Safety of probiotics: comparison of two popular strains

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Mounting clinical evidence shows that nutritional supplements of live micro-organisms (probiotics) have health advantages to humans. The appeal of probiotic therapy lies in the fact that it not only represents a non-invasive attempt to recreate natural flora rather than a disruption of nature, but it is also an approach that is both cheap and effective.

However, the concept of willingly ingesting live bacteria remains somewhat counterintuitive. Although probiotic therapy is generally considered harmless, rare reports of systemic infections involving probiotic bacteria have raised clinical concerns. We therefore conducted a scientific review of the safety of these organisms. For the purpose of this review, we assumed therapeutic effectiveness and concentrated primarily on evaluating the safety of this treatment. Although many such reviews exist, previous authors have taken a uniform approach—they have mostly reported anecdotal case reports of infection or infection rates with the strain under investigation and then generalised their findings to all probiotics. We have tried to isolate the different safety profiles of diverse probiotic strains.

Background

The human intestine is home to more than a trillion live bacteria from about 400 species. The average adult body contains about 20 times more bacteria than it does cells.¹ In the natural environment a delicate symbiosis evolves between these endogenous bacteria and

their host. The vital contribution of natural flora to normal intestinal development is underscored by studies of animals raised in a germ-free environment. These animals have hypoplastic intestinal epithelia, reduced gut immunity, and impaired peristalsis—all of which improve only when normal gut flora are introduced.²

Exogenous probiotics are given therapeutically in situations where this naturally beneficial symbiosis has been disturbed, in an attempt to restore normal flora, as in the above animal model. A 2004 Cochrane review reported probiotic therapy to be effective in reducing diarrhoea,³ and a recent report summarising 185 studies found that probiotics successfully treated 68 different conditions in widely diverse populations.⁴

Retrospective reviews

In 1990 *Lactobacillus rhamnosus* GG was introduced universally into dairy products in Finland. National surveillance of bloodstream infections by Finland's National Public Health Institute showed that bacteraemia due to *Lactobacillus* did not increase with increased consumption.⁵ *Lactobacilli* were found in 0.02% of all blood cultures and 0.2% of blood cultures with some bacterial growth.

A subsequent study reviewed the records of 89 patients with lactobacillaemia from this same Finnish population.⁶ The patients were mostly aged over 60 and had severe underlying diseases; 39% had polymicrobial bacteraemia. However, despite the widespread supplementation of dairy products with *Lactobacillus*, the retrospective data did not allow us to tell which people ate dairy products and thus ingested probiotics. Another retrospective review of patients with lactobacillaemia also showed a predominance of severe underlying conditions and multiple organisms, and probiotic ingestion was not mentioned in any of the patients.⁷

Lactobacillaemia is probably under diagnosed in non-supplemented populations, as the growth of *Lactobacillus* requires special media and long incubation periods, its morphology resembles that of members of other genera, and it is often dismissed as a contaminant. One series from Vanderbilt University, USA, reviewed 53 cases accumulated over a 12 year period,⁷ and another retrospective literature review presents 200 cases over a 53 year interval.⁸ Analysis of these retrospective reviews provides little evidence that ingested probiotic bacteria pose a risk of infection

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Pills containing two different species of *Lactobacillus*

Sources and selection criteria

This review is based on the conclusions of recent randomised clinical trials, Cochrane controlled trials, and European Society of Paediatric Gastroenterology, Hepatitis, and Nutrition reviews of probiotic therapy. We also searched Medline using the keywords “probiotics”, “*Lactobacillus*”, “*Bifidobacterium*”, “sepsis”, and “bacteremia”.

We reviewed prospective randomised trials of probiotic therapy, looking for reports of intercurrent sepsis, as well as case reports of potentially probiotic associated infections not related to ongoing studies and retrospective population based reviews. We gave preference to articles published after 1995.

greater than that associated with endogenous commensal strains.

Prospective studies

Although immunocompromised patients are especially vulnerable to infection, prospective studies have shown that probiotics are safe in immunocompromised adults and children with HIV.^{9–10} In preterm neonates, another relatively immunocompromised population, probiotics reduce the incidence and severity of necrotising enterocolitis, with no secondary probiotic infections seen to date.^{11–12}

Because the numbers studied were small, individual prospective studies were insufficiently powered to exclude slight increases in sepsis. Even when they are all pooled, however, no cases of sepsis due to *Lactobacillus* were reported among them.

Case reports of infection

Anecdotal cases of *Lactobacillus* infection do exist, mostly in elderly patients. A 74 year old woman with diabetes who ingested *L. rhamnosus* for four months developed a liver abscess infected with this organism.¹³ A 67 year old man with mitral valve regurgitation who regularly consumed probiotic capsules, which he opened and chewed, developed an infection with *L. rhamnosus* after a tooth extraction.¹⁴ Most of the rare cases of infection with lactobacilli have occurred in elderly patients, but anecdotal case reports also exist in infants. Land et al described a 6 week old infant, with severe underlying medical problems, who developed sepsis due to *Lactobacillus* after ingesting lactobacilli.¹⁵ Two other case reports describe borderline premature neonates with short gut syndrome and chronic intestinal inflammation who developed sepsis due to *Lactobacillus* after treatment with *Lactobacillus* GG. The authors thought that the inflamed friable mucosa in these infants allowed increased translocation of otherwise non-pathogenic bacteria, although they warn that inadvertent contamination and line sepsis cannot be excluded. The organisms responsible for the sepsis were typed and attributed to the probiotic supplements in one case only.¹⁶

Analysis

Lactobacillus infections are rare, especially as these organisms are abundant in normal flora and

ubiquitous in the human diet. Lactobacillaemia may thus occur naturally, without exogenous administration. Which infections are caused by natural flora becoming pathogenic as a result of breached mucosal barriers and which are due to probiotic ingestion is difficult to assess.

We need to weigh potential benefits against possible harm, knowing that the data will probably never be absolute. Relevant data can be divided into two categories—firstly, population surveys, both retrospective and prospective; and secondly, anecdotal case reports that retrospectively try to establish some connection to prior ingestion of probiotics. Neither category provides a truly scientific evidence based overview of the safety of probiotics, and definitive data will probably never exist. If, based on Finnish estimates, 0.02% of blood cultures are positive for lactobacilli, more than 166 000 patients would need to be studied prospectively to detect a 10% increase in bacteraemia due to *Lactobacillus* (calculated for power=0.80, $\alpha=0.05$). But even this is an underestimate, as blood was cultured in the Finnish study for clinical indications; the expected yield would be lower if we routinely cultured blood from healthy patients who ingested probiotics prophylactically.

Furthermore, safety cannot be defined as an absolute risk-free condition but should be evaluated in context. The risk and morbidity of sepsis due to *Lactobacillus*, which usually resolves with simple antibiotics, should be weighed against the potential for sepsis due to more pathological bacteria and the morbidity of the diseases we are trying to prevent (such as necrotising enterocolitis). In fact, the presence of lactobacillaemia has been proposed as a marker of serious underlying illness and poor long term prognosis.¹⁷

On the basis of existing data, probiotics have been declared safe, even in immunocompromised populations such as premature neonates. Between September 2000 and the end of January 2001 a workshop was convened.¹⁸ Recognised experts critically reviewed the current scientific and medical literature. They concluded that “Current evidence suggests that the risk of infection with probiotic lactobacilli or bifidobacterium is similar to that of infection with commensal strains, and that consumption of such products presents a negligible risk to consumers, including immunocompromised hosts.”

Finally, and perhaps most importantly, cases of probiotic associated bacterial sepsis that have been

Additional education resources

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Summary points

Lactobacilli and bifidobacteria are ubiquitous in the human diet and healthy intestine, and systemic infections with these bacteria may occur naturally, unrelated to ingestion of probiotics

Sepsis due to *Lactobacillus* has not been reported in prospective randomised studies of probiotics

The risk of sepsis due to *Lactobacillus* should be weighed against that of sepsis with more pathological species of bacteria and against that of the disease which probiotic therapy is meant to prevent (such as necrotising enterocolitis)

Most reported cases of bacteraemia or sepsis have been secondary to *Lactobacillus rhamnosus* GG or *Lactobacillus casei*

Different strains of probiotics have different safety profiles, which should be taken into account. Systemic infection has rarely been reported with *Bifidobacterium*

reported have mostly been secondary to lactobacilli. Bifidobacteria only rarely cause septic complications. A Medline search of "*Bifidobacterium*" and "sepsis" that went back 15 years yielded one case report of sepsis caused by *Bifidobacterium longum* in a 19 year old man after acupuncture.¹⁹ He had not ingested probiotics and completely recovered within 10 days. In contrast, a similar search found hundreds of cases of sepsis due to *Lactobacillus*.

Current state of the art

At present in the European Union, micro-organisms intended for human use are regulated only within the context of the Novel Food Regulation EU 258/97.²⁰ In early 2002, the United States Food and Drug Administration accepted a "generally regarded as safe (GRAS)" notice (notice GRN 000049) from Nestlé USA, for the use of *Bifidobacterium lactis* and *Streptococcus thermophilus* in formula milk for healthy infants aged 4 months or more. In its response to Nestlé, the administration "[had] no questions ... regarding Nestlé's conclusion that *B lactis* and *S thermophilus* strains are GRAS for their intended use as ingredients in milk-based infant formula that is intended for consumption by infants four months and older at levels not to exceed good manufacturing practice."²¹ The European Society of Paediatric Gastroenterology, Hepatitis, and Nutrition committee on nutrition recently summarised its approach to probiotics as follows, "probiotics so far used in clinical trials can be generally considered as safe. However, surveillance for possible side effects, such as infection in high-risk groups, is lacking and is needed."²²

Conclusion

The benefits of probiotics seem to outweigh the potential danger of sepsis. Anecdotal reports of sepsis do exist, however, and these reports have raised some

concern. We should proceed with caution in clinically advancing probiotic therapeutics and concentrate on the use of organisms other than *Lactobacillus*.

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Endpiece

Einstein on research

Not everything that counts can be counted.

Albert Einstein

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