

The role of probiotics in preventive health

A multidisciplinary group of health experts engaged in a patient-centred roundtable discussion at the Royal Society of Medicine, London, to examine the role of probiotic drinks in preventive health and self-care. The primary goal of the meeting was to review the growing evidence-base behind probiotic drinks in an attempt to answer the many questions that have been raised about their health claims. As healthcare professionals strive to provide their older patients with the best evidence-based treatment and care at all times, discussions like these are useful to raise awareness of potential opportunities, such as probiotic drinks, to do so.

Panel members:

- Ian Rowland** (Chair) Professor of Human Nutrition, University of Reading
- Juliet Gray** Registered Public Health Nutritionist, Guildford
- Lisa Melton** Research Immunologist, London
- Chris Bulpiitt** Emeritus Professor of Geriatric and Cardiovascular Medicine, Imperial College London
- Mary Hickson** Research Dietitian, Imperial College Healthcare NHS Trust, London
- Mike Smith** Specialist in Preventive Medicine, General Practitioner, and Freelance Journalist, London
- Julie Foxton** Specialist Community Public Health Nurse/Health Visitor, Reading
- Satish Keshav** Consultant Gastroenterologist, Oxford

The importance of prevention and self-care

Over a third of the UK population is older than 50, and there are nearly 12 million pensioners, a figure that is projected to grow by 60% in the next 25 years.^{1,2} In light of the UK's ageing population, it is increasingly important that healthcare practitioners support older patients in staying healthy, independent, and in control of their lives.

Several government initiatives and strategy documents including *The NHS Improvement Plan*,³ *Creating a Patient-*

Led NHS,⁴ and *Our Health, Our Care, Our Say: A New Direction for Community Services*⁵ have highlighted the goal of transforming the NHS from a sickness service to a health service by promotion of self-care and prevention. This means that healthcare practitioners will need to work in partnership with individuals, especially older patients, to support them in choosing healthier approaches to their lives.

One area of recent interest is the addition of functional foods, such as probiotic drinks (box 1), to the diet as a way to improve overall nutrition and to support the immune system. As older patients take an increasingly proactive approach to health, geriatricians have a unique role in empowering patients with general dietary and lifestyle advice to improve their wellbeing.

Box 1: What are probiotics?

The term probiotic, which means for life, is often applied to food supplements containing live bacteria that confer a health benefit.

According to an expert committee of the UN Food and Agriculture Organization (FAO) and the WHO, probiotics are **“live organisms which, when administered in adequate quantities, confer a health benefit to the host”**.

A probiotic food should meet the following criteria:

- Contain sufficient live, active 'good' bacteria
- Be stable and viable for the life of the product
- Survive stomach acids
- Provide clinically proven health benefits
- Be safe and amenable for human consumption

The growing probiotic evidence base

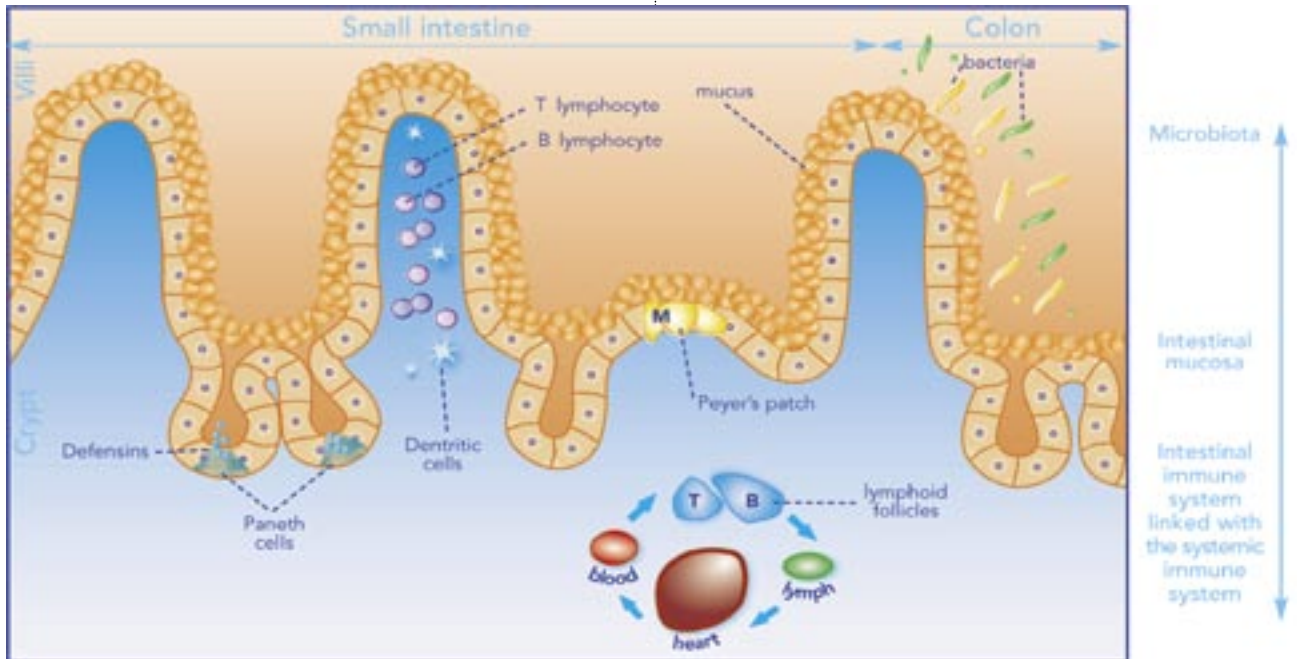
Probiotics have been the subject of international studies since the middle of the twentieth century. Between 1961 and 1998, 143 clinical trials with probiotics were conducted involving more than 7,500 participants, none of whom reported any side-effects.⁶ Since then, examining the health benefits and mechanisms of action of probiotics has become an increasingly active field of research. There is growing evidence that probiotics may produce beneficial effects such as reducing risk factors for disease and they could also improve bodily functions (table).

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Table: Reported effects and proposed mechanisms of action of probiotics

	Condition	Proposed mechanism
Benefit to general gut health	Irritable bowel syndrome; symptoms generally affecting the gastrointestinal tract (constipation, non-pathogenic diarrhoea, distension, flatulence, cramp, halitosis of a digestive cause)	Change in the populations or activities of intestinal microbes ⁹
	Lactose intolerance	Delivery of microbial lactase to the small intestine ¹⁰
Defensive benefits	Allergy (atopic eczema, allergy to milk, rheumatoid arthritis)	Translocation; barrier effect ^{11,12}
	Dental caries	Changes in the populations and activity of oral bacteria, or their ability to adhere to teeth ¹³
	Cancer, mutagens, and tumours	Absorption of the mutagen; stimulation of the immune system; inhibition of carcinogen production by intestinal microbiota ^{14,15}
	Diarrhoea linked to antibiotics; diarrhoea caused by rotavirus; colitis caused by <i>Clostridium difficile</i> ; nosocomial diarrhoea	Competitive exclusion; translocation or barrier effect; promotion of immune response ¹⁶
	<i>Helicobacter pylori</i>	Antipathogenic activity ¹⁷
	Immunomodulation (immune status, response to vaccination)	Interaction with immune cells or cell receptors leading to increases in phagocytic activity of white blood cells; increased IgA levels after exposure to antigen; increased proliferation of intraepithelial leukocytes; regulation of Th1/Th2 ratio; induction of cytokine synthesis ¹⁸
	Intestinal inflammation; ulcerative colitis; Crohn's disease; pouchitis	Downregulated immune response ¹⁹
	Excessive intestinal bacterial growth	Antimicrobial activity, competitive exclusion ²⁰
Other benefits	Vaginosis; urinary infections	Antipathogenic activity; competitive exclusion ²¹
	Blood cholesterol	Lowered by deconjugation of bile acids ²²
	Endotoxaemia combined with cirrhosis	Inhibition of endotoxin production by intestinal microbes ²³
	Hypertension	Cellular constituents of peptides derived from fermentation acting as inhibitors of angiotensin-converting enzyme ²⁴
	Renal calculi	Changes in digestive microbiota influencing breakdown of oxalate ²⁵

Figure: Illustration of the natural defence systems of the intestine



The first line of defense is the intestinal microbiota, which protect against pathogens by preventing their colonisation. The second line of defense is the intestinal mucosa: its main protective mechanisms are the layer of mucus, the tight junctions between cells, and the Paneth cells that secrete antimicrobial peptides (defensins). The third line of defence is the immune system. Antigens are captured by M cells in the Peyer's patches, contributing to an immune response involving IgA, T lymphocytes, B lymphocytes, and dendritic cells. The immune response in the intestine is connected with the circulatory and lymphatic systems.

Today, many probiotic products are available including probiotic yogurts, drinks, and tablets, but not all are backed by evidence-based clinical trials.^{26–30} The variety of probiotics can cause confusion among healthcare professionals and patients as to which are most effective—because potential benefits may be product-specific, depending on the strain of probiotic used. The strains are characterised by a code or brand name referring to a collection or to the manufacturer's brand.

Since probiotic bacteria do not colonise the gut, they must be taken on a daily basis, meaning that, beyond effectiveness, a probiotic also needs to be palatable to patients to ensure compliance to a daily regimen. Therefore, a probiotic that is available in a variety of flavours or sugar or fat content is able to suit patients' preferences.

The ageing immune system

The human body has evolved a complex natural defence system, a major component of which is the gastrointestinal tract. The intestine, in particular, is

responsible not only for digesting food, but also for an entire range of other hormonal, motor, nervous, and immune functions, several of which are responsible for instituting effective defence against external challenges. Thus, the intestine plays a complex and important role in the body's defences (figure).

The important defensive function of the intestine is based on the three intestinal lines of defence: the microbiota, the mucosa and the intestinal immune tissue, known as the gut-associated lymphoid tissue. Impairment of one or more of these components can enable certain diseases to develop.

Age can weaken the body's natural defences, which explains why people over the age of 60 have an increased susceptibility to infectious and non-infectious disease. The decline in lymphoid cell activity, the loss of cell-proliferation capacities, and degeneration of tissues and organs are among the most important phenomena of the ageing process. These factors may have an effect on the integrity of the intestinal epithelium.

WHO data show a 400-fold increase in the

Box 2: Supporting data for use of probiotics for prevention of winter infections in older people

- Probiotics (*Lactobacillus rhamonosus*, *Bifidobacterium lactis*) exert immunostimulatory action and help to restore depressed function, as can occur in older persons³⁶—15 other studies have investigated this effect
- Five clinical studies have looked at probiotic effects on infection rates in older people
- *Lactobacillus johnsonii* Lc³⁶ reduced infection rates in enterally fed inpatients older than 70 years (5.7% vs 15.4%)
- For independent-living people over 60 years, *Lactobacillus casei* DN-114 001 administered twice a day shortened the duration of winter infections (7.0 vs 8.7 days)³⁷

mortality rate due to gastrointestinal infections in older persons compared with young adults. In addition, older people experience a large drop in their gastrointestinal microbiota, typically with a 1000-fold decrease in 'good' bacteria when compared with younger adults. Thus, a non-invasive means of enhancing cellular immunity is desirable in this patient population, especially because they are more susceptible to serious complications of infections such as seasonal colds and flu, and diarrhoea associated with antibiotics and *Clostridium difficile*.

Preventing winter infections

Previous reports suggest that dietary supplements, such as probiotics, could be an effective way to enhance the activity of the immune system in older people. Bacteria prime and drive mucosal inflammatory response. Thus, modification of this environment by probiotics provides a possible health benefit by inducing protective immune responses modulating the production of inflammatory cytokines. Some research suggests that probiotics help regulate critical components of the immune system such as lymphocytes, antibodies and natural killer cells following probiotic-mediated signalling in the gut.^{31–35}

After reviewing the evidence in this area (box 2), the panel agreed the best approach for older patients, especially those with a poor diet who frequently experience winter colds or flu, was to empower them to do something for themselves by offering general lifestyle advice. This may include counselling on diet, exercise, smoking cessation and getting sun to improve

vitamin D levels. While recognising that probiotics are not harmful to patients, the panel recommends more research to confirm the benefits of probiotics suggested by current evidence for these patients.

Preventing antibiotic-associated diarrhoea

As three quarters of NHS clients are aged 65 and over, the majority of patients in hospital are older people.³⁸ Within this setting, patients receiving antibiotics develop antibiotic-associated diarrhoea in 5–30% of cases, and this rate increases with broad-spectrum antibiotics.³⁹ This may result from the inadvertent disruption of the microbiota balance caused by the antibiotic. The effects on the patient may include a longer hospital stay, an increased risk of other infections, more advanced and potentially life-threatening disease including colitis or toxic megacolon, early discontinuation of their prescribed antibiotic, and significant increases to the cost of patient care.

In 20–30% of cases, the *C. difficile* pathogen is the cause of antibiotic-associated diarrhoea.⁴⁰ In 2006, the number of *C. difficile* cases in patients aged 65 years and over reported in England to the Health Protection Agency was 55,634, a 7% increase on the previous year.⁴¹ The number of reported deaths associated with *C. difficile* infection also increased. In England and Wales, the number of times *C. difficile* was mentioned on death certificates rose from 975 in 1999 to 3,807 in 2005. The comparable figure for MRSA in 2005 was 1,629.⁴¹

Box 3: Supporting data for use of probiotics for antibiotic-associated diarrhoea and *C. difficile*-associated diarrhoea

- More than 20 clinical studies have looked at probiotic effects on antibiotic-associated diarrhoea
- Probiotics, especially *Lactobacillus rhamonosus* GG and *Saccharomyces boulardii*, prevent antibiotic-associated diarrhoea⁴⁴ (Relative risk 0.43, 95% CI 0.31–0.58, $p < 0.001$)
- Only *S. boulardii*⁴⁴ and more recently *L. casei* DN-114 001⁴³ are effective against *C. difficile*
- For the over 50s, taking a probiotic drink containing *L. Casei* DN-114 001 twice a day while on antibiotics in hospital significantly reduced the incidence of diarrhoea by 22% and *C. difficile*-associated diarrhoea by 17%.⁴³

Just how serious is *C. difficile*?

On 11 October 2007, a report released by the Health Commission revealed that the superbug *C. difficile* was responsible for 90 deaths at Kent's Maidstone and Tunbridge Wells NHS Trust. The report also stated that it was definitely a contributing factor in the a further 124 deaths and a probable factor in another 55 patients. The report recommended carefully considered protocols for antibiotic prescribing as they can destroy many of the bacteria that normally live in the intestine, making it easier for *C. difficile* to thrive.⁴⁰

The report's lead author, Heather Wood, commented: "I think it's certainly a call to arms for the National Health Service. I would think the lessons, not just about cleanliness, hygiene, and infection control, but the care provided to patients who contract *C. difficile* is something that has wider lessons for the NHS. For many of these patients there may well have been a good chance that they would have recovered if all steps had been taken."

Strategies for prevention

The recently published guidance, *The Code of Practice for the Prevention and Control of Healthcare Associated Infections*,⁴² called for Primary Care Trusts to have a specific policy for the prevention and control of *C. difficile* infections. A potential strategy to reduce these rates and protect the microbial barrier in patients receiving antibiotics is through the use of probiotics.

Two members of the panel, Dr Mary Hickson and Professor Chris Bulpitt, were authors of a randomised, double-blind, placebo-controlled trial published recently in the *British Medical Journal* that showed, for people older than 50, drinking a probiotic containing the *L. casei* strain DN-114 001 (used in Danone Actimel) twice-daily significantly reduced the incidence of all diarrhoea by 22% and *C. difficile*-associated diarrhoea by 17%.⁴³ This study supports the findings from other randomised, double-blind, placebo-controlled trials showing various probiotic preparations to effectively prevent antibiotic-associated diarrhoea.^{26-28,30,44}

Considering that probiotics are well-tolerated, even in older patient populations,^{30,45,46} and the cost to administer them is minimal, the panel agreed after reviewing the evidence (box 3) that probiotics should be given as an adjunctive preventive treatment alongside antibiotics in hospitals. Patients should take probiotics during and after their hospital stay to reduce the risk of acquiring antibiotic-associated diarrhoea or, if

Box 4: Consensus points

On the basis of the clinical evidence presented, the multidisciplinary panel of health experts agreed on several points as listed below. These panel recommendations are positive steps for healthcare professionals and the public toward an evidence-based approach to probiotic drinks in health prevention and self-care, especially for older patients.

- Older people with reduced immune function and poor diet may benefit from a daily probiotic drink as part of general health advice, although more research is needed in this area.
- Patients receiving antibiotics in hospital, and potentially in the community, should take a probiotic drink with a strain that has a proven clinical evidence-base during and after the course of antibiotics to reduce the risk of development or the severity and duration of antibiotic-associated diarrhoea, especially that caused by *C. difficile*.
- The format of probiotic delivery could affect overall effectiveness. Thus, yogurt or fermented-milk probiotics may offer advantages over freeze-dried probiotic capsules in that they also provide potentially beneficial byproducts of fermentation.
- When selecting a probiotic drink, it is best to choose one with strain that has a proven clinical evidence base. Since the reported effectiveness of probiotics is strain-specific, further studies that evaluate and compare the therapeutic potential of probiotic strains are needed.

acquired, its severity and duration. This could be particularly useful for reducing the incidence, severity and duration of *C. difficile*-associated diarrhoea in the hospital and potentially in the community.

Conclusions

The care of older people requires a holistic approach that includes prevention and self-care strategies in line with the main goal of older people: to maintain an active and independent lifestyle. In a patient-centred and cost-effective NHS, there is an increasing role for resources that promote preventive health and self-care amongst patients. The needs of older people are central to these aims and the transition of the NHS to a health service from a sickness service, solely because they are the major users of its services.

From reviewing the evidence, it is clear that older patients could benefit from inclusion of probiotics in dietary and lifestyle advice to empower them to maintain a healthy and active life (box 4). Additionally, for older people in hospital who are receiving antibiotics, probiotics should be promoted to reduce the risk, severity, and duration of diarrhoea associated with antibiotics and *C-difficile* diarrhoea. This may even extend to the community setting where antibiotics are prescribed.

The primary goal of this meeting was to encourage discussion around the role of probiotic drinks in preventive health and self-care in light of the growing evidence-base behind them. Because healthcare professionals strive to provide their patients with the best evidence-based treatment and care at all times, such debates are useful in raising awareness of potential opportunities, such as the use of probiotic drinks, to do so.

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