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Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea

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SUMMARY

Background: Antibiotic-associated diarrhoea can be attributed in part to imbalances in intestinal microflora. Therefore, probiotic preparations are used to prevent this diarrhoea. However, although several trials have been conducted, no conclusive evidence has been found of the efficacy of different preparations, e.g. *Lactobacillus* spp. and *Saccharomyces* spp.

Aim: To conduct a meta-analysis of the data in the literature on the efficacy of probiotics in the prevention of antibiotic-associated diarrhoea.

Methods: A literature search was performed of electronic databases, Abstract Books and single paper references. Data were also obtained from the authors. Only placebo-controlled studies were included in the search. The Mantel–Haenszel test was used to estimate the relative risk for single studies and an overall combined relative risk, each study being submitted to the Mantel–Haenszel test for homogeneity.

Results: Twenty-two studies matched the inclusion criteria. Only seven studies (881 patients) were homogeneous. The combined relative risk was 0.3966 (95% confidence interval, 0.27–0.57).

Conclusions: The results suggest a strong benefit of probiotic administration on antibiotic-associated diarrhoea, but further data are needed. The evidence for beneficial effects is still not definitive. Published studies are flawed by the lack of a placebo design and by peculiar population features.

INTRODUCTION

Probiotics are defined as living microorganisms which may, on administration, colonize the human intestine and beneficially affect health.[1] Starting from this vague definition, moving towards a disease-orientated therapeutic approach with probiotics is complicated. The probiotic species used in clinical practice include *Lactobacillus* spp., *Saccharomyces* spp., *Bacillus subtilis*, *Bifidobacterium* spp. and many others.

Although a thorough scientific basis for the efficacy of probiotics in several conditions is lacking, preparations of different bacteria are commonly prescribed worldwide to overcome problems such as acute traveller's diarrhoea and antibiotic-associated diarrhoea, and even as adjuvant treatment of some complications in inflammatory bowel disease.

Acute diarrhoea, either viral or antibiotic-associated, has a high epidemiological relevance in developing countries, and also affects a consistent portion of the population in Western countries.[2] In particular, diarrhoea is a common side-effect of both the short- and long-term use of antibiotics. In the latter case, the negative influence of antibiotics on the bacterial steady state of the intestine is accepted as a possible mechanism.[3–7] It occurs in hospitalized patients and out-patients, and may be the reason for antibiotic withdrawal or further referral to care.

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The use of probiotics dates back decades, and results of single-centre studies have been encouraging in most cases. The efficacy of probiotics has been attributed to their possible immunostimulatory effect or to their role in keeping the bowel microecology stable by restoring resident flora.[8–10] However, there has been no systematic review evaluating the combined results of different published treatment trials on this topic.

The aim of this study was to perform a meta-analysis of published trials on the efficacy of probiotics in reducing the incidence of antibiotic-associated diarrhoea. For this purpose, only placebo-controlled trials were included in the analysis. Despite diarrhoea is closer to a clinical hard end-point than to a subjective symptom report, we preferred to include a lower number of placebo-controlled studies rather than a larger amount which included uncontrolled studies to improve validity of the present analysis. We included trials using *Lactobacillus* spp. or *Saccharomyces* spp. to restrict analysis to the most widely studied agents.

METHODS

We performed a computer-based search of MedLine and Cochrane registers and a manual search of Abstract Books of all major gastroenterology congresses and meetings over the past 15 years, searching for all studies performed between 1966 and 2001. Key words used for the computer-based search included diarrhoea, probiotic, *Lactobacillus*, *Saccharomyces boulardii*, antibiotic side-effects, with both and and OR as combination terms. The search was limited to randomized studies. The search also included papers published in languages other than English. In addition, personal unpublished data from authors and international experts were sought and, if relevant, considered. Two independent investigators, who did not take part in any of the trials initially selected, evaluated the quality of the trials according to quality criteria published by Nicolucci *et al.*[11] After excluding studies with serious design flaws (e.g. unclear definition of end-point, ambiguous treatment scheme), 22 trials were included in the initial analysis. Our intention, however, was to exclude all uncontrolled results. With this purpose in mind, the following inclusion criteria were used: studies with a placebo design, with diarrhoea considered as the primary end-point, and with a minimum of 2 weeks of follow-up. In addition, to provide a homogeneous definition of diarrhoea, we included data based on the presence/absence of diarrhoea, but excluded results based on differences in the amount of daily stool discharge. Where available, raw data from the authors of single studies were used. However, such data collection was not possible in all studies and statistical analysis was conducted on the basis of summary statistics.

Only seven placebo-controlled trials matched our inclusion criteria. The trials included were performed either with *Lactobacillus* spp. or *Saccharomyces boulardii*.[12–18]

The Mantel–Haenszel test of homogeneity was performed to assess the eligibility and level of comparability of the trials. Homogeneity was considered to be significant when $P < 0.05$, according to a chi-squared data distribution.[19, 20]

After study inclusion, a combined relative risk among studies was calculated according to the Mantel–Haenszel method. Confidence intervals were calculated according to the Cornifield formula.[21] The efficacy of treatment was evaluated from a per protocol analysis of the results of single studies. The level of significance for the determination of a beneficial effect of probiotic treatment on diarrhoea was a combined relative risk and confidence interval lower than 1.0. Data were collected and processed using STATA Software (Texas University, USA), version 6.0.[22]

In addition, a funnel scatterplot was drawn to estimate possible publication bias by plotting the odds ratios of the studies against the sample sizes.[23, 24]

RESULTS

Our initial search gave a total number of 41 studies published on probiotics and antibiotic-associated diarrhoea. After initial discrimination for randomized trials, 22 papers were found. Of these, only seven studies matched our criteria for randomized, placebo-controlled design, with a minimum of 2 weeks of follow-up and with the administration of a single probiotic species (Table 1).

Given the differences in methods and scales used to define and quantify diarrhoea, the trials accepted allowed the consideration of the occurrence of antibiotic-associated diarrhoea as a binomial (yes/no) variable. The threshold for patient loss at follow-up was a minimum of 15% in the studies considered.

A total number of 881 patients was studied in the included trials. Patients were all given either probiotic

Table 1. Design of single, randomized, placebo-controlled trials

Study	No. of patients	Age (range)	Antibiotic(s) used	Probiotic species	Therapy duration
Armuzzi *et al.*[18]	60	40 ± 12 years	Tinidazole, clarithromycin	*Lactobacillus GG*	14 days
Arvola *et al.*[15]	119	2 weeks–12.8 years	Oral antibiotic treatment	*Lactobacillus GG*	7–14 days
Gotz *et al.*[16]	79	Adult population	Ampicillin	*Lactobacillus* spp.	5 days
Lewis *et al.*[14]	62	Elderly population	Antibiotic treatment	*Saccharomyces boulardii*	7–14 days
McFarland *et al.*[17]	193	Adult population	β-Lactam antibiotic	*Saccharomyces boulardii*	7–14 days
Surawicz *et al.*[13]	180	Adult population	Penicillin, clindamycin, cephalosporins	*Saccharomyces boulardii*	7–14 days
Vanderhoof *et al.*[12]	188	6 months–10 years	Oral antibiotic treatment	*Lactobacillus GG*	7–14 days

or placebo during the course of antibiotic treatment. Of the seven clinical trials eligible for the review, three assessed the decrease in the occurrence of antibiotic-associated diarrhoea during administration of *Saccharomyces boulardii*,[13, 14, 17] and four during the administration of *Lactobacillus* spp.[12, 15, 16, 18]

The numbers of patients are presented in Table 1. A test for homogeneity gave $\chi^2 = 6.001$ with six degrees of freedom, with $P = 0.42$. The relative risks for individual studies are shown in Table 2. Three studies were significant with a relative risk and confidence interval lower than 1.0, two of which contained the highest numbers of subjects included. The Mantel–Haenszel combined relative risk was 0.3966 (95% confidence interval, 0.275–0.571) (Figure 1). Overall, probiotic supplementation was a protective factor with respect to the incidence of diarrhoea measured as a binomial (yes/no) variable.

The patient number can be used to indicate which are the most incisive studies for the evaluation of probiotic efficacy in the prevention of antibiotic-associated diarrhoea. Four randomized placebo-controlled trials included in the present meta-analysis enrolled more than 100 patients, with *Lactobacillus* spp. used in two studies and *Saccharomyces boulardii* in the other two. The remaining randomized controlled trials were conducted on a minimum of 60 patients in each study.

In the study conducted by McFarland *et al.*, 193 eligible, hospitalized patients received a β-lactam antibiotic as a new prescription and lyophilized *Saccharomyces boulardii* or placebo, with a relative risk, adjusted for two independent risk factors (age and days of cephalosporin administration), for antibiotic-associated diarrhoea significantly protective for *Saccharomyces boulardii* (relative risk, 0.29; 95% confidence interval, 0.08–0.98).[17] In addition, Surawicz *et al.* investigated

Table 2. Relative risks and confidence intervals from single studies

Study	Relative risk	95% confidence interval
Armuzzi *et al.*[18]	0.13	0.02–0.93
Arvola *et al.*[15]	0.3	0.08–1.05
Gotz *et al.*[16]	0.39	0.11–1.36
Lewis *et al.*[14]	1.13	0.38–3.30
McFarland *et al.*[17]	0.49	0.21–1.17
Surawicz *et al.*[13]	0.43	0.21–0.89
Vanderhoof *et al.*[12]	0.28	0.13–0.62

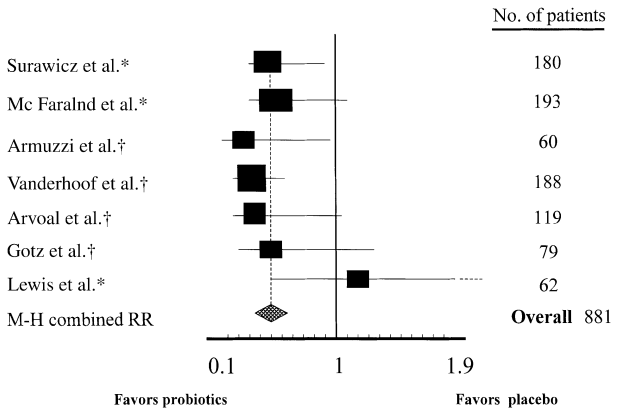

Figure 1. Forest diagram showing crude and combined risk ratios for eligible studies. *Study performed with *Saccharomyces boulardii*. †Study performed with *Lactobacillus* spp. M–H, Mantel–Haenszel; RR, relative risk.

Table 3. Definition of antibiotic-associated diarrhoea and additional testing in the different trials

Study	Definition of diarrhoea	Parallel laboratory testing
Armuzzi *et al.*[18]	Increased frequency of evacuation, loose stools	None
Arvola *et al.*[15]	Stool frequency and consistency	Viral and bacterial assessment of stool samples, metabolic activity of gut microflora
Gotz *et al.*[16]	Stool frequency	None
Lewis *et al.*[14]	Interdefecatory interval, stool form graded 1–4 (hard to liquid)	Four-day analysis of stool samples for *Clostridium difficile* toxin
McFarland *et al.*[17]	Loose or watery stools for at least 2 days	Presence of *Clostridium difficile* or its toxin in stools
Surawicz *et al.*[13]	Three or more loose or watery stools per day for at least 2 days	Presence of *Clostridium difficile* or its toxin in stools
Vanderhoof *et al.*[12]	Stool frequency and line drawings depicting stools numerically graded	None

the effect of *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in hospitalized patients given antibiotics and probiotic or placebo. Of the 180 patients enrolled, 22% of the placebo-treated patients experienced diarrhoea, but only 9.5% of the *Saccharomyces boulardii* group; it was concluded that the probiotic was a protective factor against antibiotic-associated diarrhoea. In addition, the authors evaluated whether there was an association between the presence of *Clostridium difficile* or cytotoxin and antibiotic-associated diarrhoea, and found no significant results.[13] The role of *Lactobacillus GG* in reducing the incidence of antibiotic-associated diarrhoea in children was studied by Vanderhoof *et al.* in 188 children with acute infectious disorders. *Lactobacillus GG* or placebo was co-administered with an antibiotic, and the data obtained showed the occurrence of diarrhoea in 25 patients in the placebo group compared with only seven children treated with *Lactobacillus GG*.[12] The aim of the study conducted by Arvola *et al.* was to evaluate the incidence of diarrhoea in 119 children treated with antibiotics for respiratory infection and *Lactobacillus GG* or placebo. Antibiotic-associated diarrhoea occurred in 5% of patients who received *Lactobacillus GG* and in 16% of the placebo group, indicating a significant preventative role of the probiotic. When diarrhoea occurred, viral and bacterial analyses of faecal samples were performed, and the activities of faecal urease, β-glucosidase and β-glucuronidase were measured. The data showed bacterial positivity for *Clostridium difficile* in two cases and for Norwalk-like calicivirus in three cases, and the metabolic activity of the intestinal flora changed after the administration of the antibiotic (faecal urease and β-glucuronidase, but not β-glucosidase).[15] The follow-up period of these studies ranged from 2 to 7 weeks. The largest studies, by McFarland *et al.*[17] and Vanderhoof *et al.*,[12] had follow-up times of 7 weeks and 10 days, respectively. Table 3 lists the different methods used to define diarrhoea in the selected studies.

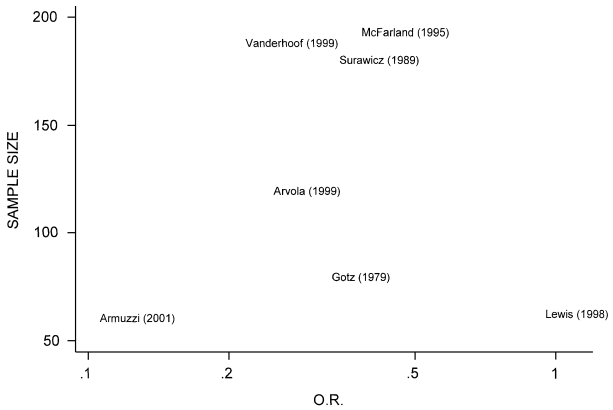

Figure 2. Funnel plot for studies: odds ratios (O.R.) vs. sample sizes.

In Figure 2, a funnel scatterplot shows the symmetrical distribution of the studies evaluated.

DISCUSSION

Although the rationale for probiotic effectiveness in antibiotic-associated diarrhoea is supported by a large number of animal studies, clinical data are disappointingly few. The somewhat vague definition of probiotics includes many species with many peculiar characteristics, all of which are safe and beneficial to human health. The beneficial effects result from several actions, including the restoration of 'normal' gut microflora, direct protection of the bowel wall and the stimulation of intestinal immunity against common pathogens.

However, different strains show different activities. Indeed, some commonly used bacteria may adhere to the bowel wall, thus remaining for some time at the required site of action, whilst others may not.[25–27] Some probiotics have been reported to stimulate local immunity in mice, some have been shown to produce substances toxic to pathogenic microorganisms and, moreover, anti-tumorigenic activity has recently been postulated.[28–32] Modulation of the intestinal permeability has also been reported for *Lactobacillus GG*.[33] Probiotic combinations have also shown encouraging results in clinical trials in patients with inflammatory bowel disease.[34, 35]

In addition, there are many forms of probiotic administration and, in particular, considerable differences in the number of microorganisms present in commercial preparations. It is not known to what extent variability in bacterial charge may result in a reduction or even elimination of the activity of commonly used preparations. Preparations available commercially usually contain more than 1 billion bacterial units.

To date, despite the extensive use of probiotics for antibiotic-associated diarrhoea by both primary care practitioners and specialists, no meta-analysis of literature data has been performed. Despite this lack of definitive data, the probiotic market is growing rapidly, with an estimated increase of 2 billion US dollars per year.[36]

In our study, we included investigations performed with *Lactobacillus* spp. and *Saccharomyces boulardii*, which represent the most widely studied species for the prevention of diarrhoea, and the only species on which results on antibiotic-associated diarrhoea have been published.

Although disagreement remains on the optimal doses required to obtain sufficient gut colonization, in all studies, an amount of probiotic was administered with a bacterial charge well above the minimum dose present in commercial preparations; it has been reported that several billions of microorganisms should be introduced into an organism.[27]

It is a flaw of all the published studies that no systematic assessment of the faecal recovery of *Lactobacillus* and *Saccharomyces boulardii* was performed parallel to administration. Such a procedure, although having the ability to detect a positive result in terms of the restoration of the microecology of the gut, would have been economically and technically demanding, especially when dealing with large sample sizes.

There are numerous case reports and case series using such probiotics present in the literature. Our decision to exclude non-placebo-controlled trials led to a considerable reduction in the number of studies considered for meta-analysis, but the reliability of the data was increased.

To overcome differences in the parameters used by different authors with regard to the registration and measurement of diarrhoeal events, the occurrence of antibiotic-associated diarrhoea was considered as a binomial (yes/no) variable, and data on phenomenon severity were not combined. However, only raw data were available for some of the studies, and this did not allow a complete evaluation of the results.

Our results showed an overall reduction in the risk of antibiotic-associated diarrhoea during probiotic administration in the studies considered.

As with other topics treated in clinical trials, publication bias should be considered. Indeed, especially in the case of probiotics, for which there are no highly specific or well-established pharmacodynamics, studies with negative results may not have been submitted or considered for publication.[37, 38] A funnel plot is a useful tool for the detection of bias in meta-analyses.[23] If no bias is present, the plot should resemble an inverted funnel. The number of studies included in our meta-analysis was seven. However, the shape of the plot was not asymmetrical or skewed. This can be taken as an index of adequate study selection.

It should also be considered that not all probiotics act in the same way or exert an identical final effect, and the conclusions drawn for a particular probiotic strain cannot be automatically extended to other microorganisms. Hence, conclusions from the studies included must not be regarded as valid for probiotic species other than those tested in the trials.

In addition, the subjects enrolled in the clinical trials considered here included paediatric patients. Therefore, the reader should not draw definitive conclusions applicable to adult populations. The subjects also came from various geographical areas and from widely heterogeneous socio-economic backgrounds, with developing countries representing a consistent portion.

Although antibiotic-associated diarrhoea in the considered trials was attributed to several antimicrobial agents, it should be borne in mind that at least one main pathogenic determinant of diarrhoea (i.e. microflora disruption) is common to all agents used. The analysis of the impact of single antimicrobial agents in

diarrhoea may be helpful in providing an explanation of the data, but data on the incidence of side-effects during antibiotic administration are discordant and difficult to calculate rigorously.

Although our data suggest an interesting role for probiotics in antibiotic-associated diarrhoea, confirming the uncontrolled experience from general practice world-wide, large-scale, multicentre, prospective data on the primary prevention of antibiotic-associated diarrhoea should be obtained. The lack of standardization of the probiotic preparations used calls for more equivalent formulations. Some authors have postulated the potential for an individually targeted probiotic approach, aiming to replace, in each patient, the bacterial species needed at that precise moment.[39] In the specific case of antibiotic-associated diarrhoea, probiotic preparations could be used to replace specific resident bacteria known to be sensitive to the antibiotic used. This latter approach will be better addressed when broader evidence on the specific immunomodulatory effects of different strains has been provided by *in vivo* studies. This could eventually result in the development of standardized, planned combinations of probiotics with fixed doses made available for specific conditions.

A complete message for prescribers, however, should include a cost–benefit analysis. Such an evaluation should be undertaken in future investigations, given the low cost and easy availability of probiotics in different countries and the relevance of antibiotic gastrointestinal side-effects in general practice, but also due to the increasing propensity of physicians to use agents which are cheap and often of uncertain effectiveness.

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