98; I = 0%). When probiotics were administered either only prenatally or only postnatally, no effects of probiotics on atopy and food hypersensitivity were observed.	Probiotics administered prenatally and postnatally appears to be a feasible way to prevent atopy and food hypersensitivity in young children. The long-term effects of probiotics, however, remain to be defined in the follow-up of existing trials.
Zuccotti et al., Allergy 2015[32] 17 studies, reporting data from 4755 children (2381 in the probiotic group and 2374 in the control group) evaluating the use of probiotics during pregnancy or early infancy for prevention of allergic diseases	Infants treated with probiotics had a significantly lower RR for eczema compared with controls (RR 0.78 [95% CI: 0.69–0.89], P = 0.0003), especially those supplemented with a mixture of probiotics (RR 0.54 [95% CI: 0.43–0.68], P < 0.00001). No significant difference in terms of prevention of asthma (RR 0.99 [95% CI: 0.77–1.27], P = 0.95), wheezing (RR 1.02 [95% CI: 0.89–1.17], P = 0.76) or rhino-conjunctivitis (RR 0.91 [95% CI: 0.67–1.23], P = 0.53) was documented.	The prevention of infantile eczema represents a potential indication for probiotic use during pregnancy and early infancy
Osborn et al., Cochrane Database Syst Rev 2007[33] 6 studies, that compared the use of a probiotic to a control (placebo or no treatment), or used a specific probiotic compared with a different probiotic, or used a specific probiotic compared with the same probiotic combined with a prebiotic ('symbiotic'), enrolling 2080 infants but reporting outcomes for only 1549 infants.	There were excess losses in patient follow-up (17% to 61%). Meta-analysis of 5 studies reporting the outcomes of 1477 infants found a significant reduction in infant eczema (typical RR 0.82, 95% CI 0.70, 0.95). One study reported that the difference in eczema between groups persisted to 4 y age. When the analysis was restricted to studies reporting atopic eczema (confirmed by skin prick test or specific IgE), the findings were no longer significant (typical RR 0.80, 95% CI 0.62, 1.02). All studies reporting significant benefits used probiotic supplements containing L. rhamnosus and enrolled infants at high risk of allergy. No other benefits were reported for any other allergic disease or food hypersensitivity outcome.	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.
	ALLERGIC RHINITIS ADULT + PEDIATRIC	
Peng et al., Am J Rhinol Allergy 2015[34] 22 randomized, double-blind, placebo-controlled studies (n = 2242, n =1953 after losses to follow-up)	Seventeen trials showed significant benefit of probiotics clinically, whereas 8 trials showed significant improvement in immunologic parameters compared with placebo. All 5 studies with *Lactobacillus paracasei* (LP) strains demonstrated clinically significant improvements compared with placebo. Probiotics showed significant reduction in nasal and ocular SS (standardized mean difference [SMD], −1.23, p < 0.001; and SMD, −1.84, p < 0.001; respectively), total, nasal, and ocular QoL scores compared with placebo (SMD, −1.84, p < 0.001; SMD, −2.30, p = 0.006; and SMD, −3.11, p = 0.005; respectively). Although heterogeneity was high, in subgroup analysis, SMD for total nasal and ocular symptoms with patients with seasonal AR and for nasal QoL scores for studies with *LP-33* strain were significant and homogenous. Scores of nasal blockage, rhinorrhea, and nasal itching were significantly lower in the probiotic group compared with placebo. The meta-analysis studies SS the Japanese guidelines revealed a significant, homogenous SMD score of −0.34 for individual nasal SS, above the minimal important clinical difference value of 0.3. The T-helper 1 to T-helper 2 ratio was significantly lower in the probiotic group compared with placebo (SMD,-0.78; p = 0.045).	Despite high variability among the studies, synthesis of available data provided significant evidence of beneficial clinical and immunologic effects of probiotics in the treatment of AR, especially with seasonal AR and *LP-33* strains.
Guvenc et al., Am J Rhinol Allergy 2016[35] 11 randomized, controlled trials of the use of probiotics for the prevention and treatment of allergic rhinitis (n = 1833)	Probiotic intake was associated with a significant overall improvement of the quality of life scores and nasal symptom scores of patients with AR (MD −2.97 [95% CI, −4.77 to −1.16)]; p = 0.001). No improvements with regard to prevention or immunologic parameters were noted in the patients with AR.	The current evidence is not sufficiently strong to verify a preventive role of probiotics in AR, but probiotics may improve the overall quality of life and nasal symptom scores. Because the available data were generated from only a few trials with a high degree of heterogeneity, routine use of probiotics for prevention and treatment in patients with AR cannot be recommended.

Table 5. Other disease.

Authors and study partecipants	Results	Evidences
	LIVER DISEASES ADULT	
Xu et al., Hepatobiliary Pancreat Dis Int 2014[42] 6 randomized controlled trials involving 496 liver cirrhotic patients	The results showed that probiotic therapy significantly reduced the development of overt hepatic encephalopathy (OR [95% CI]: 0.42 [0.26, 0.70], P = 0.0007). However, probiotics did not affect mortality, levels of serum ammonia and constipation (mortality: OR [95% CI]: 0.73 [0.38, 1.41], P = 0.35; serum ammonia: WMD [95% CI]: −3.67 [−15.71, 8.37], P = 0.55; constipation: OR [95% CI]: 0.67 [0.29, 1.56], P = 0.35).	Probiotics decrease overt hepatic encephalopathy in patients with liver cirrhosis.
Ma et al., World J Gastroenterol 2013[40] 4 randomized trials involving 134 NAFLD/NASH patients	Probiotic therapy significantly decreased alanine aminotransferase (ALT), aspartate transaminase (AST), total-cholesterol (T-chol), high density lipoprotein (HDL), tumor necrosis factor (TNF)-α and homeostasis model assessment of insulin resistance (HOMA-IR) [ALT: weighted mean difference (WMD) −23.71, 95%CI: −33.46–13.95, P < 0.00001; AST: WMD −19.77, 95%CI: −32.55–7.00, P = 0.002; T-chol: WMD −0.28, 95%CI: −0.55–0.01, P = 0.04; HDL: WMD −0.09, 95%CI: −0.16–0.01, P = 0.03; TNF-α: WMD −0.32, 95%CI: −0.48–0.17, P < 0.0001; HOMA-IR: WMD −0.46, 95%CI: −0.73–0.19, P = 0.0008]. However, the use of probiotics was not associated with changes in body mass index (BMI), glucose (GLU) and low density lipoprotein (LDL) (BMI: WMD 0.05, 95%CI: −0.18–0.29, P = 0.64; GLU: WMD 0.05, 95%CI: −0.25–0.35, P = 0.76; LDL: WMD −0.38, 95%CI: −0.78–0.02, P = 0.06).	Probiotic therapies can reduce liver aminotransferases, total-cholesterol, TNF-α and improve insulin resistance in NAFLD patients. Modulation of the gut microbiota represents a new treatment of NAFLD.
McGee et al., Cochrane Database Syst Rev 2011[41] 7 randomized, controlled trials with 550 participants. 4 of the 7 trials compared a probiotic with placebo or no treatment in 245 participants, another trial compared a probiotic with lactulose in 40 participants , and the remaining 2 trials compared a probiotic with both placebo and lactulose in 265 participants	When probiotics were compared with no treatment, there was no significant difference in all-cause mortality (2 trials, 105 participants; 1/57 (2%) vs. 1/48 (2%): RR 0.72; 95% CI 0.08 to 6.60), lack of recovery (4 trials, 206 participants; 54/107 (50%) vs. 68/99 (69%): RR 0.72; 95% CI 0.49 to 1.05), adverse events (3 trials, 145 participants; 2/77 (3%) vs. 6/68 (9%): RR 0.34; 95% CI 0.08 to 1.42), quality of life (1 trial, 20 participants contributed to the physical quality of life measurement, 20 participants contributed to the mental quality of life: MD Physical 0.00; 95% CI −5.47 to 5.47; MD Mental 4.00; 95% CI −1.82 to 9.82), or change of/or withdrawal from treatment (3 trials, 175 participants; 11/92 (12%) vs. 7/83 (8%): RR 1.28; 95% CI 0.52 to 3.19). No trial reported sepsis or duration of hospital stay as an outcome. Plasma ammonia concentration was significantly lower for participants treated with probiotic at one month (3 trials, 226 participants: MD −2.99 μmol/L; 95% CI −5.70 to −0.29) but not at 2 months (3 trials, 181 participants: MD −1.82 μmol/L; 95% CI −14.04 to 10.41). Plasma ammonia decreased the most in the participants treated with probiotic at 3 months (1 trial, 73 participants: MD −6.79 μmol/L; 95% CI −10.39 to −3.19). When probiotics were compared with lactulose no trial reported all-cause	While probiotics appear to reduce plasma ammonia concentration when compared with placebo or no intervention, is not possible to conclude that are efficacious in altering clinically relevant outcomes. Demonstration of unequivocal efficacy is needed before probiotics can be endorsed as effective therapy for hepatic encephalopathy.

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Table 5. (*Continued*)

Authors and study partecipants	Results	Evidences
	mortality, quality of life, duration of hospital stay, or septicaemia. There were no significant differences in lack of recovery (3 trials, 173 participants; 47/87 (54%) vs. 44/86 (51%): RR 1.05; 95% CI 0.75 to 1.47), adverse events (2 trials, 111 participants; 3/56 (5%) vs. 6/55 (11%): RR 0.57; 95% CI 0.06 to 5.74), change of/or withdrawal from treatment at one month (3 trials, 190 participants; 8/95 (8%) vs. 7/95 (7%): RR 1.10; 95% CI 0.40 to 3.03), plasma ammonia concentration (2 trials, 93 participants: MD −6.61 μmol/L; 95% CI −30.05 to 16.84), or change in plasma ammonia concentration (1 trial, 77 participants: MD 1.16 μmol/L; 95% CI −1.96 to 4.28).	
	ACUTE PANCREATITIS ADULT	
Xu et al. Hepatobiliary Pancreat Dis Int 2014[42] 6 trials comprising an aggregate total of 536 patients	Systematic analysis showed that probiotics did not significantly affect the pancreatic infection rate (RR = 1.19, 95% CI = 0.74 to 1.93; P = 0.47), total infections (RR = 1.09, 95% CI = 0.80 to 1.48; P = 0.57), operation rate (RR = 1.42, 95% CI = 0.43 to 3.47; P = 0.71), length of hospital stay (MD = 2.45, 95% CI = −2.71 to 7.60; P = 0.35) or mortality (RR = 0.72, 95% CI = 0.42 to 1.45; P = 0.25)	Probiotics showed neither beneficial nor adverse effects on the clinical outcomes of patients with predicted SAP. However, significant heterogeneity was noted between the trials reviewed with regard to the type, dose and treatment duration of probiotics, which may have contributed to the heterogeneity of the clinical outcomes. The current data are not sufficient to draw a conclusion regarding the effects of probiotics on patients with predicted SAP.
	BACTERIAL VAGINOSIS ADULT	
Gou et al., Crit Care 2014[43] 12 trials with 1304 patients	The pooled result showed that probiotics supplementation can significantly improve the cure rate in adult BV patients [risk ratio (RR) 1.53; 95 % confidence interval (CI) 1.19–1.97]. Findings were slightly different when analyses were restricted to 9 high-quality studies (RR 1.60; 95 % CI 1.16–2.22). In a subgroup meta-analysis, a statistically significant beneficial effect of probiotics was observed in Europe populations and short-term follow-up days.	Compared with the control arm, the limited evidence suggests that probiotics show a beneficial effect in patients who are having BV. However, the results should be interpreted cautiously because of the heterogeneity among study designs.
Huang H, et al. Arch Gynecol Obstet. 2014[44] 14 randomized controlled trials comparing probiotics with placebo, probiotics used in conjunction with conventional antibiotics compared with placebo or probiotics alone compared with conventional antibiotics for the treatment of women of any age diagnosed with bacterial vaginosis, (n = 452)	There was a beneficial outcome of microbiological cure with the oral metronidazole/probiotic regimen (OR 0.09 (95% CI 0.03 to 0.26)) and the probiotic/estriol preparation (OR 0.02, (95% CI 0.00 to 0.47)). For the probiotic/estriol preparation, the OR and 95% CI for physician-reported resolution of symptoms was OR 0.04 (95% CI 0.00 to 0.56).	There is no sufficient evidence for or against recommending probiotics for the treatment of BV. The metronidazole/probiotic regimen and probiotic/estriol perparation appear promising but well-designed randomized controlled trials with standardized methodologies and larger patient size are needed

	VENTILATOR-ASSOCIATED PNEUMONIA ADULT	
Bo et al., Cochrane Database Syst Rev 2014[36] 8 randomized controlled trials comparing probiotics with placebo or another control (excluding RCTs that use probiotics in both study groups) to prevent VAP, with 1083 partecipants	The use of probiotics decreased the incidence of VAP (odds ratio (OR) 0.70, 95% confidence interval (CI) 0.52 to 0.95, low quality evidence). However, the aggregated results were uncertain for ICU mortality (OR 0.84, 95% CI 0.58 to 1.22 very low quality evidence), in-hospital mortality (OR 0.78, 95% CI 0.54 to 1.14, very low quality evidence), incidence of diarrhea (OR 0.72, 95% CI 0.47 to 1.09, very low quality evidence), length of ICU stay (mean difference (MD) −1.60, 95% CI −6.53 to 3.33, very low quality evidence), duration of mechanical ventilation (MD −6.15, 95% CI −18.77 to 6.47, very low quality evidence) and antibiotic use (OR 1.23, 95% CI 0.51 to 2.96, low quality evidence). Antibiotics for VAP were used for a shorter duration (in days) when participants received probiotics in one small study (MD −3.00, 95% CI −6.04 to 0.04). However, the CI of the estimated effect was too wide to exclude no difference with probiotics. There were no reported events of nosocomial probiotic infections in any included study.	Evidence suggests that use of probiotics is associated with a reduction in the incidence of VAP. However, the quality of the evidence is low and the exclusion of the one study that did not provide a robust definition of VAP increased the uncertainty in this finding. The available evidence is not clear regarding a decrease in ICU or hospital mortality with probiotic use. Three trials reported on the incidence of diarrhea and the pooled results indicate no clear evidence of a difference. The results of this meta-analysis do not provide sufficient evidence to draw conclusions on the efficacy and safety of probiotics for the prevention of VAP in ICU patients.
Gu et al., Chest 2012[37] 7 randomized controlled trials comparing probiotics with control for VAP in adult patients undergoing mechanical ventilation (1142 patients)	Probiotics did not significantly decrease the incidence of VAP (OR, 0.82; 95% CI, 0.55–1.24; P 5 .35), with low heterogeneity among the studies (I 2 5 36.5%, P 5 .15). Probiotics also did not appear to significantly alter any of the other meta-analysis end points.	The limited evidence suggests that probiotics show no beneficial effect in patients who are mechanically ventilated; thus, probiotics should not be recommended for routine clinical application. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity among study designs. Future studies should focus on the safety of probiotics.
	RESPIRATORY TRACT INFECTIONS PEDIATRIC	
Wang et al., Medicine (Baltimore) 2016[38] A total of 23 trials involving 6269 children	Probiotic consumption significantly decreased the number of subjects having at least 1 RTI episode (17 RCTs, 4513 children, relative risk 0.89, 95% CI 0.82–0.96, P = 0.004). Children supplemented with probiotics had fewer numbers of days of RTIs per person compared with children who had taken a placebo (6 RCTs, 2067 children, MD −0.16, 95% CI −0.29 to 0.02, P = 0.03), and had fewer numbers of days absent from day care/school (8 RCTs, 1499 children, MD −0.94, 95% CI −1.72 to −0.15, P = 0.02). However, there was no statistically significant difference of illness episode duration between probiotic intervention group and placebo group (9 RCTs, 2817 children, MD −0.60, 95% CI −1.49 to 0.30, P = 0.19). ADULT + PEDIATRIC	Probiotics consumption appears to be a feasible way to decrease the incidence of RTIs in children.

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Table 5. (*Continued*)

Authors and study partecipants	Results	Evidences
Hao et al., Cochrane Database Syst Rev 2015[39] 13 RCTs , which involved 3720 participants including children, adults (aged around 40 years) and older people	probiotics were better than placebo when measuring the number of participants experiencing episodes of acute upper respiratory tract infections (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 3 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.	Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTI, the mean duration of an episode of acute URTI, antibiotic use and cold-related school absence. However, the quality of the evidence was low or very low.
	URINARY TRACT INFECTIONS ADULT + PEDIATRIC	
Senok et al., Cochrane Database Syst Rev 2009[45] 9 randomized controlled trials of 735 susceptible patients (e.g. past history of urinary tract infections -UTI) or healthy people in which any strain, formulation, dose or frequency of probiotic was compared with placebo or active comparators. 4 studies compared probiotic with placebo, 2 compared probiotic with no treatment, 2 compared probiotics with antibiotics in patients with UTI, and 1 study compared probiotic with placebo in healthy women	Overall, there was a high risk of bias in the included studies which lead to inability to draw firm conclusions and suggesting that any reported treatment effects may be misleading or represent overestimates. There was no significant reduction in the risk of recurrent symptomatic bacterial UTI between patients treated with probiotics and placebo (6 studies, 352 participants: RR 0.82, 95% CI 0.60 to 1.12; $I(2) = 23\%$) with wide confidence intervals, and statistical heterogeneity was low. No significant reduction in the risk of recurrent symptomatic bacterial UTI was found between probiotic and antibiotic treated patients (1 study, 223 participants: RR 1.12, 95% CI 0.95 to 1.33).The most commonly reported adverse effects were diarrhea, nausea, vomiting, constipation and vaginal symptoms. None of the included studies reported numbers of participants with at least one asymptomatic bacterial UTI, all-cause mortality or those with at least one confirmed case of bacteraemia or fungaemia. Two studies reported study withdrawal due to adverse events and the number of participants who experienced at least one adverse event. One study reported withdrawal occurred in 6 probiotic participants (5.2%), 15 antibiotic participants (12.2%), while the second study noted one placebo group participant discontinued treatment due to an adverse event.	No significant benefit was demonstrated for probiotics compared with placebo or no treatment, but a benefit cannot be ruled out as the data were few, and derived from small studies with poor methodological reporting. There was limited information on harm and mortality with probiotics and no evidence on the impact of probiotics on serious adverse events. Current evidence cannot rule out a reduction or increase in recurrent UTI in women with recurrent UTI who use prophylactic probiotics. There was insufficient evidence from one randomized controlled trial to comment on the effect of probiotics vs. antibiotics.

	PERIODONTITIS ADULT	
Schwenger et al., Cochrane Database Syst Rev 2015[46] 4 randomized controlled trials comparing scaling and root planing (SRP) + probiotic vs. SRP were included in the systematic review (n = 130). 3 trials were included in the meta-analysis.	Meta-analysis showed a statistically significant CAL gain (−0.42 mm, p = 0.002) and bleeding on probing (BOP) reduction (−14.66, p = 0.003) for SRP + probiotic treatment vs. SRP (scaling and root planning) at short-term. Only a tendency (p = 0.06) has been observed in terms of overall PPD reduction, whereas results were significant when stratified for moderate (−0.18, p = 0.001) and deep pockets (−0.67, p < 0.001).	The findings of the meta-analysis seem to support the adjunctive use of *L. reuteri* to SRP in CP treatment at short-term, especially in deep pockets. Heterogeneity and limited available data may reduce the impact of these conclusions.
	DEPRESSION ADULT	
Martin-Cabezas et al., J Clin Periodontol 2016[47]	Probiotics significantly decreased the depression scale score (MD (depressive disorder) = −0.30, 95% CI (−0.51–0.09), p = 0.005) in the subjects. Probiotics had an effect on both the healthy population (MD = −0.25, 95% CI (−0.47–0.03), p = 0.03) and patients with major depressive disorder (MDD) (MD = −0.73, 95% CI (−1.37–0.09), p =0.03).	Probiotics were associated with a significant reduction in depression, underscoring the need for additional research on this potential preventive strategy for depression.
5 trials, involving 183 cases and 182 controls	Probiotics had an effect on the population aged under 60 (MD = −0.43, 95% CI (−0.72–0.13), p = 0.005), while it had no effect on people aged over 65 (MD = −0.18, 95% CI (−0.47–0.11), p = 0.22).	
	POST-TRAUMATIC OUTCOMES ADULT + PEDIATRIC	
Huang et al., Nutrients 2016[48] 5 randomized controlled trials comparing the use of probiotics with a control in trauma patients (n= 281)	The use of probiotics was associated with a reduction in the incidence of nosocomial infections (5 trials; RR, 0.65; 95% CI, 0.45–0.94, P = .02), VAP (3 trials; RR, 0.59; 95% CI, 0.42–0.81, P = .001), and length of ICU stay (2 trials; SMD, −0.71; 95% CI, −1.09 to −0.34, P < .001) but no reduction in mortality (4 trials; RR, 0.63; 95% CI, 0.32–1.26, P = .19).	The use of probiotics is associated with a reduction in the incidence of nosocomial infections, VAP, and length of ICU stay but is not associated with an overall mortality advantage. However, the results should be interpreted cautiously due to the heterogeneity among study designs.
	PRETERM INFANTS	
Gu et al., JPEN J Parenter Enteral Nutr 2013[49] 37 randomized controlled trials (N = 9416)	Probiotics significantly decreased the risk of LOS (675/4852 [13.9%] vs 744/4564 [16.3%]; relative risk, 0.86; 95% confidence interval, 0.78–0.94; P = .0007; I(2) = 35%; number needed to treat, 44). The results were significant even after excluding studies with high risk of bias.	Probiotic supplementation reduces the risk of LOS in preterm infants.
Rao et al., Pediatrics 2016[50] 25 trials involving 6104 preterm neonates	Pooled analysis indicated that enteral probiotic supplementation significantly reduced the risk of any sepsis (25 RCTs; RR 0.83, 95% CI 0.73–0.94; I = 26%), bacterial sepsis (11 RCTs; RR 0.82, 95% CI 0.71–0.95; I = 0%), and fungal sepsis (6 RCTs; RR 0.57, 95% CI 0.41–0.78; I = 0%). This beneficial effect remains in very low birth weight infants (< 1500 g) (19 RCTs; RR 0.86, 95% CI 0.75–0.97; I = 18%), but not in extremely low birth weight infants (< 1000 g) (3 RCTs; RR 0.73, 95% CI 0.45–1.19; I = 53%). All the included trials reported no systemic infection caused by the supplemental probiotic organisms.	Current evidence indicates that probiotic supplementation is safe, and effective in reducing the risk of LOS in preterm neonates in neonatal intensive care units. Further studies are needed to address the optimal probiotic organism, dosing, timing, and duration.

(*continued on next page*)

Table 5. (*Continued*)

Authors and study partecipants	Results	Evidences
Sung et al., JAMA Pediatr 2013[52] 24 trials involved preterm infants < 37 weeks and birth weight < 2500 g, or both (2761 infants treated with probiotics and 2768 control infants) with enteral administration of probiotics	Enteral probiotics supplementation significantly reduced the incidence of severe necrotizing enterocolitis (NEC) (stage II or more) (typical relative risk (RR) 0.43, 95% confidence interval (CI) 0.33 to 0.56; 20 studies, 5529 infants) and mortality (typical RR 0.65, 95% CI 0.52 to 0.81; 17 studies, 5112 infants). There was no evidence of significant reduction of nosocomial sepsis (typical RR 0.91, 95% CI 0.80 to 1.03; 19 studies, 5338 infants). The included trials reported no systemic infection with the supplemental probiotics organism. Probiotics preparations containing either *Lactobacillus* alone or in combination with *Bifidobacterium* were found to be effective.	Enteral supplementation of probiotics prevents severe NEC and all cause mortality in preterm infants. This updated review of available evidence strongly supports a change in practice. Head to head comparative studies are required to assess the most effective preparations, timing, and length of therapy to be used.
Zhang et al., Medicine (Baltimore) 2016[51] 12 randomized, controlled trials that randomized infants 3 months or younger to oral probiotics vs placebo or no or standard treatment with the outcome of infant crying, measured as the duration or number of episodes of infant crying/distress or diagnosis of "infant colic (1825 infants)	6 studies suggested that probiotics reduced crying, and 6 did not. Three of the 5 management trials concluded probiotics effectively treat colic in breastfed babies; 1 suggested possible effectiveness in formula-fed babies with colic, and 1 suggested ineffectiveness in breastfed babies with colic. Meta-analysis of 3 small trials of breastfed infants with colic found that Lactobacillus reuteri markedly reduced crying time at 21 d (median difference, −65 minutes/d; 95% CI, −86 to −44). However, all trials had potential biases. Meanwhile, of 7 prevention trials, 2 suggested possible benefits. Considerable variability in the study populations, study type, delivery mode/dose of probiotic supplementation, and outcomes precluded meta-analysis.	Although *L. reuteri* may be effective as treatment of crying in exclusively breastfed infants with colic, there is still insufficient evidence to support probiotic use to manage colic, especially in formula-fed infants, or to prevent infant crying.

probiotics were better than placebo in reducing the number of people who had episodes of acute infection of the upper respiratory tract, in reducing the average episode length of acute infection of the upper respiratory tract, and in reducing the use of antibiotics and the number of days school/work off.

Liver diseases

As for the effectiveness of probiotics in patients with liver disease, such as non-alcoholic fatty liver disease (NAFLD) and hepatic encephalopathy, today in the literature we find 3 meta-analyses, shown in Table 5, 2 of which address adult patients with hepatic encephalopathy, and one on patients with NAFLD. The meta-analysis on NAFLD[40] showed that there is a decrease in the levels of liver aminotransferases and an improvement of insulin resistance. Conversely, there are conflicting results in 2 meta-analyses that consider probiotics in patients with hepatic encephalopathy: the 2011 Cochrane study,[41] despite the reduction of plasma ammonia in comparison with placebo, reported no demonstrated effectiveness in improving clinical outcomes, while the other meta-analysis,[42] despite also demonstrating no change in clinical outcomes, reports that probiotics can be helpful in the prevention of the occurrence of overt encephalopathy.

Acute pancreatitis

With regard to the effectiveness of probiotics in patients with acute pancreatitis, the only meta-analysis to date in the literature,[43] reported in Table 2, have shown no significant effect.

Bacterial vaginosis

As for the effectiveness of probiotics in patients with bacterial vaginosis, the 2 meta-analyses,[44,45] shown in Table 5, have not shown sufficient evidence to recommend the use of probiotics for women who suffer from this condition, although the early results are promising.

Urinary tract infections

Concerning the effectiveness of probiotics in adult patients with urinary tract infections, the only meta-analysis published in the literature to date,[46] shown in Table 5, pointed out that the available data do not allow to establish a valid conclusion.

Periodontitis

As for the effectiveness of probiotics in patients with peridodontitis, the only meta-analysis,[47] reported in Table 5, assessed the effects of using probiotics as an adjunct to non-surgical periodontal treatment of chronic periodontitis, showed that combination of SRP treatment (scaling and root planing) with the intake of *Lactobacillus reuteri* may be useful in the short term. However, due to the heterogeneity of the studies and the lack of abundance data available, further investigations are needed to verify than assumed.

Depression

With regard to the effectiveness of probiotics in patients with depression, the only meta-analysis to date in the literature,[48] reported in Table 5, showed that the intake of probiotics results in an improvement of mood, assessed by a decrease in the score of the scales used to assess the degree of depression in the population under 60.

Patients post-trauma

As for the effectiveness of probiotics in post-trauma patients, both adults and children, the only meta-analysis present in the literature,[49] reported in Table 5, considered the effectiveness of an early intake of probiotics, through enteral nutrition, on clinical outcomes, such as incidence of hospital infections, ventilator-associated pneumonia, the hospital stay in ICU and mortality. The meta-analyses showed that probiotics are a valuable aid to reduce the incidence of hospital infections, ventilator-associated pneumonia and hospitalization time in intensive care, but treatment with probiotics is not associated with reduce of mortality.

Premature birth

As for the effectiveness of probiotics in born pre-term patients, 2 meta-analysis,[50,51] shown in Table 5, which evaluated the correlation between probiotic supplementation (per os or enterally) and late-onset sepsis, bring into evidence that treatment with probiotics is capable of reducing the disease of bacterial and fungal origin, even if there are no indications about the type of probiotic used in the studies. Another meta-analysis of 2013,[52] which analyzed the presence of the "infant colic crying" with the supplementation of probiotics, in particular *Lactobacillus Reuteri*, showed that there

is still insufficient evidence to support probiotic use to manage colic or to prevent infant crying.

Concerning the necrotising enterocolitis in premature infants, the 2014 Cochorane study shows that supplementation with *Lactobacillus* or with the combination of *Lactobacillus* and *Bifidobacterium* reduces the incidence of this serious disease.[53]

Discussion

As regards the metabolic diseases (diabetes, dyslipidemia, obesity and hypertension), the meta-analysis showed that to demonstrate the efficacy of probiotics in favourably modifying the specific major metabolic outcomes (total cholesterol, LDL cholesterol, blood glucose, decreased body weight, decreased blood pressure), further well-conducted studies are required. Concerning the probiotic strains, 2 meta-analyses[10,11] agree that there is a greater efficacy of *Lactobacillus Acidophilus* than the other species in the reduction of total and LDL cholesterol.

As for the effectiveness of probiotic intake in both adult and pediatric patients, receiving treatment of the eradication of 'Helicobacter Pylori, 5[17-21] of the 6 meta-analyses published to date, agree on a significant improvement of the eradication rate of bacteria when probiotics were used in combination with standard therapy for the eradication. The meta-analysis do not specify whether there are any more effective strains in treatment, although in 2 meta-analysis[17,20] are taken into account combinations of probiotics containing *Acidophilus* and *Lactobacilus Bifidobactemium animalis*, and then the authors conclude that association of these 2 strains is more effective than the single strain.

Either in case of antibiotic-associated diarrhea (in adults and children) or in case of diarrhea associated to Clostridium difficile (in adults and elderly), the efficacy of probiotics was considered evidence based.

Regarding the effectiveness of probiotics in patients with antibiotic-associated diarrhea, among the various strains evaluated, in particular *Lactobacillus rhamnosus* and *Saccharomyces boulardii* taken in quantity 50[11] of colony-forming units/day, have proven useful by the 2015-published Cochrane analysis,[28] also given the low probability of the occurrence of adverse events.

Concerning Clostridium difficile-associated diarrhea (CDAD), Cochrane Database 2013[29] demonstrated that probiotics are both safe and effective for preventing CDAD; in particular, the results of this Cochrane study suggest that when probiotics are given with antibiotics, they reduce the risk of developing CDAD by 64%. Although probiotics are clearly superior to placebo or no treatment of preventing CDAD, further head-to-head trials are warranted to distinguish optimal strains and dosages: in fact, covariates of clinical interest such as strain and dose need to be evaluated further. The authors began with the hypothesis that the mechanism of action of various probiotics was similar and that any variation in effect would be due to chance.

As for the effectiveness of probiotics in adult patients with constipation, the only meta-analysis published today[27] shows that their use may improve intestinal transit, the evacuation frequency and consistency of the faeces, with a subgroup analyzed would indicate that the beneficial effects of *Bifidobacterium Lactis* in particular.

For irritable bowel syndrome, chemotherapy-associated diarrhea and IBD, the efficacy has yet to be demonstrated, though recently a meta-analysis by Fujiya[25] demonstrated that probiotic treatment is a practical option for ulcerative colitis patients as both remission induction and maintenance therapy, but such treatment is not effective in Crohn Disease patients.

In case of respiratory tract infection, the efficacy of probiotics (in adults and children) to reduce the number of infection episodes and the number of days of absence from school/work was considered evidence-based: the Cochrane study published in 2015[39] showed that probiotics were better than placebo in reducing both the number of people who have had episodes of acute infection of the upper respiratory tract, in reducing the average length of an episode of acute infection of the upper respiratory tract, and in reducing the use of antibiotics and the number of days school/work off. Although probiotics are clearly superior to placebo or no treatment of preventing respiratory tract infection, further trials are warranted to distinguish optimal strains and dosages, therefore the Cochrane study did not identify the types of strains and the dosages of administration.

Concerning allergic rhinitis (AR), despite high variability among the studies and therefore the need for further studies, synthesis of available data provided significant evidence of beneficial clinical and immunologic effects of probiotics in the treatment of AR,

especially with seasonal AR and in particular with *Lactobacillus paracasei-33* strains, as demonstrated by 2016 meta-analysis by Guvenc.[35]

Regarding ventilator-associated pneumonia in adults and children admitted to ICU, the efficacy of probiotics to modify the major clinical outcomes and mortality needs further well-conducted studies.

Considering liver diseases, vaginosis, urinary tract infections, periodontitis, depression and pancreatitis, the efficacy of probiotics has yet to be demonstrated with well-conducted studies. As for the effectiveness of probiotics in patients with peridodontitis, the only meta-analysis[47] assessed the effects of using probiotics as an adjunct to non-surgical periodontal treatment of chronic periodontitis, and showed that combination of SRP treatment (scaling and root planing) with the intake of *Lactobacillus reuteri* may be useful in the short term. However, due to the heterogeneity of the studies and the lack of abundance data available, further investigations are needed.

Concerning the necrotising enterocolitis in premature infants, the 2014 Cochorane study shows that supplementation with *Lactobacillus* or with the combination of *Lactobacillus* and *Bifidobacterium* reduces the incidence of this serious disease.[53]

In conclusion, some effects of probiotics are well documented, and their use alone or in combination with other therapies can therefore be considered "evidence-based," such as for antibiotic-associated diarrhea (in adults and children), and Clostridium difficile-associated diarrhea (in adults and elderly). In other clinical conditions, however, further studies are needed, because the available evidence is insufficient to show the efficacy of probiotics themselves. Carefully designed clinical trials are needed to validate the effects of particular strains of probiotics given at specific dosages and for specific treatment durations.

Disclosure of potential conflicts of interest

The authors report no conflict of interest.

ORCID

Mariangela Rondanelli http://orcid.org/0000-0001-8336-4851
Simone Perna http://orcid.org/0000-0002-2720-1473

References

[1] Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. Nat Rev Gastroenterol Hepatol 2010; 7:503-14; https://doi.org/10.1038/nrgastro.2010.117
[2] Egger M, Dickersin K, Smith GD. Problems and limitations in conducting systematic reviews. In: Egger M, Smith GD, Altman DG editors. Systematic Reviews in Health Care: Meta-Analysis in Context. London (UK): BMJ Books; 2001. 2nd ed, chapter 3
[3] Owens DK, Lohr KN, Atkins D, Treadwell JR, Reston JT, Bass EB, Chang S, Helfand M. Grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol 2010; 5(63):513-23; https://doi.org/10.1016/j.jclinepi.2009.03.009
[4] ISS (Istituti Superiore di Sanità). PNLG Programma Nazionale per le Linee Guida). Manuale Metodologico. Come produrre, diffondere e aggiornare raccomandazioni per la pratica clinica. 2002
[5] Zhang Q, Wu Y, Fei X. Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Medicina (Kaunas) 2016; 52:28-34; PMID:26987497; https://doi.org/10.1016/j.medici.2015.11.008
[6] Samah S, Ramasamy K, Lim SM, Neoh CF. Probiotics for the management of type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Res Clin Pract 2016; 118:172-82; https://doi.org/10.1016/j.diabres.2016.06.014
[7] Kasińska MA, Drzewoski J. Effectiveness of probiotics in type 2 diabetes: A meta-analysis. Pol Arch Med Wewn 2015; 125:803-13; PMID:26431318
[8] Ruan Y, Sun J, He J, Chen F, Chen R, Chen H. Effect of probiotics on glycemic control: A systematic review and meta-analysis of randomized, controlled trials. PLoS One 2015; 10:e0132121; PMID:26161741; https://doi.org/10.1371/journal.pone.0132121
[9] Sun J, Buys NJ. Glucose- and glycaemic factor-lowering effects of probiotics on diabetes: A meta-analysis of randomised placebo-controlled trials. Br J Nutr 2016; 115:1167-77; https://doi.org/10.1017/S0007114516000076
[10] Shimizu M, Hashiguchi M, Shiga T, Tamura HO, Mochizuki M. Meta-analysis: Effects of probiotic supplementation on lipid profiles in normal to mildly hypercholesterolemic individuals. PLoS One 2015; 10:e0139795; PMID:26473340; https://doi.org/10.1371/journal.pone.0139795
[11] Sun J, Buys N. Effects of probiotics consumption on lowering lipids and CVD risk factors: A systematic review and meta-analysis of randomized controlled trials. Ann Med 2015; 47:430-40; https://doi.org/10.3109/07853890.2015.1071872
[12] Guo Z, Liu XM, Zhang QX, Shen Z, Tian FW, Zhang H, Sun ZH, Zhang HP, Chen W. Influence of consumption of probiotics on the plasma lipid profile: A meta-analysis of randomised controlled trials. Nutr

Metab Cardiovasc Dis 2011; 21:844-50; https://doi.org/10.1016/j.numecd.2011.04.008

[13] Cho YA, Kim J. Effect of probiotics on blood lipid concentrations: A meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015; 94:e1714; PMID:26512560; https://doi.org/10.1097/MD.0000000000001714

[14] Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: A systematic review and meta-analysis of randomized, controlled trials. Hypertension 2014; 64:897-903; PMID:25047574; https://doi.org/10.1161/HYPERTENSIONAHA.114.03469

[15] Zhang Q, Wu Y, Fei X. Effect of probiotics on body weight and body-mass index: A systematic review and meta-analysis of randomized, controlled trials. Int J Food Sci Nutr 2015; 67:571-80; https://doi.org/10.1080/09637486.2016.1181156

[16] Park S, Bae JH. Probiotics for weight loss: A systematic review and meta-analysis. Nutr Res 2015; 35:566-75; https://doi.org/10.1016/j.nutres.2015.05.008

[17] McFarland LV, Huang Y, Wang L, Malfertheiner P. Systematic review and meta-analysis: Multi-strain probiotics as adjunct therapy for Helicobacter pylori eradication and prevention of adverse events. United European Gastroenterol J 2016; 4:546-61; https://doi.org/10.1177/2050640615617358

[18] Zhang MM, Qian W, Qin YY, He J, Zhou YH. Probiotics in Helicobacter pylori eradication therapy: A systematic review and meta-analysis. World J Gastroenterol 2015; 21:4345-57; https://doi.org/10.3748/wjg.v21.i14.4345

[19] Zhu R, Chen K, Zheng YY, Zhang HW, Wang JS, Xia YJ, Dai WQ, Wang F, Shen M, Cheng P, et al. Meta-analysis of the efficacy of probiotics in Helicobacter pylori eradication therapy. World J Gastroenterol 2014; 20:18013-21; PMID:25548501

[20] Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases Helicobacter pylori eradication rate: Evidence from a meta-analysis. Rev Esp Enferm Dig 2013; 105:445-53; https://doi.org/10.4321/S1130-01082013000800002

[21] Li S, Huang XL, Sui JZ, Chen SY, Xie YT, Deng Y, Wang J, Xie L, Li TJ, He Y, et al. Meta-analysis of randomized controlled trials on the efficacy of probiotics in Helicobacter pylori eradication therapy in children. Eur J Pediatr 2014; 173:153-61; https://doi.org/10.1007/s00431-013-2220-3

[22] Chao L, Jianzhong S, Haijian H, Xingyong W, Yiming L, Lan L, Youming L, Chaohui Y. Probiotic supplementation does not improve eradication rate of Helicobacter pylori infection compared to placebo based on standard therapy: A meta-analysis. Sci Rep 2016; 6:23522; PMID:26997149; https://doi.org/10.1038/srep23522

[23] Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2011; CD007443; PMID:22161412

[24] Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2006; CD004826; PMID:17054217

[25] Fujiya M, Ueno N, Kohgo Y. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: A meta-analysis of randomized controlled trials. Clin J Gastroenterol 2014; 7:1-13; PMID:26183502; https://doi.org/10.1007/s12328-013-0440-8

[26] Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. World J Gastroenterol 2015; 21:3072-84; https://doi.org/10.3748/wjg.v21.i10.3072

[27] Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K. The effect of probiotics on functional constipation in adults: A systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014; 100:1075-84; https://doi.org/10.3945/ajcn.114.089151

[28] Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev 2015; CD004827; PMID:26695080

[29] Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 2013; CD006095; PMID:23728658

[30] Wang YH, Yao N, Wei KK, Jiang L, Hanif S, Wang ZX, Pei CX. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: A systematic review and meta-analysis. Eur J Clin Nutr 2016; 70:1246-1253; PMID:27329608; https://doi.org/10.1038/ejcn.2016.102

[31] Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for Prevention of atopy and food hypersensitivity in early childhood: A PRISMA-Compliant systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016; 95:e2562; PMID:26937896; https://doi.org/10.1097/MD.0000000000002562

[32] Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, Fantini MP, Gori D, Indrio F, Maggio L, et al. Probiotics for prevention of atopic diseases in infants: Systematic review and meta-analysis. Allergy 2015; 7:1356-71; https://doi.org/10.1111/all.12700

[33] Osborn DA, Sinn J Probiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev 2007; CD006475; PMID:17943912

[34] Peng Y, Li A, Yu L, Qin G. The role of probiotics in prevention and treatment for patients with allergic rhinitis: A systematic review. Am J Rhinol Allergy 2015; 29:292-8; https://doi.org/10.2500/ajra.2015.29.4192

[35] Guvenc IA, Muluk NB, Mutlu FS, Eski E, Altintoprak N, Oktemer T, Cingi C. Do probiotics have a role in the treatment of allergic rhinitis?: A comprehensive systematic review and meta analysis. Am J Rhinol Allergy 2016; [Epub ahead of print]; PMID:27442711

[36] Bo L, Li J, Tao T, Bai Y, Ye X, Hotchkiss RS, Kollef MH, Crooks NH, Deng X. Probiotics for preventing

ventilator-associated pneumonia. Cochrane Database Syst Rev 2014; CD009066; PMID:25344083

[37] Gu WJ, Wei CY, Yin RX. Lack of efficacy of probiotics in preventing ventilator-associated pneumonia probiotics for ventilator-associated pneumonia: A systematic review and meta-analysis of randomized controlled trials. Chest 2012; 142:859-68; PMID:22797719; https://doi.org/10.1378/chest.12-0679

[38] Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, Zhang Y, Ho W, Yu G, Zhang T. Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016; 95:e4509; PMID:27495104; https://doi.org/10.1097/MD.0000000000004509

[39] Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev 2015; CD006895; PMID:25927096

[40] Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: A meta-analysis. World J Gastroenterol 2013; 19:6911-8; https://doi.org/10.3748/wjg.v19.i40.6911

[41] McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. Cochrane Database Syst Rev 2011; CD008716; PMID:22071855

[42] Xu J, Ma R, Chen LF, Zhao LJ, Chen K, Zhang RB. Effects of probiotic therapy on hepatic encephalopathy in patients with liver cirrhosis: An updated meta-analysis of six randomized controlled trials. Hepatobiliary Pancreat Dis Int 2014; 13:354-60; https://doi.org/10.1016/S1499-3872(14)60280-0

[43] Gou S, Yang Z, Liu T, Wu H, Wang C. Use of probiotics in the treatment of severe acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. Crit Care 2014; 18:R57; PMID:24684832; https://doi.org/10.1186/cc13809

[44] Huang H, Song L, Zhao W. Effects of probiotics for the treatment of bacterial vaginosis in adult women: A meta-analysis of randomized clinical trials. Arch Gynecol Obstet 2014; 289:1225-34; https://doi.org/10.1007/s00404-013-3117-0

[45] Senok AC, Verstraelen H, Temmerman M, Botta GA. Probiotics for the treatment of bacterial vaginosis. Cochrane Database Syst Rev 2009; CD006289; PMID:19821358

[46] Schwenger EM, Tejani AM, Loewen PS Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev 2015; CD008772; PMID:26695595

[47] Martin-Cabezas R, Davideau JL, Tenenbaum H, Huck O. Clinical efficacy of probiotics as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: A systematic review and meta-analysis. J Clin Periodontol 2016; 43:520-30; https://doi.org/10.1111/jcpe.12545

[48] Huang R, Wang K, Hu J. Effect of probiotics on depression: A systematic review and Meta-Analysis of randomized controlled trials. Nutrients 2016; 8:pii: E483; https://doi.org/10.3390/nu8080483

[49] Gu WJ, Deng T, Gong YZ, Jing R, Liu JC. The effects of probiotics in early enteral nutrition on the outcomes of trauma: A meta-analysis of randomized controlled trials. JPEN J Parenter Enteral Nutr 2013; 37:310-7; https://doi.org/10.1177/0148607112463245

[50] Rao SC, Athalye-Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic supplementation and Late-Onset sepsis in preterm infants: A Meta-analysis. Pediatrics 2016; 137:e20153684; PMID:26908700; https://doi.org/10.1542/peds.2015-3684

[51] Zhang GQ, Hu HJ, Liu CY, Shakya S, Li ZY. Probiotics for preventing late-onset sepsis in preterm neonates: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016; 95:e2581; PMID:26937897; https://doi.org/10.1097/MD.0000000000002581

[52] Sung V, Collett S, de Gooyer T, Hiscock H, Tang M, Wake M. Probiotics to prevent or treat excessive infant crying: Systematic review and meta-analysis. JAMA Pediatr 2013; 167:1150-7; https://doi.org/10.1001/jamapediatrics.2013.2572

[53] AlFaleh K, Anabrees J Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev 2014; CD005496; PMID:24723255