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Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis

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Abstract

Objective To evaluate efficacy of probiotics in prevention and treatment of diarrhoea associated with the use of antibiotics.

Design Meta-analysis; outcome data (proportion of patients not getting diarrhoea) were analysed, pooled, and compared to determine odds ratios in treated and control groups.

Identification Studies identified by searching Medline between 1966 and 2000 and the Cochrane Library.

Studies reviewed Nine randomised, double blind, placebo controlled trials of probiotics.

Results Two of the nine studies investigated the effects of probiotics in children. Four trials used a yeast (*Saccharomyces boulardii*), four used lactobacilli, and one used a strain of enterococcus that produced lactic acid. Three trials used a combination of probiotic strains of bacteria. In all nine trials, the probiotics were given in combination with antibiotics and the control groups received placebo and antibiotics. The odds ratio in favour of active treatment over placebo in preventing diarrhoea associated with antibiotics was 0.39 (95% confidence interval 0.25 to 0.62; $P < 0.001$) for the yeast and 0.34 (0.19 to 0.61; $P < 0.01$) for lactobacilli. The combined odds ratio was 0.37 (0.26 to 0.53; $P < 0.001$) in favour of active treatment over placebo.

Conclusions The meta-analysis suggests that probiotics can be used to prevent antibiotic associated diarrhoea and that *S boulardii* and lactobacilli have the potential to be used in this situation. The efficacy of probiotics in treating antibiotic associated diarrhoea remains to be proved. A further large trial in which probiotics are used as preventive agents should look at the costs of and need for routine use of these agents.

Introduction

The term "probiotic" was first used to describe "a live microbial supplement, which beneficially affects the host by improving its microbial balance."¹ Since then, research has looked at possible clinical uses for these agents. In 1995, when a greater understanding of their properties had developed, the term "biotherapeutic agents" was proposed to describe micro-organisms with specific therapeutic properties that also inhibit the growth of pathogenic bacteria.²

Probiotics and their uses

- Probiotics are live organisms that improve the microbial balance of the host
- Probiotics have special properties that make them useful in fighting infections of mucosal surfaces such as the gut and vagina
- Different species of lactobacilli and the yeast *Saccharomyces boulardii* have the potential for use in clinical practice
- Probiotics are becoming increasingly available as capsules and dairy based food supplements sold in health food stores and some supermarkets
- The relative lack of side effects makes probiotics a possible way of preventing antibiotic associated diarrhoea

A number of agents have been isolated and studied with a view to clinical use. *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, commonly used in the dairy food industry, were among the first to be studied. Other strains that have been used are *Bifidobacterium bifidum*, *B longum*, *Enterococcus faecium*, *Saccharomyces boulardii*, *L acidophilus*, *L casei*, and *Lactobacillus GG*. However, doctors are still reluctant to use these agents in clinical practice.

In this paper, we review the results from various trials carried out to study their benefits. We also look at the properties of biotherapeutic agents and options for further research.

Materials and methods

Literature search

We searched Medline between 1966 to 2000 with the terms "probiotics," "biotherapeutic agents," "lactobacilli," "antibiotic associated diarrhoea," and "*Clostridium difficile*." We also searched the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews. We included all randomised double blind trials that compared the effects of probiotic therapy and placebo (both given in combination with antibiotics).

Ten double blind placebo controlled trials were relevant to our area of interest (nine published in English and one in French).³⁻¹² Our meta-analysis included nine that looked at prevention of diarrhoea. We excluded the other trial, which looked at treatment of diarrhoea.¹²

Editorial by Barbut and Meynard

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Table 1 Probiotics studied in trials and patients with absence of diarrhoea at end of trial

Trial	Probiotic	Dose	Duration of treatment	Antibiotic studied	% of patients without diarrhoea	
					Active group	Placebo group
Adam et al ³	<i>S boulardii</i>	4 capsules/day	Variable	Mixture	96	83
Gotz et al ⁴	<i>L acidophilus</i> and <i>L bulgaricus</i>	1 sachet Lactinex four times a day	5 days	Ampicillin	100	86
Surawicz et al ⁵	<i>S boulardii</i>	1 g/day	Variable	Mixture	91	78
Wunderlich et al ⁶	<i>E faecium</i> SF68	1 capsule twice a day	7 days	Mixture	91	73
Tankanow et al ⁷	<i>L acidophilus</i> and <i>L bulgaricus</i>	1 g Lactinex four times a day	10 days	Amoxicillin	34	31
Orrhage et al ⁸	<i>L acidophilus</i> and <i>Bifidobacterium longum</i>	Fermented milk with cultures 250 ml twice a day	21 days	Clindamycin	80	30
McFarland et al ⁹	<i>S boulardii</i>	1 g/day	49 days	Mixture	93	85
Lewis et al ¹⁰	<i>S boulardii</i>	113 mg twice a day	14 days	Mixture	79	83
Vanderhoof et al ¹¹	<i>Lactobacillus</i> GG	1-2 capsules a day (10 ¹⁰ colonies per capsule)	10 days	Mixture	93	74

Meta-analysis and data abstraction

The meta-analysis was carried out according to the recommendations of the QUOROM statement.¹³ The key outcome data taken for analysis included the sample size, treatment regimens, and numbers of patients in both arms of the study who had an absence of diarrhoea (table 1).

Results

Nine trials were included in the final analysis (fig 1). The study regimens used probiotics combined with one antibiotic or a variety of antibiotics (table 1). All trials studied the efficacy of a probiotic in the prevention of antibiotic associated diarrhoea. The numbers of patients and the duration of follow up varied greatly from study to study, but the patients' characteristics were similar for the active treatment and placebo groups within each study.

We calculated the odds ratio on the basis of the proportion of patients free of diarrhoea on treatment compared with that in control groups. After tests of

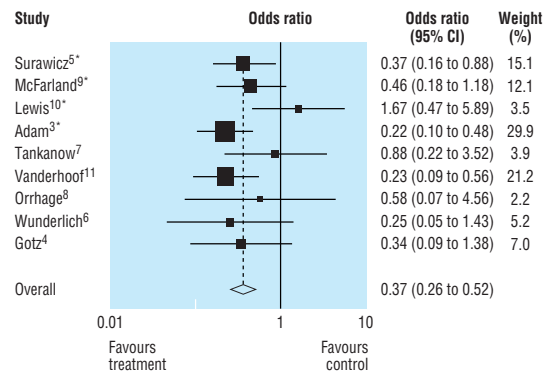


Fig 2 Plot of the log of odds ratios for the proportion of patients free of diarrhoea in treatment groups compared with control groups

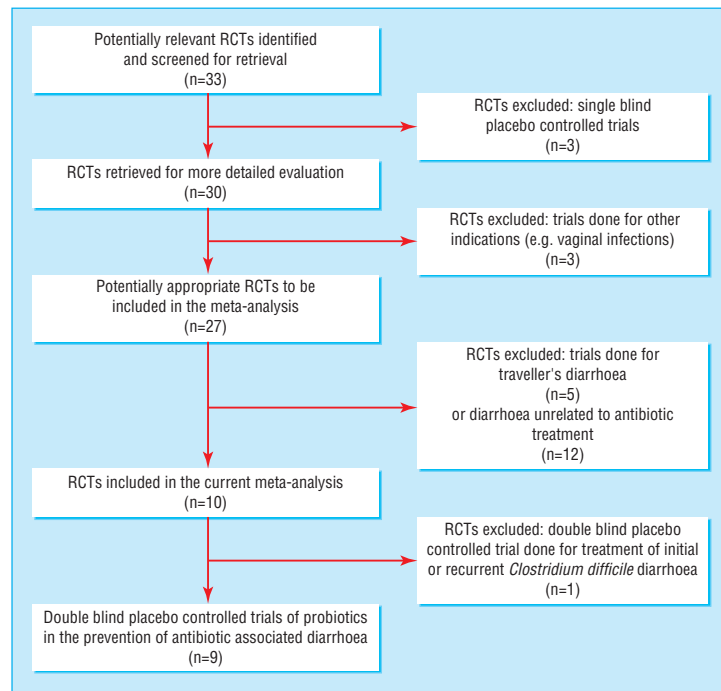


Fig 1 Meta-analysis profile summarising trial flow. RCT=randomised controlled trial

homogeneity, summary odds ratios and 95% confidence interval limits were provided for the combined data of the four trials that used *S boulardii* (yeast trials), the five non-yeast trials, and all nine trials together. The combined odds ratios for the four yeast trials and for the five non-yeast trials were similar (0.39 (95% confidence interval 0.25 to 0.62) and 0.34 (0.19 to 0.61), respectively); both favoured active treatment over placebo in the prevention of antibiotic associated diarrhoea. The odds ratio for pooled data from all nine trials was in favour of active treatment over placebo in the prevention of antibiotic associated diarrhoea (0.37; 0.26 to 0.53). Six studies showed a significant benefit of probiotic treatment compared with placebo (P<0.05) (fig 2).^{3 5 6 8 9 11} One study showed benefit for only a subgroup of patients who did not receive non-antibiotic drugs likely to induce diarrhoea, such as magnesium hydroxide (for constipation), lactulose, and bisacodyl (for hepatic encephalopathy).⁴

Discussion

Our meta-analysis of trials that used live organisms to prevent diarrhoea associated with antibiotics shows that probiotics may be effective in preventing antibiotic associated diarrhoea. We had only a small number of trials in our meta-analysis, and it should be noted that the different antibiotics used in the trials may have altered the risk of patients getting diarrhoea and their response to the probiotics. Although probiotics have been used to prevent or treat diarrhoea of other

causes—namely traveller's diarrhoea and infantile infectious diarrhoea—we did not include trials that investigated probiotics in these indications; however, most of these studies showed positive results, and some reviews have been encouraging.¹⁴

The way in which probiotics affect the gut has drawn much interest. To combat the problems of gastrointestinal infection, probiotics must be non-pathogenic and must act against pathogens by different mechanisms from antibiotics—for example, by competition. More importantly, they should have a fairly rapid onset of action and survive the challenges of gastric acid, bile, or concurrent antibiotics. It is also desirable that they modify immune processes to destroy the invading organism. *Saccharomyces boulardii* and lactobacilli display these common properties.

A few live organisms have been used in many trials. *S. boulardii*, a non-pathogenic yeast, is one such organism. It has a growth temperature of 37°C, rapidly colonises the bowel, does not alter the normal gut flora, and is cleared from the colon after treatment is discontinued.¹⁵ Of the four yeast trials, three studies individually showed significant benefit,^{3 5 9} but one did not¹⁰; differences in the dose and duration of treatment with *S. boulardii* and variations in the period of follow up may explain this disparity. Interestingly, *S. boulardii* can also destroy the receptor site for *C. difficile* toxin A and B by producing a protease¹⁶; this could explain how *S. boulardii* was noted to reduce the frequency of toxin B positivity.¹²

The other probiotic agent used widely in clinical trials is the *Lactobacillus* species. The mechanism of action of lactobacilli may be through multiple means: *Lactobacillus* GG has shown beneficial effects on intestinal immunity; it increases the numbers of cells that secrete immunoglobulin A and other immunoglobulins in the intestinal mucosa, and it stimulates the local release of interferon.¹⁷ It also facilitates antigen transport to underlying lymphoid cells, and shows increased uptake in Peyer's patches.¹⁷ *Lactobacillus* GG has also been shown to produce an antimicrobial substance that inhibits the growth of *Escherichia coli*, streptococci, *Clostridium difficile*, *Bacteroides fragilis*, and *Salmonella*.¹⁸ *L. casei shirota* also showed good survival in the gut in separate studies, and mucosal antibody titres (specific to lactobacilli) were increased in the presence of this agent.^{19 20} Although there was no discernible change to the numbers of clostridia or enterococci, there was an increase in the numbers of excreted bifidobacteria—a normal bowel anaerobe.^{19 20} It is possible that this increase in bifidobacteria interferes with the pathogenic potential of *C. difficile*.

Probiotics are a possible solution in the prevention of antibiotic-associated diarrhoea. *Clostridium difficile* infection is increasingly prevalent in today's hospital setting, particularly in elderly patients, in whom 10-20% of such cases occur.²¹ The incidence of antibiotic associated diarrhoea depends on the antibiotic used and each individual patient's risk factors. The standard regimens to treat colitis associated with *Clostridium difficile* are metronidazole and vancomycin; although these drugs are successful in 80% of cases, about 20% of patients suffer from recurrence.²² In light of the need to control costs in these days of managed health care, we must re-examine the benefits of using live organisms.

What is already known on this topic

Probiotics are well known for their microbiological properties and have been used to treat gastrointestinal and vaginal mucosal infections

Conflicting results have prevented probiotics from being accepted as viable alternatives to conventional treatments for antibiotic associated diarrhoea

The commercial availability of probiotics is increasing

What this study adds

Probiotics may prevent antibiotic associated diarrhoea

The potential of specific probiotics to prevent *Clostridium difficile* infection secondary to the use of antibiotics should be re-examined

A large trial looking at the efficacy of probiotics in preventing antibiotic associated diarrhoea, particularly in elderly patients, with an emphasis on the optimal dose and cost benefits is needed

Whether the use of probiotics can actually reduce the length of hospital stay by reducing the incidence of infection with *C. difficile* and the need to use antibiotics such as metronidazole and vancomycin are issues that need to be addressed in a clinical trial.

Conclusion

Our meta-analysis of nine trials shows that biotherapeutic agents may be useful in preventing antibiotic associated diarrhoea.

The increasing availability, lower costs, and relative lack of side effects of probiotics contrast with the problems associated with current antibiotic regimens. Commercially available strains are being marketed in capsules and yoghurt based drinks, but their potential benefit needs further investigation. Data from trials have provided us with clear evidence on the efficacy of some strains in the gut, but we still need to see confirmation of their clinical benefit.

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Science commentary: Probiotics

Probiotics are microbes that protect their host, and in some cases they can prevent disease. They are immunomodulating bacteria that have very low virulence compared with the more pathogenic gut flora such as *Escherichia coli* and clostridia. *Lactobacilli* and bifidobacteria are examples of probiotics found in the large intestine.

Lactobacillus GG can prevent diarrhoea and atopy in children.^{1,2} In the gut, probiotic bacteria are thought to occupy binding sites on the gut mucosa, preventing pathogenic bacteria from adhering to the mucosa. *Lactobacilli* also produce proteinaceous compounds—bacteriocins—that act as local antibiotics against more pathogenic organisms. But what is known about what happens in vitro cannot necessarily be extrapolated to the complexity of the ecosystem of the human gut.

Diarrhoea associated with antibiotics is presumed to result from the antibiotics disrupting the normal flora in the gut of a healthy person. Such disruptions cause dysfunction of the gut's ecosystem, and they may allow pathogenic bacteria to colonise the gut and gain access to the mucosa. Whether probiotic supplements stop this process by reducing the disruption or by acting as substitutes for the healthy flora is unclear. Probiotics may compete with pathogens for the nutrients the pathogens need to grow, or they may modify toxins produced by pathogens or toxin receptors

found in the gut wall, or they may stimulate immune responses to pathogens.

The exact mechanisms by which probiotics prevent atopy are also under debate.³ One suggestion is that the establishment and maintenance of innate immune tolerance is mediated by T helper 1 cells and linked in some way to the faecal flora. If the Th1 response is particularly robust, the allergic response mediated by T helper 2 cells tends not to be so strong. Probiotics may prevent atopy by supporting the faecal flora, strengthening the Th1 response, and reducing the allergic response.

In the countries of continental Europe, probiotics are regarded as medicines, and they are prescribed alongside antibiotics. In other countries, probiotics are marketed as supplements and are sold over the counter—although preparations such as “bioyoghurts” do not always contain probiotic strains proved to be clinically useful.

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A memorable patient Can you hear me?

The young woman, brought by the police, looked past me, perplexed, eyes darting around the room. Some of my questions obtained brief answers, some none. Not all the answers were for me; “But he can't be dead” seemed a response to another voice than mine.

As I was about to launch into further questions to establish a diagnosis, I was caught by a recollection of an earlier voice. It was that of the ward sister on the busy medical ward where, as a psychiatric registrar, I would assess people who had taken overdoses. I had noticed the young woman lying unconscious for over a week and had wondered, as I passed, whether she would ever recover. Approaching the next bed I heard the voice of the ward sister—a woman I regarded as efficient and a little

intimidating. I paused and listened (psychiatrists are generally inquisitive). Her voice was soft and barely audible above the bustle and beeping monitors, as she gently reminded the young woman where she was, what was happening, and who had visited, even adding snippets of ward gossip.

The woman in front of me now seemed lost in a world of voices, confusion, and fears. I realised that, while I needed to elicit symptoms to clarify diagnosis and establish a rational treatment plan, I must also try to explain what was and was not happening and, as far as possible, help her contact some reality through the fears provoked by psychotic symptoms.

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