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science for health®

Probiotic Bulletin

A Newsletter for Healthcare Professionals

The gut microbiota, probiotics & constipation

All of us may experience constipation at some time in our lives, but certain people experience a severe and sometimes chronic problem, even necessitating a visit to the GP. In fact, constipation is one of the most prevalent gastrointestinal complaints in the UK (estimates vary from 8.2% - 52%).

In 2009 GP-diagnosed constipation was estimated at a rate of 12.8 per 1000,[1] and in 2010 the estimated prevalence of idiopathic childhood constipation in England was estimated at 15%.[2] Constipation-predominant irritable bowel syndrome (IBS-C) should also be considered: a survey of IBS patients in five European countries including the UK, estimated the prevalence of IBS-C at 1-44%.[3]

Risk factors[4 5 6] include: female gender, older age, low fibre diet, low calorie intake (malnutrition), lack of physical activity, number of medications, certain conditions (e.g. depression, Parkinson's disease), lower socioeconomic status, physical and sexual abuse.

In this issue:

Clinicians are presented with a range of symptoms but diagnosis is facilitated by use of the Rome III diagnostic criteria for functional gastrointestinal disorders.[10] These define functional constipation as active symptoms within the last three months with symptom onset at least six months previously. In clinical practice, functional constipation is often referred to as chronic constipation (CC), which indicates the symptoms are long-lasting but not IBS.[11] Constipation can have a serious and negative impact on the quality of life and social functioning of sufferers.[12]

Constipation. Snippets from earlier days

- Constipation comes from the Latin word *constipare* (to crowd together). Famous sufferers include Elvis Presley, Samuel Taylor Coleridge, King George II and Abraham Lincoln.
- In 1857, a popular US health manual decreed that without a daily evacuation of the bowels, *'the entire system will become deranged and corrupted.'*[7]
- Between 1900 and 1920, a famous surgeon at Guy's Hospital surgically removed the colons of hundreds of patients as a radical treatment for 'autointoxication' (self-poisoning from harmful substances produced in the colon by putrefying microbes and absorbed into the body). It was believed constipation (which *'shortens life'*) contributed to this.[8]
- In 1902, JF Goodhart[9] highlighted the effect of constipation on quality of life: *'I have known …. the happiness of a whole household to hang daily on the regularity of an old man's bowels…*"Master's bowels have not acted today", *from the lips of the faithful butler and the house is shrouded in gloom.'*
- Laxatives became popular in the 1920s and 1930s: the *'golden age of purgation'*.

Did you know…?

- One in every seven adults and up to one in every three children in the UK has constipation at any one time (nhs.uk).
- Globally, 20% of community-dwelling individuals and 50% of institutionalized elderly individuals report constipation type symptoms (WGO, 2010).
- In 2006 more than 13 million GP prescriptions in the UK were written for laxatives (WGO, 2010).
- The Bristol Stool Form Scale is used to help patients report their stool consistency (order free HCP pocket sized guides from science@yakult.co.uk).

Constipation in brief [13]

Constipation is defecation that is unsatisfactory because of infrequent stools, difficult stool passage, or seemingly incomplete defecation. Stools are often dry and hard, and may be abnormally large or abnormally small. Functional constipation: chronic constipation without a known cause.

Secondary constipation is caused by a drug or medical condition (e.g. endocrine and metabolic diseases, myopathic and neurological conditions, certain bowel conditions).

Faecal loading/impaction is retention of faeces to the extent that spontaneous evacuation is unlikely.

Two pathophysiologies are associated with constipation: intestinal transit disorders (either decreased colonic activity or increased but uncoordinated colonic activity) and evacuation disorders (difficulty in fully evacuating stools from the rectum).

Variations in motility along the gut are one of the factors determining the size and diversity of its microbiota but, conversely, the microbiota can influence motor patterns in the gut. For example, it has been suggested that small intestinal bowel overgrowth (SIBO) in the elderly may be linked to age-related changes in small intestinal motility.[14 15] Disturbances in the intestinal microbiota have been linked to various functional bowel disorders.[16 17 18] The consequence of any such change is an altered profile of the metabolites produced in the gut, which may affect gut function. For instance, excretion of methane, a gas produced by certain microbes in the gut, has been linked to constipation;[19] levels of sulphate-reducing bacteria may be higher in IBS-C patients,[20] and an association has been shown between low levels of detectable hydrogen produced in the gut and constipation.[21]

Three mechanisms may explain how the gut microbiota influences gut motor function[22]:

- Through the release of bacterial substances or end-products of bacterial metabolism, such as lipopolysaccharides, short chain fatty acids, gas (volume or type), and deconjugated bile salts (influencing stool form and consistency).
- Via intestinal neuroendocrine factors, e.g. production of neurotransmitter peptides or nitric oxide (an inhibitory neurotransmitter gas).
- Indirectly by means of mediators released by the gut immune response.

Such observations have led to research into whether modulation of the gut bacteria may benefit constipation.[23] Although there are fewer studies compared to IBS, systematic reviews are starting to appear. For example, in 2013, one such review identified 11 clinical trials with 13 treatment effects representing 464 subjects, and found that overall, short-term probiotic intake was associated with improved (decreased) intestinal transit time.[24] Further research is required in order to evaluate with certainty the effect of probiotic administration on constipation; an earlier systematic review of probiotics and constipation, conducted in 2010, included only five trials with 377 subjects in total.[25]

Extensive research in this area has been conducted with *Lactobacillus casei* Shirota. Endpoints in the trials (a few examples are cited) include gastrointestinal symptom questionnaires, wellbeing questionnaires, stool consistency, defecation frequency and colonic transit time, as well as faecal microbiota and metabolites.[26 27 28 29] Most studies examined relatively healthy people but one study has been conducted with Parkinson's disease patients, a group who commonly suffer constipation.[30]

A full list of *L. casei* Shirota studies can be found at www.yakult.co.uk/hcp or on request (science@yakult.co.uk).

Tilley L *et al* (2014) A probiotic fermented milk drink containing *Lactobacillus casei* strain Shirota improves stool consistency of subjects with hard stools. *Int J Probiotics Prebiotics* 9(1)[31]

This placebo-controlled, double-blind, randomised trial was conducted with 120 patients aged 18 to 65 years, suffering from mild constipation and hard stools (defined as four or less defecation movements per week and lumpy or hard stools in at least 25% of the defecations; Rome III diagnostic criteria). Stool consistency was assessed on a daily basis before, during and after intervention with the fermented milk drinks (test or verum for four weeks). Microbial analysis was conducted on a sub-set of volunteers.

The main positive finding was that the probiotic was associated with softer stools of a higher liquid content; a significant difference compared to the placebo. This was assessed by comparing the data before and after ingestion, and between the probiotic and placebo groups. The stool-softening effect disappeared during the wash-out period when the probiotic was no longer being taken.

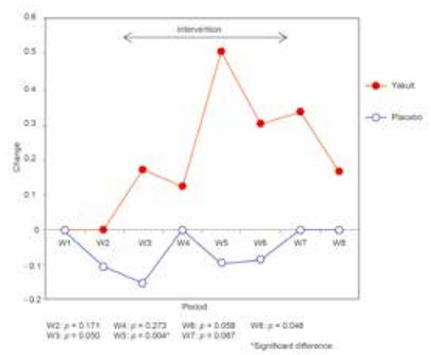


Figure: Evolution of changes of stool consistency (Bristol stool scale; median values)

A list of references is available at **www.yakult.co.uk/hcp** or from **science@yakult.co.uk**

| HCP Insight

Prevention of relapse of *Clostridium difficile* infection with *Lactobacillus casei* Shirota

Lee YWL *et al* (2013) *International Journal of Probiotics & Prebiotics* 8(4): 145-148

This independent study, published at the end of last year, was conducted by gastroenterologists at Milton Keynes Hospital. Their concern was the risk that patients previously diagnosed with and treated for *Clostridium difficile* infection (CDI), would suffer a recurrence of this illness. As is well known, *C. difficile* can reside in the gut without causing any problem, but it can grow and produce toxins if the protective commensal gut microbiota is disrupted by antibiotics, particularly if these are broad-spectrum (PHE, 2014).

Despite significant decreases in CDI being achieved since 2009, Public Health England reported that the UK incidence in 2013 remained at 26.7 cases per 100,000. Worryingly, recurrence rate is high - up to 35% (Barbut F *et al*, 2000). This is a major issue not just for patients' quality of life but for the high cost of their healthcare. It has been estimated that the cost of re-treating one patient with recurrent CDI could be as much as £11,000 per episode, mainly due to a need for prolonged hospital stay (Ghantoji *et al* 2010). This explains why clinicians are investigating strategies that may help to prevent CDI recurrence.

The Milton Keynes study was a single-site, cohort-control study of patients previously diagnosed with CDI. Recurrence was defined as those who had both developed diarrhoea and had a positive stool test using an enzyme-immunosorbent assay for *C. difficile* toxins A or B, and this had happened more than 28 days after the symptoms of their initial CDI episode were resolved. Sixty-six hospital inpatients were followed up for a median period of 7.9 months (median age 78 years; 36.4% male). At the time of the initial CDI episode, the patients had either been treated with a single dose of metronidazole or vancomycin, or the antibiotic together with a probiotic (*Lactobacillus casei* Shirota; approximately two bottles).

The clinicians' investigations revealed that readmission for diarrhoea within three months was lower if the patients had been given the probiotic with the original antibiotic treatment (Table 1). There was also a significant reduction in the incidence of recurrent *C. difficile* infection (p= 0.007).

Table 1

Endpoint	LcS group (n=31)	Control group (n=35)	*P*
Re-admission for diarrhoea within 3 months	19.4%	35.1%	not stated
Recurrent *C. difficile* infection	3.2%	20%	0.007

| Flu Fighter Campaign

Congratulations to the Walton Centre NHS Foundation Trust!

Their Flu Fighter team were finalists in the most recent NHS Employers national awards for their creative campaign to encourage staff to have a flu vaccination.

Their 'Bring a Buddy' initiative rewarded any staff member who referred a colleague to have their flu jab, by entering them all into a prize raffle.

We were proud to help their campaign by supplying two weeks' supply of our probiotic to all those who had a jab. By the end of the campaign, the Trust had vaccinated more than 77% of their front line staff.

The Walton Centre in Liverpool is the UK's only specialist neurosciences NHS Trust, helping people suffering from long term neurological conditions. Their experts diagnose and treat injuries and illnesses affecting the brain, spine and peripheral nerves and muscles.

L to R: Senior Communications Officer Paul Mannion, Sister Sue Kewn and Lead Flu Fighter Chris Jessop

| BSG

The British Society of Gastroenterology

The BSG is a registered charity founded in 1937 and a society focused on the promotion of gastroenterology within the UK. Its members include physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians and other healthcare professionals. The BSG runs a series of scientific meetings, offering platforms for scientific presentations and publications. Throughout 2014, these meetings will cover all aspects of medical and surgical gastroenterology and hepatology, with cutting edge clinical and basic scientific research.

The theme of the BSG Research Workshop on 11th April in the Academy of Medical Sciences (London) was 'The Microbiome, Dysbiosis and GI Disease'. The workshop provided a rare opportunity to hear state-of-the-art reviews on specific pathologies and to discuss the potential of therapeutic strategies specifically targeting the microbiome. Eminent academics and clinicians covered a range of topics including dysbiosis in cancer, inflammatory bowel disease and liver disease, as well as sharing insights into the current data on the gut microbiome. Yakult was proud to support this event. The annual BSG meeting will be held at the Manchester Central Convention Complex, from 16th – 19th June. For more information about the BSG visit: **www.bsg.org.uk**

| Gut Health Awareness Campaign

Would you like to run a Gut Health Awareness Campaign in your clinic, hospital, surgery or workplace?

Visit www.loveyourgut.com/HCP, email **info@loveyourgut.com** or call 020 8842 7600 to order a FREE Gut Health Awareness Campaign pack of leaflets, posters, and other material and help promote the importance of gut health!

Between April and October, anyone who orders a Gut Health pack will be automatically entered into a monthly draw for the chance to win a 12-month health and lifestyle magazine subscription package. And if you tell us about how your campaign went, you will also be entered into a one-off draw for the chance to win a Kindle Fire HD!

Love Your Gut (Gut Week) is a public health awareness campaign from the digestive health awareness charities Core and the IBS Network, supported by Yakult UK Limited, which aims to increase public understanding and awareness of gut health.

Core **(www.corecharity.org.uk)** is a national charity that funds medical research into the prevention, cure and treatment of digestive disorders, and provides information for patients and sufferers.

The IBS Network **(www.theibsnetwork.org)** is the UK's national charity for irritable bowel syndrome, informing, advising and supporting people with IBS and working with healthcare professionals to facilitate self-management through its comprehensive IBS Self Care Plan.

Love Your Gut and Gut Week are public health awareness campaigns from Core and the IBS Network in association with Yakult UK Limited. Neither Core nor the IBS Network endorses any specific commercial or pharmaceutical products. For full terms and conditions please visit **www.loveyourgut.com/HCP**

| Royal Voluntary Service

A Royal Delight

Yakult and the Royal Voluntary Service

In February, we proudly announced our support of Royal Voluntary Service's Big Sunday Lunch, a nationwide initiative that encourages people to gather together and enjoy a meal, whilst raising funds for the charity. This follows on from our involvement with last year's Great Brew Break campaign, which raised over £95,000 to support the charity's work.

Yakult shares many of the same values as Royal Voluntary Service, based on the importance of mind, body and community. Echoing the important work of Royal Voluntary Service's volunteers, Yakult employs 40,000 Yakult Ladies in Japan, who, as part of their role distributing Yakult products, routinely visit and support older people within the community.

As an ongoing supporter of the charity, we were fortunate enough to be invited to the 2014 Diamond Champions reception, held at London's historic Lancaster House. The event celebrated the invaluable contribution that people over the age of 60 make to society through volunteering.

L to R: HRH The Duchess of Cornwall, Catherine Woodhead (Deputy Development Director for Royal Voluntary Service), and Dr Linda Thomas.

As you can see, our Science Director Dr Linda Thomas had the privilege of meeting HRH The Duchess of Cornwall at this inspirational event. The Duchess is president of Royal Voluntary Service and, along with HRH Prince Charles, patron of the Diamond Champions scheme. Royal Voluntary Service supports over 100,000 older people each month.

For more information about the charity's work, please visit **www.royalvoluntaryservice.org.uk**

ROYAL VOLUNTARY SERVICE

| Yakult's Student Awards

The brightest achievers of 2013

Every year Yakult UK Limited sponsors a range of awards, from those for academic achievement to national awards recognising outstanding healthcare professionals. In 2013, the company sponsored 25 awards, including 22 within universities. We congratulate all the winners and thought we would share pictures of a few of them with you.

Jack Stone studied Sports Science BSc (Hons) at Bangor University and was awarded the Yakult Award for the Best Physiology Third Year Project for his research entitled *'Can Sitting-to-Standing blood pressure change be used as a marker of hydration?'*

Storm McCready-Fallon studied Microbiology MSc at Cardiff University and was awarded the Yakult Award for the Best Final Year Project. Her project involved isolating and characterising *Bacillus thuringiensis* strains from soil samples.

Steven Dunn studied at Nottingham Trent University and was awarded the Yakult Highest Achievement in Final Year Project in Human Biosciences for his project on the isolation of *Campylobacter* from retail poultry.

Chris Mountford MBBS (Hons) MSc (Distinction) MRCP (UK) was awarded the Yakult prize for outstanding achievement on the Nutritional Medicine MSc programme at the University of Surrey. Chris, a Specialist Trainee in Gastroenterology and General Internal Medicine, studied Nutritional Medicine, as a sound and practical knowledge of nutrition in health and disease is essential to his day-to-day work.

To see the full roll of honour and other photos, visit our website (http://hcp.yakult.co.uk/resources/awards).
If you are a past winner, we would love to hear about your subsequent career. Write to us at science@yakult.co.uk.

| Research Round-up

Recent publications of studies, including those with *Lactobacillus casei* Shirota (LcS)

Reduction of allergic immune response in hay fever sufferers

This was a 16-week double-blind, placebo-controlled, randomised trial (DBPCRT) in 60 patients with allergic rhinitis given oral probiotic (LcS) or placebo. It was conducted outside of the hay fever season, so clinical effects were monitored by giving the subjects a single nasal allergen challenge. Whilst probiotic intake was associated with modification of some immune parameters relating to allergic inflammation at the nasal mucosa, no clinical benefit was observed. The researchers speculated this may have been because the test method had not accurately represented natural allergen exposure.

Ivory K *et al* (2013) PLoS ONE 8(11): e78650

Effect of a probiotic drink on oral health

This was a small study investigating healthy dentate people, who drank an LcS-drink for four weeks. The findings confirmed that the presence of the probiotic bacteria in the mouth was temporary and intake-dependent. No broad ecological changes were observed during the drinking period, although the Halimeter scores of a few individuals were significantly reduced whilst they were taking the probiotic – an effect that might be worth investigating further in subjects at greater risk of oral infection.

Sutula J *et al* (2013) *Microbial Ecology in Health & Disease* 24:21003

Lactobacilli regulate *Staphylococcus aureus* pro-inflammatory T cell response in vitro

An interesting Swedish study showing that S. *aureus* induced a strong inflammatory response in intestinal epithelial cells and a prominent Th12 and Th17 response by immune cells. The latter was modulated by the lactobacilli strains tested (which included LcS). S. *aureus* is a frequent coloniser in early life; lactobacilli have been shown to be low in children developing allergy.

Hailesalassie Y *et al* (2013). *PLoS ONE* 8(1):e77893

Review of LcS studies relating to cancer

There is a surprisingly large body of research into various cancers with this probiotic strain. This short review covers this, summarising epidemiological and intervention studies that have been done, and describing evidence relating to the possible mechanisms of activity involved.

Shida K & Nomoto K (2013) *Indian Journal of Medical Research* 138: 808-814

Transmission of bifidobacteria from mother to baby

Research from Yakult's European institute in Belgium has shown that babies born by vaginal delivery can become colonised by unique family-specific bifidobacteria from their mothers. The maternal gut appears to be an important source of the strains that initially colonise the intestines of such babies.

Makino *et al* (2013) *PLoS ONE* 8(11):e78331

Yogurt and probiotic bacteria: health messages in the EU

The authors searched for health messages that mention probiotics or fermented milk with live bacteria in the EU, and found that five EU member states have such nutritional guidelines or recommendations.

Smug LN *et al* (2014) *Beneficial Microbes* 5(1):61-6

Life Ascending: The Ten Great Inventions of Evolution by Nick Lane

Recommended by Linda Thomas.

This book won the Royal Society Prize for Science Books in 2010, but I only discovered it after attending a lecture by the author at UCL. I've always been interested in the general area of origin of life and evolution but this book has blown away all my outdated ideas and totally refreshed my knowledge. Dr Lane asks why or how ten biological phenomena occurred, including the origin of life itself, DNA, photosynthesis, the complex cell, sex and death. He beautifully describes complex biological mechanisms, but then stands back and draws it all together to challenge current theories and explain new ones. Reading this book reminded me how much I love and am amazed by biology.

Have you got any good science books to share with us?
Why not let us know by emailing science@yakult.co.uk

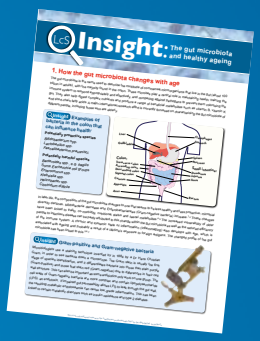
NEW HCP resources for you

Your Guide to Probiotics

Recently commissioned by the *British Journal of Nursing and Gastrointestinal Nursing*, **'Your Guide to Probiotics'** was authored by Dr Linda Thomas and Professor Kevin Whelan (King's College London). This six-page A5 brochure provides a concise expert overview of probiotics, including a section on safety.

Order hard copies from us **(science@yakult.co.uk)** or download from the resource section of our website **(www.yakult.co.uk/hcp)**.

LcS Insight



The first article in our new educational series **(LcS Insight)** explains the latest research into how the gut microbiota affects the health of older people, and gives an update on how dietary changes can provide benefit.

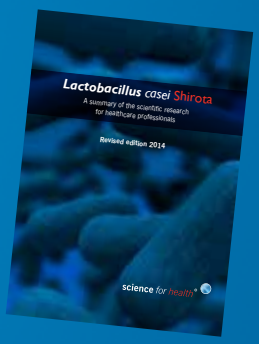
Order hard copies from us **(science@yakult.co.uk)** or download from the resource section of our website **(www.yakult.co.uk/hcp)**.

Practice Nursing

We have reprints available of the ***Practice Nursing*** paper that describes the discussions and recommendations of a multidisciplinary panel of healthcare professional who shared their experiences in treating chronic gastrointestinal symptoms.

Order hard copies from us **(science@yakult.co.uk)**

LcS Research Booklet



Recently revised for 2014, our **LcS research booklet** provides a summary of the range of scientific research for this probiotic strain.

Order hard copies from us **(science@yakult.co.uk)** or download from the resource section of our website **(www.yakult.co.uk/hcp)**.

Contact science@yakult.co.uk for:

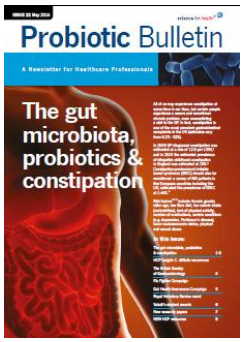
- ✓ **A free educational talk for your department or surgery**
- ✓ **Advice on probiotics**
- ✓ **Copies of our newsletter, reprints and other material**
- ✓ **Free trial period of product (subject to discussion)**

Find the science behind Yakult at yakult.co.uk/hcp

www.yakult.co.uk/hcp

This booklet is intended for healthcare professionals. Not to be distributed to patients.

Tel: 020 8842 7600; Email: science@yakult.co.uk



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Page 4 HCP Insight: Prevention of *Clostridium difficle* infection relapse using *Lactobacillus casei* Shirota

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For further information visit our website: **www.yakult.co.uk/hcp**
Contact the UK science team on **science@yakult.co.uk** or **0208 8427 600.**
Contact the Irish science team on **science@yakult.ie** or **01 804 7695**