



Insight: The gut microbiota and healthy ageing

1. How the gut microbiota changes with age

The gut microbiota is the name used to describe the multitude of commensal microorganisms that live in the gut (about 100 trillion in adults), with the majority found in the colon. These microbes play a central role in maintaining health: training the immune system to respond appropriately and effectively, and competing against pathogens to prevent them colonising the gut. They also help digest complex nutrients and produce a range of beneficial metabolites such as vitamin B, vitamin K and short-chain fatty acids. A major international research effort is currently focussed on characterising the gut microbiota of different people, including those who are elderly.

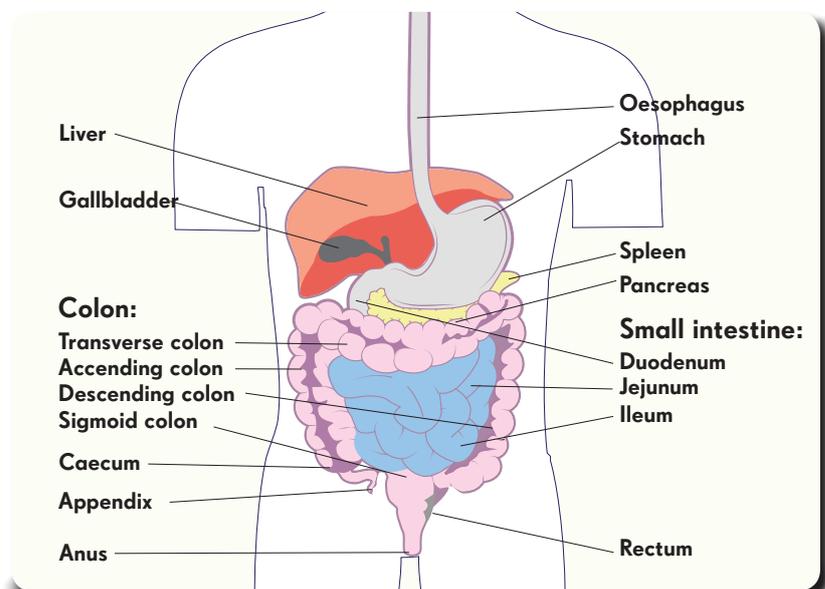
QInsight Examples of bacteria in the colon that can influence health¹

Potentially protective species

Bifidobacterium spp.
Lactobacillus spp.
Faecalibacterium prausnitzii.

Potentially harmful species

Bacteroides spp., e.g. *fragilis*
Some *Escherichia coli* groups
Enterococcus spp.
Klebsiella spp.
Helicobacter spp.
Clostridium difficile



In later life, the composition of the gut microbiota changes to one that seems to be less healthy and less protective: microbial diversity declines, bifidobacteria decrease and Enterobacteriaceae (Gram-negative bacteria) increase.¹⁻³ These changes have been linked to frailty, co-morbidity, nutritional status and faecal metabolites.⁴⁻⁵ The increased vulnerability of older people to infectious disease can be partly attributed to this change within the gut microbiota as well as the reduced efficiency of the immune system. A chronic and systemic state of inflammation (inflammaging) also develops with age, which is associated with ageing and probably a result of a lifetime's exposure to foreign antigens. The changed profile of the gut microbiota has been linked to this.^{3,6,7}

QInsight Gram-positive and Gram-negative bacteria

Microbiologists use a staining technique invented by in 1884 by a Dr Hans Christian Gram, in order to see bacteria down a microscope. The Gram stain is usually the first stage of species identification, and it differentiates bacteria into those that stain purple (Gram-positive) and those that stain red (Gram-negative) due to differences in their cell wall structure. This can also be important as some antibiotics only work on one group. The cell walls of Gram-negative bacteria are more complex and contain lipopolysaccharide (LPS), an endotoxin. If impaired gut permeability allows LPS to leak through the gut wall, the resulting metabolic endotoxaemia can cause low-grade inflammation. This has been linked to certain metabolic disorders such as insulin resistance and type 2 diabetes.





Relevant research with *Lactobacillus casei* Shirota (LcS)

Immune function in healthy older people⁸ In this randomised placebo-controlled, single-blind crossover study, the immune-modulatory effects of a probiotic LcS-fermented milk drink were investigated in 30 healthy elderly volunteers. A more anti-inflammatory immune response was observed in the probiotic group as well as a significant increase ($P=0.008$) in natural killer (NK) cell activity. (NK cells target viral-infected and tumour cells.) This was considered beneficial for these older people.

Cigarette smoking reduces NK cell activity⁹ A double-blind, placebo-controlled, randomised study was conducted with 72 male smokers who were given LcS powder or placebo for three weeks. The probiotic was associated with significantly increased NK cell activity ($P<0.001$).

Diet has a rapid and strong influence on the composition of the gut microbiota.¹⁰ Eating foods that promote healthy species in the gut (e.g. prebiotic-containing vegetables such as onions, leeks, asparagus, chicory and Jerusalem artichokes) can become difficult in old age, particularly if there are dental problems or little appetite due to poor taste or smell.

Q Insight Key observations regarding the gut microbiota of older people^{2,3,5,11}

- Diet has been shown to have a strong influence on the gut microbiota. Studies have shown microbial diversity to be higher in people eating healthy foods. A poor diet was associated with a less diverse and potentially less beneficial microbiota, linked to increased frailty and inflammation, and to reduced levels of short-chain fatty acid-producing bacteria.
- A person's place of residence affected the microbiota profile: it was less diverse for those in institutionalised care compared to those in the community. For the former, the loss of bacterial species that were commonly found in community-dwellers, was linked to increasing frailty and indications of poor health. The gut microbiota of the oldest and frailest subjects produced less short-chain fatty acids compared to younger people.
- Older people in residential homes ate a more unhealthy diet. They were offered healthy foods but made bad dietary choices, possibly due to inadequate dietetic advice and support.

2. The risks associated with antibiotic treatment for older people

Antibiotic therapy disturbs the gut microbiota, increasing the risk of diarrhoea and gut-related infections. Levels of bifidobacteria, for instance, can become significantly reduced, particularly in long-stay care residents.¹² Antibiotic use and old age are both risk factors for *Clostridium difficile* infection (CDI), which is a cause of hospital-acquired diarrhoea. Carriage rates of this spore-forming pathogen appear to vary according to residential location: from 1.6% for older people living in the community, to 95% in outpatient settings, and to 21% for hospital patients.¹²

C. difficile is present in the gut of up to 3% of healthy adults but rarely causes problems as it is kept in check by the normal bacteria in the gut.¹³ Recurrence rates are high (up to 35%),¹⁴ which is a major issue for patients' quality of life and consequent healthcare costs. Patients who develop *C. difficile* diarrhoea have been shown to have a less diverse gut microbiota. These observations explain why there is interest in using probiotics to reduce the risk of both antibiotic-associated diarrhoea (AAD) and CDI. Recent systematic reviews and meta-analyses have concluded that (i) probiotics reduce risk of CDI¹⁵⁻¹⁶ and (ii) probiotic use is associated with a reduction in AAD.¹⁷⁻¹⁸





Relevant research with *Lactobacillus casei* Shirota (LcS)

An Austrian hospital study¹⁹ involving 678 inpatients of mean age approximately 70 years, who were prescribed a range of antibiotics. One group (340) received a daily probiotic (LcS) during antibiotic treatment and for three days after; the other group (338) received no probiotic. The groups were matched in terms of age, sex,

Incidence	LcS group	Control group	<i>P</i>
AAD	5%	18.6%	<0.001
CDI	0.3%	6.2%	<0.001

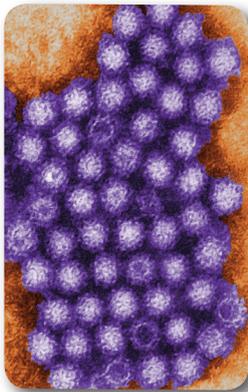
duration of hospital stay and types of antibiotics they were receiving. The antibiotics were shown to affect the diversity and composition of the gut microbiota, affecting production of butyrate. The probiotic reduced both AAD and CDI, equivalent

to a relative risk reduction of 73.2% for AAD ($P<0.001$) and 95.3% for CDI ($P<0.001$).

An evaluation of LcS use in two hospitals in an UK NHS Trust²⁰ found that a daily LcS probiotic given to all patients over 65 years of age, irrespective of their antibiotic treatment, helped reduce risk of CDI in the hospital.

Prevention of recurrent CDI²¹ was investigated in this UK cohort-controlled hospital study, which looked at 66 patients (median age 78 years) with CDI who had been treated with either antibiotics alone or with antibiotics plus the LcS probiotic. Relapse rates following CDI were reduced in the LcS group: 3.2% vs 20.0% ($P=0.007$). Hospital readmission rates were also lower: 19.4% vs 35.1%.

3. Other common infectious illnesses affecting older people.



CDC/ Charles D. Humphrey

In a residential setting, common infections such as colds and tummy bugs spread easily and, in elderly people, may develop into more serious illnesses. Outbreaks of diarrhoea and vomiting, for instance, are often caused by norovirus (otherwise known as the winter vomiting bug). This is an incredibly contagious pathogen, easily spread by person to person contact and the advice to prevent this is to wash hands frequently, not share towels and flannels, and disinfect any surfaces touched by an infected person (but note that the virus can survive for several days). The illness is self-limiting, and the best strategy is to drink plenty of water and rest, avoiding other people.



Relevant research with *Lactobacillus casei* Shirota (LcS)

Norovirus gastroenteritis²² In elderly people, fever may indicate a risk that the illness may become severe. In a case-controlled study of 77 long-stay frail elderly residents, conducted during a winter month with a norovirus outbreak, the probiotic did not have any effect on gastroenteritis incidence. The probiotic was, however, associated with significant reduction of mean duration of fever ($>37^{\circ}\text{C}$) ($P<0.05$). Faecal analysis showed increases in bifidobacteria ($P<0.05$) and lactobacilli ($P<0.01$) after the residents had taken the probiotic for one month. Levels of Gram-negative Enterobacteriaceae decreased ($P<0.05$).

Residential long-term nursing home study²³ The effects of six months' intake of a daily LcS-fermented milk drink were investigated, comparing the health status and gut microbiota profile of the elderly subjects. During the probiotic period there were fewer days of fever, constipation and diarrhoea (all $P<0.05$). At baseline, faecal analysis showed reduced numbers of bifidobacteria and higher numbers of clostridia in the elderly residents compared to the staff in the home. After the intervention, levels of bifidobacteria and lactobacilli increased (both $P<0.01$), and *C. difficile* decreased ($P<0.05$).

Upper respiratory tract infections²⁴ (URTIs) This double-blinded, randomised, placebo-controlled study investigated 154 elderly people attending four day care centres in winter. Intervention was with an LcS-fermented milk or placebo for a period of five months, with an observation period of a further two months. The main finding was that the probiotic was associated with a shorter duration of acute URTI ($P=0.037$).

4. Gut-related problems affecting older people

Due to dietary differences, lack of exercise, use of certain medications and poor bowel habits, older people have an increased risk (x5) of suffering constipation compared to younger adults.²⁵ (NHS choices: www.nhs.uk).



Relevant research with *Lactobacillus casei* Shirota (LcS)

Chronic constipation²⁶ A double-blind, placebo-controlled, randomised trial in 70 people with chronic constipation found four weeks' intervention with an LcS-fermented milk drink resulted in significant improvement in severity of constipation and in stool consistency. The benefit was observed after a week of being given the daily probiotic.

Improved stool consistency²⁷ A randomised, controlled study in people who produced hard or lumpy stools in $\geq 25\%$ of bowel movements, investigated three weeks' intervention with an LcS-fermented milk drink. This significantly reduced the proportion of subjects suffering the problem, from 73.7% to 36.8% ($P=0.002$). This was not observed in the control group.

Cancer incidence increases exponentially with age. The proportion of people aged 65 years and over is increasing, which means that certain cancers have become more prevalent. For instance in the UK, there was an average of 8,788 cases of bowel cancer per year between 2008 - 2010 for men aged over 75 years, (making it the 3rd most common cancer in this age group). For women of the same age, there was an average of 8,628 cases of bowel cancer per year (making it the second most common cancer in this age group).²⁸



Relevant research with *Lactobacillus casei* Shirota (LcS)

Colorectal cancer²⁹ A randomised controlled trial in 398 patients (mean age, mid-50s) who had previously had surgery for colorectal cancer, found that four years' intervention with LcS powder resulted in a significant reduction in occurrence of tumours of moderate atypia or higher (OR 0.65; 95% CI 0.43-0.98).



5. Conclusions

The gut microbiota changes with age, increasing the vulnerability of older people to infection and gastrointestinal problems. If considering recommending a probiotic for an older person, choose a good quality product: the label should show the name of the strain(s) and their live number, and there should be evidence of strain survival through the gut (an important characteristic for such products) and relevant health benefit.³⁰ Healthcare professionals should be able to get this information from the manufacturer.

To find out more about the science of *Lactobacillus casei* Shirota, and for other educational resources (educational seminars, leaflet, booklets, etc) log onto www.yakult.co.uk/hcp or contact the science team (020 8842 7600; science@yakult.co.uk)

The references for this leaflet can be found at www.yakult.co.uk/hcp in the resources/scientific publications section.

