LcS Insight: A study day report

Yakult HCP Study Day 2014

Current insights into the gut microbiota and its influence on health

This article describes presentations given by internationally renowned experts (see p16) at a healthcare professional study day on 1st October 2014 at the Royal College of Physicians. All the speakers have approved the summaries of their talks, which covered the following aspects of the gut microbiota's influence on health:

1. Making sense of the gut microbiota: insights from new technology

We all harbour a vast community of commensal bacteria in our intestines. The profile of this microbial ecosystem is unique to each person, and reflects early life events (eg, whether breast-fed or bottle-fed, vaginal-birth or C-section). This talk by **Dr Julian Marchesi** provided a timely update on the new results, technologies and terms in this line of research.

The importance of the gut microbiota is seen clearly in germ-free animals: their immune system is poorly developed and many organs do not function properly. Furthermore, an aberrant gut microbiota has been observed in several diseases (eg, asthma, eczema, inflammatory bowel disease (IBD), heart disease, liver disease, and obesity-related disease). It is not always clear, however, whether this dysbiosis results from or causes the disease. This might determine whether the gut microbiota could be a therapeutic target. Dr Marchesi described how the microbiome of colorectal cancer (CRC) tumours is distinctly different from that of adjacent healthy mucosa.[1] Potential pathogens were underrepresented in the tumours whilst several commensal species were overrepresented, suggesting that the altered microbiome was a result of the cancer, not the cause.

The human microbiome varies considerably but each of us probably carries about 160 different species. Approximately half of these are common to everyone (eg, *Faecalibacterium prausnitzii*) although it is probably more important that several microbial *functions* are common, such as production of short-chain fatty acids (eg, butyrate, acetate, propionate). As not all gut bacteria can be cultured in the lab, researchers analyse the microbes' genes and other biomarkers in order to understand which species are present and what they do. These new methods often have the suffix '-omics' (meaning a field of biological study) and a prefix indicating the particular area of interest (eg, proteomics, genomics, etc.). 'Meta' means that this is a collection of data relating to all microbes in a particular community. Knowledge of the gut microbiota's genome and metabolites will help us understand the microbiota's functions and influence on the body, perhaps leading to new disease-reduction strategies.

Insight — What does it all mean? Terms used in the study of the gut microbiota

Microbiota: the qualitative and quantitative information about the different microbes present - ie, what is there and how abundant they are. (The term 'microflora' is out of date - *'bacteria are not flowers'*.)

Microbiome: the functions (and genes) of the microbiota - ie, what they do. For example, bile metabolism and the microbial genes involved in this.

Metagenomics: analysis of all the genes (in the gut microbiota) to create catalogues that provide information about what the microbes do. Communication from the gut microbiota to its host is via proteins and metabolites, so this is important information.

Metataxonomics: the creation of 16S rRNA gene inventories used to define the microbiota. 16S rRNA is found in bacteria but not in humans; the DNA sequence of its gene is used to identify bacterial species.

Metabolomics: the catalogue of all the metabolites present; these are the end products of gene expression. 'Metabonomics' is sometimes used inter-changeably but actually refers to the study of how the metabolome changes in response to nutrition, drugs or disease. Faecal analysis shows bacterial responses to these changes; urine is a better reflection of the host response.

Degradomics: cataloguing the complete set of proteases present.

Dr Marchesi explained how different 'omic' datasets can be 'married' in order to correlate species with metabolites, and to see how they vary with different disease states or diets, etc. This has been done with bariatric surgery patients. Bariatric surgery causes rapid changes in the gut microbiota (eg, increased Gram-negative *Enterobacter hormaechei*) and microbial metabolites. This creates a more cytotoxic environment in the gut, increasing risk of CRC.[2] But the gut microbiota also modifies bile acids. The faecal profile of these biological signalling molecules changes following surgery. Animal studies have shown that reducing bile acids helps improve metabolic syndrome.[3] This might explain the rapid resolution of type 2 diabetes that can follow bariatric surgery.[4]

'Omics' methods have also been used to explore whether enzymes that degrade proteins (ie, proteases; collectively termed the 'degradome') play a part in IBD. Certain gut bacteria members produce these whilst other species can inactivate proteases that originate from the pancreas.[5,6] Use of targeted protease inhibitors reveals distinct differences in faecal samples from patients compared to healthy people. There is also a large variation of proteases in healthy people; this may have health implications. High levels of faecal proteases cause loss of gut barrier function, exposing the liver to higher levels of endotoxins from Gram-negative bacterial components leaking from the gut.[7] Intestinal inflammation leading to liver disease might be a further consequence.

The gut microbiota: key messages from Dr Julian Marchesi

- The human gut microbiota has co-evolved with us; without it many bodily functions (not just of the gut) would be seriously affected. *('What happens in the gut does not stay in the gut').*
- Newly developed non-culture methods have allowed scientists to identify individual species in the gut microbiota and to get an overview of the proportions of different types of bacteria in the gut microbiota.
- We are starting to understand exactly what the gut bacteria do by finding out which proteins and metabolic products are produced by the bacteria in the gut.
- Ultimately it is hoped that strategies that modulate the composition and/or function of the gut microbiota can reduce disease risk and maintain health.
- Gut microbiota modulation is certainly possible, but preferably not with antibiotics *('You wouldn't use paraquat on the whole of your lawn to get rid of weeds').*

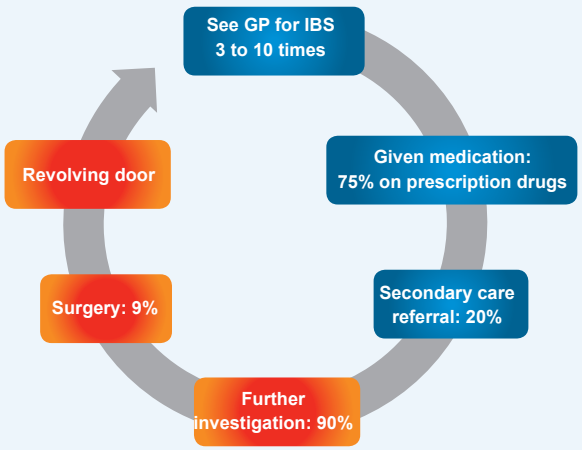
2. Irritable Bowel Syndrome (IBS)

2.1. Gut health matters: a GP's presentation

Dr John O'Malley began by describing some of the challenges faced by GPs dealing with patients presenting with gut problems. A GP himself, Dr O'Malley has spent most of his working life trying to raise the profile of gastrointestinal (GI) problems in general practice, and he painted a rather grim picture. The first problem - GPs are very busy (there are up to 350 million GP consultations per annum). They have limited time to devote to each patient; a standard consultation appointment is only ten minutes. This is not enough time to get a full case history from a patient with gastrointestinal problems and to have a full discussion with them. There are also no incentive payments for the GPs in this area of healthcare. Finally, there is poor provision of dietitians in primary care.

A further issue is the scale of IBS problems in the community. Gastrointestinal (GI) disorders account for 10-15% of all GP consultations and up to 14% of their drug budget goes towards medications for these. But GPs may be seeing just the 'tip of the iceberg'. IBS (which affects 10-15% of the population) accounts for 12% of all consultations and 50% of referrals to gastroenterologists (often the only option for the GP). Sufferers may have poor quality of life but only 10% actually seek medical advice. Patients can be fearful of the prognosis or embarrassed about discussing gut symptoms. Having sought medical help, the patients can then get caught in a vicious circle of referral between primary and secondary care. As many GPs still think of IBS as a disease diagnosed by exclusion, they may refer patients for blood tests and colonoscopies that are often unnecessary. If nothing is found, most likely the patient gets referred back to the GP. The algorithms and guidelines that are available for GPs often direct patients for secondary referral when the problem should or could be managed in primary care. Dr O'Malley wanted to see a more holistic approach involving not just GPs but also community nurses, practice nurses, dietitians and nutritionists.

The IBS circle of referral



There can also be a mismatch between the expectations of the patient and the doctor. A Dutch survey of 142 patients and 100 GPs showed this.[8] Although diagnosed as having IBS, in fact only 62% of the patients met the Manning criteria and only 18% fulfilled Rome II criteria (see below). There was a difference in what was perceived as the main aetiological dietary factor: patients thought this was food intolerance and GPs believed it to be lack of fibre. Many of the GPs managed the patients initially with dietary advice (94%), counselling (77%) and medication (55%) but while many patients expected reassurance (47%) and medication (37%), only 9% appreciated dietary intervention. There are other problems with GPs' advice. For example, it has been shown that about 50% of IBS patients have an aberrant gut microbiota thus increasing dietary fibre could make matters worse. Unfortunately many GPs do not know this and often continue to give this advice.

Insight

The main points of the diagnostic criteria that have been/are used in IBS[9,10]

Manning criteria

- Onset of pain linked to more frequent bowel movements
- Looser stools associated with onset of pain
- Pain relieved by passage of stool
- Noticeable abdominal bloating
- Sensation of incomplete evacuation > 25% of the time
- Diarrhoea with mucus > 25% of the time

Rome II criteria

At least 12 weeks (not necessarily consecutive) in preceding 12 months of abdominal discomfort or pain that has two out of three following features:

- Relieved with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

Symptoms that cumulatively support IBS diagnosis:

- Abnormal stool frequency
- Abnormal stool form
- Abnormal stool passage
- Passage of mucus
- Bloating or feeling of abdominal distension

Rome III

Recurrent abdominal pain or discomfort at least 3 days/month in last 3 months associated with ≥ two of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

[Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis]

Despite all these issues, Dr O'Malley believes a lot can be done in primary care to help people with IBS. For example, it is his policy to advise patients to take a probiotic if they are prescribed antibiotics. This is to avoid some of the consequences of this medication (eg, IBS, diarrhoea or *Clostridium difficile* illness).

One reason for the GPs' dilemma is their lack of knowledge and education. Training is very much oriented towards pharmaceuticals and meeting the Quality and Outcomes Framework (QOF), the annual reward and incentive programme detailing GP practice achievement results.[11] GPs still know little about the gut microbiota and feel very unsure about recommending or prescribing a probiotic because there is so much they do not understand:

- What product to recommend?
- Is there good quality control?
- Are there sufficient live bacteria in the preparation?
- What evidence is available?
- Which one works?
- Are they all the same?
- How often and what dosage?
- For what conditions (IBS-C, IBS-D)?
- Are they suitable for children?

Dr O'Malley finished by saying that, although there is much still to learn, primary care is the best place to use probiotics and in the best way – to maintain health and prevent disease.

Gut health in primary care: key messages from Dr John O'Malley

- IBS is a common reason for people to see their GPs yet many patients do not seek advice.
- Referral of patients to secondary care may not be the best idea; hospital tests are often unnecessary.
- Different types of healthcare professionals in primary care need to be involved (eg, community nurses, practice nurse and dietitians).
- Better education is needed on what is the most appropriate advice to give re lifestyle and dietary changes (including trying probiotics).
- Probiotics are safe and do not (usually) come out of the GP's budget. They may be worth recommending for some patients but the cynicism and lack of knowledge of GPs needs to be addressed.

2.2. Self-management: how to help people help themselves better

Dr Nick Read started his talk by discussing the dissatisfaction expressed by both irritable bowel syndrome (IBS) patients and their doctors. The patients complain their doctors are not listening (perhaps even missing something more serious), and the patients are told they just have to learn to live with it, or it's all in their mind. Sometimes the proposed treatment causes more problems than the IBS itself, and when the patients get referred to a hospital clinic, they may see a different doctor every time. On the other hand, doctors complain IBS patients are difficult, never satisfied and frequently make inappropriate and incorrect self-diagnosis. Doctors do not get enough training specifically for IBS; they are trained to rule out treatable conditions and have limited time for each consultation. So referral is an easy option. The focus on the Rome criteria[12] for diagnosis of IBS has not helped either: IBS is still a disease diagnosed by exclusion, with little focus on individual symptoms. But IBS is a big problem, with 15 million sufferers in the UK alone, and the NHS struggles with this type of chronic disease where patients often need more time and effort than those with other more identifiable diseases. Dr Read was concerned that the situation could be getting worse. NICE has introduced a new test to identify IBD: faecal calprotectin - a substance released in excess into the gut when the gut is inflamed. This should help GPs distinguish IBD from IBS, which would reduce the number of IBS patients referred to secondary care,[13] and increase the number

of patients managed in the community. Dr Read questioned whether there are sufficient medical resources for this in primary care, particularly as treatment often requires very individual and personal dietary and lifestyle changes.

The impact of chronic conditions in the NHS has led to the development of self-management programmes to help patients learn the skills to manage their own conditions better. Assessment of NHS education programmes (tutored by lay readers, rather than health professionals), showed that these increased patients' confidence in managing their disease, but were unlikely to reduce healthcare resources.[14] IBS, however, seems to be a condition that is particularly suited to self-management, particularly in the modern era when many patients seek information from the internet. Self-management could be a win-win exercise for doctors and patients. There are also some studies that indicate self-help can work (see box).[15]

Insight

Self-management by IBS patients: evidence that this can work

- Community study of 420 patients: guidebook plus self-help meeting showed a 60% reduction in consultations and 40% reduction in healthcare costs, as well as reduced symptom severity, compared to standard care.[16]
- Comprehensive IBS self-management, facilitated by nurses, showed significantly lower levels of GI symptoms, anxiety and depression at follow-up, compared to standard care.[17]
- Internet-delivered cognitive behavioural therapy (CBT) (including mindfulness and exposure-based treatment) plus therapist contact showed significant reduction in IBS symptoms compared to stress management.[18]
- A study of 188 patients showed that a comprehensive self-management programme, delivered in person or by telephone, gave better results than standard care.[19]

Dr Nick Read went on to describe various aspects of the IBS Self Care Plan (available on the IBS Network's website **www.theibsnetwork.org/the-self-care-plan/**).

This comprehensive website explains all about IBS and what causes it, and how to manage symptoms with diet and lifestyle changes. It aims to provide all the information a patient might want to understand and look after their illness in collaboration with their healthcare professional. Dr Read showed some of the webpages, which are written in easy to understand language – debunking myths and giving facts about, for example, food intolerance, acupuncture, stress and anxiety and the causes of bloating. Patients can devise their own self care plan using a symptom tracker to record how their IBS responds to changes in their life, diet or medications. The IBS Network also sends out a regular newsletter for healthcare professionals: **www.theibsnetwork.org/healthcare-professional-signup/.** Members of the IBS Network can receive professional advice by email, use the telephone help line, and receive a quarterly magazine, monthly newsletter and 'Can't Wait' cards to help them gain access to toilets in stores and offices.

Finally, some insights came from the question and answer session following Dr Read's talk. If there is limited time for a consultation, his advice was to listen to the patient and pick up on their cues. Also asking patients to score their job/exercise/stress/relationship out of 10 can be a rapid way to get to the heart of the matter.

Self-care with IBS: key messages from Dr Nick Read

- GPs often do not have the time or resources to deal adequately with IBS patients.
- Referral to secondary care for IBS may be reduced by the introduction of the faecal calprotectin test, which identifies gut inflammation.
- Guided self-management, facilitated in primary care by digestive health practitioners, is a proven and recommended option for IBS patients.
- Patients and healthcare professionals should consult the IBS Self Care plan on the IBS Network website (**www.theibsnetwork.org/the-self-care-plan/**)

2.3. Can probiotics help with IBS-type problems?

The spectrum of IBS symptoms (see below) was explained by **Yvonne McKenzie**. For example, bloating affects ca. 96% of patients and ca. 60% find symptoms worsen after eating, particularly with onset of pain. Symptoms can be triggered by a range of factors, including antibiotics, acute gastroenteritis, surgery, infection, low grade mucosal inflammation, psychosocial stress and a genetic predisposition.

Diagnosis of IBS in primary care state[20]

- Abdominal pain or discomfort that is
  - Relieved by defaecation **or**
  - Associated with altered bowel frequency or stool form

  and at least two of the following:
  - Altered stool passage (straining, urgency, incomplete evacuation)
  - Abdominal bloating
  - Symptoms made worse by eating
  - Passage of mucus
- Supporting diagnosis: lethargy, nausea, backache and bladder symptoms.

The heterogeneity of IBS makes it difficult for clinicians; treatment strategies include pharmaceuticals, dietary management and possibly complimentary/alternative treatments. In 2012 the British Dietetic Association published guidelines[21] describing a three line care pathway for IBS patients after referral. At all stages, the patient should be offered advice and reviewed for symptom changes.

Line 1: clinical assessment and assessment of diet and lifestyle: healthy eating & lifestyle

Line 2: try linseeds with constipation-predominant symptoms; evaluate if there is high consumption of fermentable carbohydrates; try a probiotic for four weeks.

Line 3: try an empirical or elimination diet for 2-4 weeks.

Sufferers may have a changed profile of bacterial species within the gut lumen matter and the mucosa.[22-24] Yvonne went on to discuss probiotics, pointing out that these should be live microorganisms that are able to reach the colon alive and in adequate numbers. The recommended dose should be effective but higher dosage does not necessarily mean better efficacy, as shown by a study testing capsules of a *Bifidobacterium infantis* strain.[25] Probiotics are considered foods or food supplements and are not medications. Currently there are no approved health claims for probiotic products in the EU but other countries (eg, Japan) have approved claims. Current advice from the BDA[21] is that probiotics are safe to use and to try/recommend one product at a time at the manufacturer's recommended dose for four weeks. It should be noted that this does not cost the NHS anything – patients purchase probiotics for themselves.

The low FODMAP diet, now increasingly popular for IBS management, involves reducing consumption of short-chain carbohydrates (oligosaccharides), disaccharides, monosaccharides and polyols poorly absorbed in the small intestine. Two studies have shown that, after 3-4 weeks, the diet reduces numbers of beneficial bacteria such as bifidobacteria.[26,27] This indicates there may be potential in advising probiotics with or after the diet, as a less beneficial microbiota could be detrimental for colonic health.

Yvonne then discussed a recent systematic review from the American College of Gastroenterology, which examined 35 probiotic randomised controlled trials (RCTs) involving 3,452 IBS patients.[28] The review estimated that seven patients need to be treated to show benefit, and found adverse events with probiotics to be rare. Persistent or unimproved IBS symptoms were much lower with probiotics compared to placebo (55.8% vs 73.1%; $P<0.001$). Although only a weak recommendation, it concluded that, overall, probiotics improve global symptoms, bloating, and flatulence. There were no recommendations regarding individual species, preparations or strains because evidence is insufficient.

A practical guide to probiotics has also been produced by the European Society for Primary Care Gastroenterology[29] based on their 2012 systematic review.[30] This concluded probiotics are safe for primary care patients and that specific probiotics can help relieve overall symptom burden in some diarrhoea-predominant IBS. Probiotics can also reduce bloating/distension and improve bowel movement frequency/consistency in some IBS patients, although no one probiotic alleviates the full range of symptoms. In some patients, improvement in symptoms led to better quality of life.

Yvonne gave a word of caution though, noting issues with some studies, including small subject numbers, lack of IBS subtyping and high placebo response. There is also a lack of follow-up and no indication for required duration of probiotic intake. The following guidelines are available:

- **NICE Clinical Guidance (2008):** Advise people with IBS who choose to try probiotics to take the product for at least four weeks while monitoring the effect. Take at the dose recommended by the manufacturer.[20]
- **BSG Guidelines (2007):** Probiotics are a more attractive means of altering the bowel microbiota compared to antibiotics. However, quality of evidence is 'moderate' with 'qualified' strength of recommendation.[31]
- **BDA Guidelines (2010):** Probiotics should be considered, ideally, after fermentable carbohydrate restriction. One product should be selected at a time and its effects monitored. Try for a minimum of four weeks.[21]
- **Map of Medicine (2010):** Recommend that patients are managed according to predominant symptoms.[32]

Probiotics and IBS: key messages from Yvonne McKenzie

- Probiotics are safe to try for IBS but there is weak and limited evidence of efficacy.
- High quality research will lead to more probiotics having proven efficacy.
- Probiotics will remain popular simply because their ingestion makes people feel better.
- Consult guidelines and systematic reviews for recommendations and individual studies.

3: Gut microbiota modulation in Inflammatory Bowel Disease (IBD)

As many as 600,000 people in the UK are affected by this chronic condition with incidence increasing, particularly in young people. IBD can develop at any age, but frequently begins at 10-40 years.[33] Symptoms vary and can be severe: diarrhoea with blood and pain, urgency, fatigue, loss of appetite and weight loss. Antibiotics, probiotics, prebiotics and faecal microbiota transplantation (FT) have all been investigated as strategies for IBD relief and management. **Dr Ailsa Hart** reviewed the supporting research.

Insight — IBD conditions

- **Ulcerative colitis (UC):** continual areas of inflammation of the colonic mucosa. It can start in the rectum and extend up the colon, affecting all or part of it. Patients can have periods of remission.[34]
- **Crohn's disease (CD)**: inflammation affecting any part of the gut, from mouth to anus, but commonly in the ileum or colon. Inflammation can extend right through the gut wall. Scarring can cause ulcers, which may develop into fistulas (tunnels that develop from the gut into other parts of the body, such as the skin or bladder).
- **Pouchitis:** inflammation of the ileal pouch - an internal reservoir surgically constructed from the small intestine. It is created when part of the colon is removed to help manage symptoms of IBD. The pouch can be linked to the anus so patients can still pass stool.

There is a strong genetic predisposition for IBD: over 160 genes have been identified that are linked to the disease. Over two thirds overlap between CD and UC; there is also overlap with mycobacterial infection, ankylosing spondylitis and other immune-mediated diseases.[35,36] IBD may have environmental triggers but the gut microbiota may also be involved, as seen by the alleviation of inflammation if the faecal stream is diverted from the gut. A much less diverse gut microbiota is seen in patients[37] with a noted decrease in the Gram-positive bacterial phylum Firmicutes[38-40] particularly *Faecalibacterium prausnitzii*. This has clinical correlation: low levels of this species are associated with greater post-operative recurrence[41] The situation is not that clear cut, however, because children with CD (who probably have fewer confounders such as smoking) actually have higher levels of *F. prausnitzii*.[42] But decreased microbial richness and diversity correlates with periods of UC relapse, and not with remission.[43] Pouchitis is also associated with reduced diversity of faecal microbiota.[44] Recent research from St. Mark's Hospital has shown anal fistula tracts generally do not harbour high levels of mucosa-associated microbiota.[45] Significant perturbation of microbial function, however, may be the more consistent microbial feature of IBD, with changes in oxidative stress pathways and nutrient transport and uptake, as well as an increase in virulence and secretion pathways in CD.[46]

Despite the challenges faced by researchers investigating IBD,[47] strategies to modulate the gut microbiota have been explored. In fact, antibiotics (metronidazole+/- ciprofloxacin, or targeted antibiotics) are now in the guidelines for pouchitis and post-operative CD, with significant symptom improvement noted. Certain probiotics have been shown to help maintain remission in pouchitis[48] and mild to moderate UC.[49] Probiotics such as VSL#3 may also decrease the disease severity in mild to moderate episodes of active disease, although it should be noted that large doses were used.[50] There is very limited evidence of any benefit with prebiotics: a recent study concluded that fructo-oligosaccharide was ineffective in active CD.[51]

Patients are, perhaps surprisingly, interested in faecal transplantation (FT). At Dr Hart's hospital ca. two-thirds of patients with refractory pouchitis would consider it. Furthermore, studies show that 53% of refractory *Clostridium difficile* patients would be willing to try FT and 97% would be willing to repeat it.[52] When the efficacy of the treatment was explained, 85% chose FT and 15% chose antibiotics.[53] Only 4% changed their mind when the details of the procedure were made known to them. Enema and colonoscopy are more acceptable than the nasogastric route; patients prefer treatment in hospital, and 77% are willing to pay.

Most interest is for treatment of refractory *C. difficile*, with efficacy indicated by the fact the gut microbiota of these patients has reduced phylogenic richness, particularly for Bacteroidetes and Firmicutes.[54] Over 500 cases of FT for recurrent *C. difficile* have been reported, with evidence reaching the level of systematic reviews. An overall success rate of >90% has been reported.[55] A multi-centre long-term follow-up of colonoscopic FT for recurrent *C. difficile* infection, with a 98% cure rate, found that patients improved within three days, and that after two weeks their stools resembled those of the donors.[56-58] In fact, the first RCT investigating FT for refractory *C. difficile* was stopped early for ethical reasons because the treated patients were so much better than the control group.[59] Their faecal microbiota also became more diverse, becoming more similar to that of the healthy donors.

The situation is not the same for IBD and pouchitis. A systematic review in 2012 found only weak and limited evidence for FT although it was acknowledged that it had potential if all other treatments had failed.[60] But a more recent study of six patients with chronic active UC, given FT by colonoscopic administration, found that although there was short-term improvement, none of the patients achieved

clinical remission despite some 'normalisation' of the gut microbiota.[61] Recent work at St. Mark's Hospital found that a single treatment was safe for pouchitis patients, but there was no clinical benefit and only a slight shift in the microbiota achieved. Dr Hart believes a single transplant is not enough and different modes of delivery are needed.

Insight

Faecal transplantation (FT): the issues that still need to be addressed

- Safety[62]
  - donors need to be logged and stool samples screened
  - governance and best practice procedures should be written[63]
  - a few adverse events have been reported
- Is it better to use a relative's sample? How much should be transplanted?
- How should it be administered?
  - Colonoscopy: more acceptable, entire colon infused, possibly more effective
  - Nasogastric tube: less acceptable, entire GI tract exposed, endoscopy not needed
- Fresh *vs* frozen (or capsules)?[64]
- Can the IBD gut microbiota be altered with FT? Which are the best species to use?

Gut microbiota modulation in IBD: key messages from Dr Alisa Hart

- A diverse microbiota may be more protective but it remains unclear which species either drive or reduce inflammation.
- Antibiotics and probiotics can modulate the gut microbiota. There is evidence indicating the benefit of certain probiotics in maintaining remission in pouchitis and UC.
- FT has proven successful for treating refractory *C. difficile* but there is little evidence of benefit with IBD. Many questions remain unanswered. Safety must be assured.
- The right stage of the disease should be tackled. It is better to treat early or even prevent where possible.

4. Chronic liver disease and the gut microbiota: Is there potential for intervention?

In 2012, the UK's Chief Medical Officer's report highlighted concern that liver disease was the only major cause of death on the increase in England.[65] Between 2000 and 2009, deaths from liver disease in the under 65s increased by around 20%, yet had decreased in most other EU countries. Newly diagnosed cases as well as hospital admissions are on the increase, with between 25,000 and 30,000 new cases of liver cirrhosis diagnosed every year. **Dr Nathan Davies** stressed that all three major causes of liver disease (obesity, undiagnosed infection and harmful drinking) are preventable. Although excessive alcohol intake (and in particular large scale habitual drinking) is generally known to cause liver disease, it is now realised that obesity may ultimately pose the most significant risk to the UK population.

Insight

The liver: in sickness and in health

- All the blood in the body is filtered by the liver up to 20 times an hour. As the most metabolically active organ in the body, it generates most of our body heat.
- We can operate with as little as 20% of a functioning liver. As much as 80% can be cut out; it would grow back in ca. three months. It can also compensate extremely well – often liver disease patients are unaware of illness until late stages, when jaundice sets in.
- **NAFLD** (non-alcoholic fatty liver disease) is linked with obesity**.** Fat accumulates in the liver, leading to inflammation and scarring (**NASH**; non-alcoholic steatohepatitis).[66] In turn this leads to **cirrhosis**, when the liver becomes scarred. This replaces healthy tissue, so that the liver can no longer function properly or recover. Portal hypertension (which increases the risk of internal bleeding) and end-stage liver disease can follow.[67]
- **ASH** (alcoholic steatohepatitis) has similar pathophysiology, but fat accumulation and damage is due to excessive intake of alcohol.

Once the liver starts to fail, it affects other organs (eg, the brain, heart or kidney) and then the chance of survival drops very quickly (~40% mortality within a month). The average time from organ failure to death rate is 10 days.[68] Patients who develop infection have a much higher rate of mortality, with infection mostly thought to come from the gut.

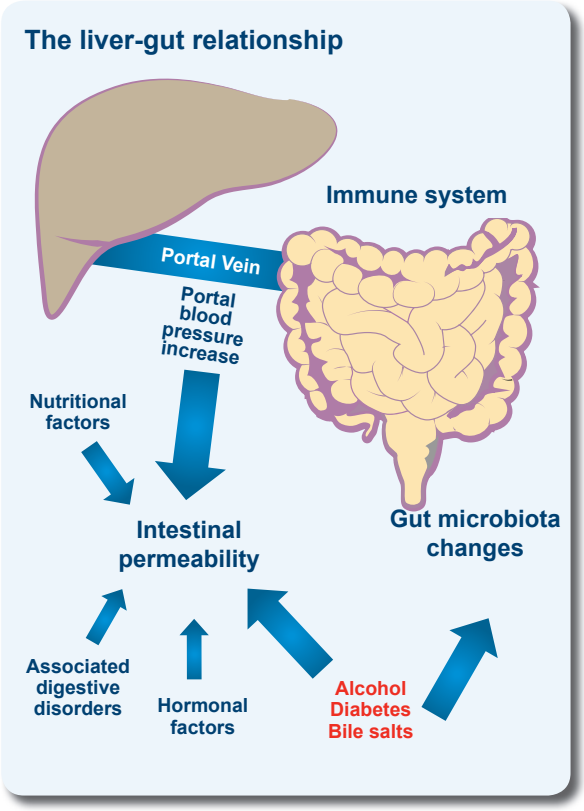
There is a strong relationship between the gut and the liver, with a two-way communication via bile, hormones, and digestive products. Importantly, blood from the gut flows into the portal vein, which then branches into smaller vessels and travels through the liver. When the liver becomes scarred, it is difficult for the blood to flow into it, causing back pressure to build up in the portal vein and leading to further complications such as spontaneous bleeding.

The gut microbiota has a strong influence on liver disease progression. Binge drinking, for example, increases gut permeability, allowing bacteria as well as their products and DNA to translocate through the gut wall to the blood, increasing serum endotoxin levels.[69] Endotoxaemia drives a non-specific systemic inflammation (perhaps the reason why people feel ill after drinking too much). Continuing to drink just perpetuates the problem. If the liver cells (ie, hepatocytes and macrophages) that help cleanse the blood of bacterial products become damaged, this protection is reduced or lost altogether.

Typically, disease progression is associated with gut microbiome changes, which further drive damage within the body.[70,71] As well as systemic inflammation, ammonia (a bacterial product) can build-up in the blood due to the failure of the liver to remove it. This can lead to neuroinflammation and hepatic encephalopathy (neuropsychiatric abnormalities that can occur with liver failure).[72]

The gut microbiota changes become more marked when the liver starts to lose its ability to recover (ie, becomes decompensated).[73] The phagocytic ability of neutrophils (ie, their ability to consume bacteria) also becomes impaired.[74] These are in the first line of defence against infection, which could explain the high mortality when patients develop infections. These findings prompted Dr Davies and his colleagues to conduct an exploratory study to investigate probiotic benefit for liver disease patients. In their small proof of concept study,[75] alcoholic cirrhotic patients were given *Lactobacillus casei* Shirota for four weeks, three times daily. Data were compared with healthy controls and similar patients not on probiotics. At baseline, the neutrophil phagocytic capacity of the patients was lower than the healthy controls (73% vs. 98%; $P<0.05$) but after probiotic intervention, it became normalised (n=10; 100%; $P<0.05$). (This did not occur with the control patients.) Certain bacterial receptor proteins on the surface of immune cells were overexpressed in the patients. Probiotic intervention was associated with normalisation of TLR4 expression. (TLR4 is the receptor that detects lipopolysaccharide, the endotoxin component of Gram-negative bacterial cell walls.)

Dr Davies concluded that this and other studies show that probiotics may make the gut environment, and the bacteria there, more benign to the rest of the body. Research with other probiotics supports this. For example, use of VSL#3 over a period of six weeks in cirrhotic patients, was associated with a reduction in portal vein pressure.[76] A more recent study in India showed that a six-month intake was associated with reduced risk of hospitalisation for hepatic encephalopathy and other indications of advanced disease.[77] Use of a non-absorbable antibiotic in a rodent model of cirrhosis may prevent the increased susceptibility of the kidneys to inflammatory damage by reducing translocation of Gram-negative bacteria from the gut.[78]



Liver disease: key messages from Dr Nathan Davies

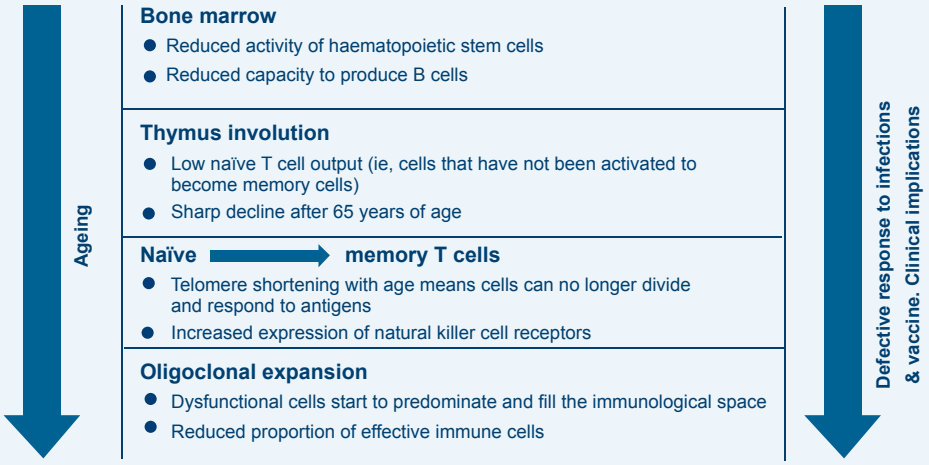
- Combinations of factors (eg, obesity, alcohol, infection) accelerate liver disease progression.
- Alcohol as an additional causative factor markedly increases the rate of liver failure.
- Only limited options are available following liver failure: transplant (only 726 liver transplants in the UK in 2011-2012) and supportive therapy.
- Liver disease progression is driven by inflammation coming from the gut.
- Modulating the gut bacterial profile may ameliorate inflammatory effects on the whole body.

5. Old age, the gut microbiota and probiotics

5.1. The impact of age-related changes on gut immunity

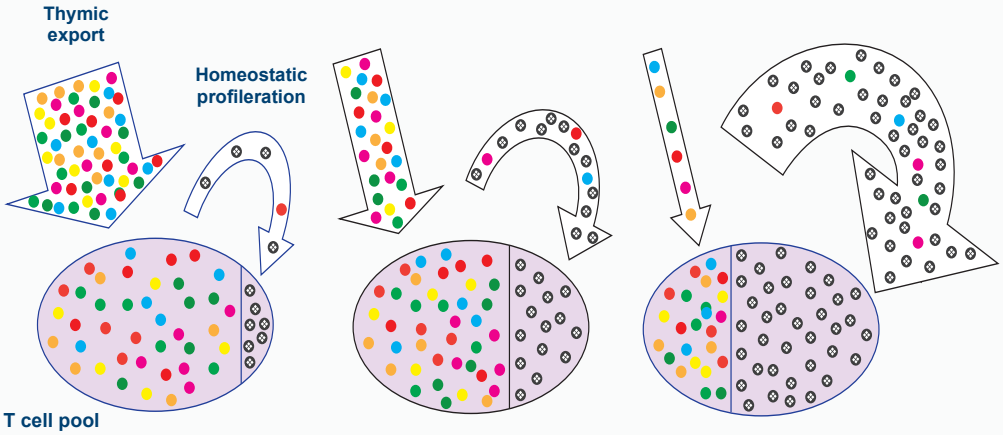
Professor Parveen Yaqoob explained how the immune system becomes weakened in later life, with decreased production of B and T lymphocytes.

The effect of age on the adaptive immune response



By the age of 50, only about 10% of thymic function is left and the function is almost gone by 65 (a phenomenon called thymus involution) so fewer naïve T cells will be circulating in the blood.[79] The capacity of dendritic cells to induce T cell activation is also significantly impaired.[80]

Age-associated decline in T cell repertoire diversity



Newborn
- Most T cells naïve phenotype
- Major contribution from thymus
- High diversity
- Few memory cells

Young adult
- Most T cells naïve phenotype
- Significant contribution from thymus
- Good diversity
- Increasing proportion of memory cells

Old adult
- Most T cells memory phenotype
- Minimal contribution from thymus
- Low diversity
- Size of pool reliant on proliferation

Not only does this make the older person much more susceptible to infection but also the efficacy of vaccination is sharply reduced, particularly after 65 years of age. As little benefit has been shown with micronutrient supplementation, there is now interest in seeing if the immune response can be improved by modulating the gut microbiota, because this influences the immune system.[81-83] The commensal microbiota (and probiotics) can communicate with the immune system via three routes:

1. **Translocation of the bacteria through M cells** to be recognised by macrophage and dendritic cells, which process the bacteria and present antigens to T and B cells in the intestinal mucosa.
2. **Dendritic cells** extend dendrons from the mucosa into the gut lumen, where they sample microbial cells and process them before antigen-presentation as above.
3. **Toll-like receptors** on the intestinal epithelial cells recognise bacteria in the gut lumen, producing soluble mediators (such as cytokines) that direct dendritic cells to respond and communicate with T and B cells.

As T and B cells communicate with the rest of the immune system, this can make the gut bacteria's effects systemic to the whole body. Microbial products can also translocate from the gut, interacting with receptors on immune cells in the respiratory tract and driving inflammatory responses.[84]

The range of immune parameters influenced by probiotics includes natural killer (NK) cell activity, phagocytosis, T-lymphocyte proliferation and antibody response to infection and vaccination. The associated clinical consequences of these effects have been shown: a Cochrane systematic review (ca. 3,500 subjects) concluded that probiotics were better than placebo in reducing episodes of acute upper respiratory tract infections (URTI).[85] But not all studies were positive and no studies on older people (the group most affected) were included.

A few probiotic/immune studies have been conducted in older people. In one such study, healthy subjects were given milk supplemented with *Bifidobacterium lactis* HN019 for three weeks, and immune enhancement was observed: eg, increased activity by neutrophils (phagocytosis) and NK cells (tumour killing ability).[86] After Professor Yaqoob's group showed *in vitro* enhancement of NK cell activity with *L. casei* Shirota,[87] they conducted a placebo-controlled study in people aged 55-75 years, which also demonstrated improved NK cell activity associated with the probiotic consumption at two bottles per day for four weeks.[88]

The mechanisms of action underlying such findings may involve the take-up of the probiotic bacteria by monocytes and macrophages, after which the indigestible cell wall components stimulate induction of cytokines such as IL-12. IL-12 upregulates NK cell activity, which targets virally infected cells. But the immune response is complex and such biomarkers do not always relate directly to clinical outcome.

Whilst IL-12 enhances anti-infective and anti-tumour immune responses, IL-10, another cytokine of probiotic interest, is considered to be anti-inflammatory and regulatory.[89] Thus there may be two categories of probiotics: those that are immunostimulatory (generally lactobacilli) and those that are immunoregulatory (generally bifidobacteria), although some probiotics can do both depending on their context.[90] Work from Professor Yaqoob's group indicates that older people may respond better to immunoregulatory probiotics and young people to immunostimulatory.[91]

Professor Yaqoob ended by discussing the criteria for, and substantiation of, clinical markers that could prove benefit.[92] The evidence in certain diseases, however, has now reached the level of meta-analysis. For example, one such review concluded an overall magnitude of probiotic protective effect for gut infections was 42%.[93]

Old age, the immune system and the gut microbiota: key messages from Professor Parveen Yaqoob

- Immunity and response to vaccination declines significantly in older people.
- There is a theoretical basis that gut microbiota modulation can influence immunity.
- There are promising data relating to probiotic effect on respiratory and gut infections.
- There are indications of differential effects of probiotics in young and older adults.
- The relevance of biomarkers for clinical benefit can be an issue.

5.2. Community living or residential care? The impact on the health, diet and gut microbiota of older people

Although pretty much sterile at birth, infants are colonised rapidly by microbes so that, after ca. 1.5 years, they have a stable gut microbiota with a profile similar to that of adults. But in later life, the gut microbiota becomes more unstable, which can directly and negatively affect health. Over the past few years, **Professor Paul O'Toole** and his research group at University College Cork (UCC) have been involved in the ELDERMET project,[94] performing a detailed study of the health and faecal microbiome of 500 people over the age of 65 living in different settings: in the community; outpatients at day hospitals; short-term rehabilitation hospital care (< 6 weeks) and long-term residential care. The research group were looking to see if there were any correlations between the subjects' microbial metagenomic and metabolomic profiles, and indicators of health and disease risk.

Changes in the stability of the gut microbiota with age.

Data analysis revealed there was a similar profile of gut bacteria for older people living in the community and those visiting day hospital, with an apparently healthy diversity of species. The gut microbiota profiles of older people in short-term rehabilitation and those in long-term residential care were similar to each other, but were of low species diversity.[95] This is clear evidence that where an older person lives has a direct effect on their gut microbiota - so what aspects of the residential dwellings cause this difference?

Four dietary groups (DG1 to DG4) were identified within UCC's cohort of older people. The best diet (DG1: low in fat/high in fibre) was most common in people living at home (ie, in the community). The least healthy diet (DG4) was high in fat and contained only moderate fibre. 84% of the long-term residential care patients were in the least healthy dietary groups (DG3-4). Further analysis revealed that diet co-segregated with different profiles of gut microbiota as well as residence location. Using shotgun sequence analysis, it was found that the different microbial types varied in their ability to convert nutrients in the gut to produce short-chain fatty acids (SCFA: butyrate, acetate, propionate). SCFAs are important for colonic and general health, so this could have clinical consequences. Analysis of associations between the microbiota and clinical markers confirmed this. There were strong links, for instance, between certain microbial profiles and measures of frailty and risk of malnutrition. Other associations were observed for gut microbiota and blood pressure, calf circumference (linked to sarcopenia), and certain immune and cognitive markers. The gut microbiota of people living in long-stay care was also less stable over time. Frailer subjects had a less diverse microbiota that was more susceptible to external perturbation: antibiotics had a much more disruptive effect and the microbiota took longer to recover.[96] The latest research has shown that it is not just gut microbiota diversity that is important for health – the right bacterial species need to be present.

With the proportion of people over the age of 65 set to double in many countries over the next 30 years, maintaining the health of older people is a major challenge - but one that must be addressed. Professor O'Toole's group is one of the partners of NU-AGE, a large multidisciplinary consortium from 16 EU countries that is investigating whether nutritional changes (eg Mediterranean diet, probiotics, prebiotics) can modulate and ameliorate inflammaging and other age-related outcomes.[97] As part of this project, UCC researchers are looking at indicators of health risk among a broad spectrum of older people with varying health status who are still living in their own homes. By plotting diet against microbiota type in a bi-cluster graph, correlations emerge and community dwellers with intermediate or long-stay like microbiota types can be identified. In fact, the gradient of microbiota type (from community-healthy to long-stay type) correlates with corresponding types of diet. And, as expected, these new diet-microbiota groups correlate with health measures of physical and mental capabilities (eg the Barthel Index and Mini-mental state exam).

Barthel Index is an ordinal scale used to measure performance in activities of daily living. The ten variables addressed are: presence or absence of faecal incontinence; presence or absence of urinary incontinence; help needed with grooming; help needed with toilet use; help needed with feeding; help needed with transfers (eg, from chair to bed); help needed with walking; help needed with dressing; help needed with climbing stairs and help needed with bathing.[98]

Mini-mental state exam or Folstein test is a sensitive, valid and reliable 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used to screen for dementia.[99]

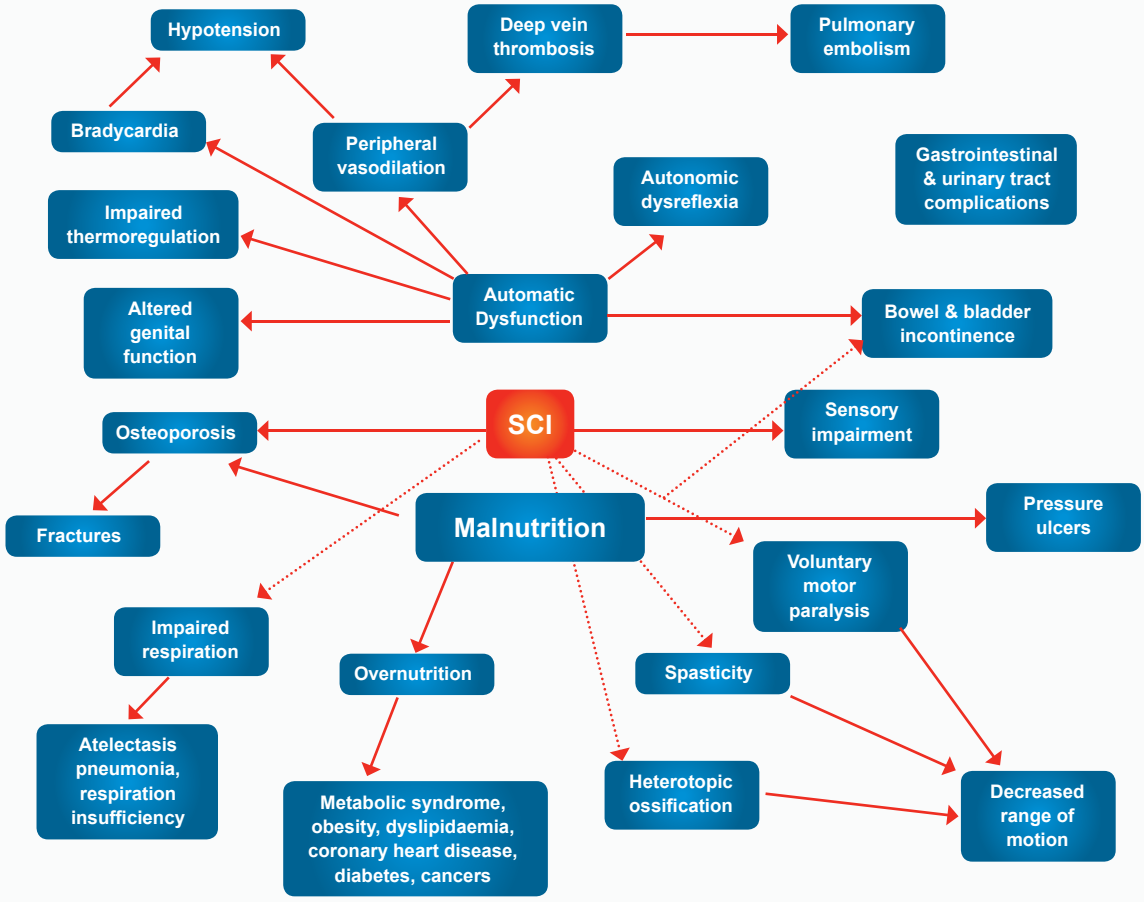
Professor O'Toole concluded by stressing the importance of diet as the driver in the microbiota shift after moving from community living to residential care. The re-location means diet changes totally within a few weeks; the gut microbiota takes longer, up to one year, to change. There have been some promising attempts to modulate the gut microbiota with interventions such as probiotics,[100-102] prebiotics[103] and bacteriotherapy ('*re-poopulating*').[104] Research will continue; we need to understand more to help people to stay healthy in later life.

The gut microbiota in later life: key messages from Professor Paul O'Toole

- Habitual diet correlates with microbiota; microbiota correlates with health.
- The gut microbiota in long-stay older people is less stable and less diverse.
- A microbiota with low diversity is characterised by differential methanogen abundance.
- Fine-detail microbiota-diet clustering in community subjects confirms health correlations.
- There is a lower gene count in low diversity microbiota.

6. Spinal cord injury patients: nutritional considerations

Common complications after spinal cord injury



Dr Samford Wong began by describing the history and achievements of the National Spinal Injuries Centre at Stoke Mandeville (NSIC), his place of work and (among other things) the birthplace of the Paralympic Games. There are now 11 spinal cord injury (SCI) centres in the UK and one in the Republic of Ireland: a total of 512 beds.[105] The aim is for patients to be moved to one of these specialised care facilities within 24-48 hours of suffering an SCI. The centres have made a huge difference to patients' subsequent rehabilitation and recovery. A marked improvement has been achieved compared to the 1950s, when 80% of patients would die within two years due to pressure ulcers and infections. Nowadays, the leading causes of death are cardiovascular disease, pneumonia and other respiratory conditions, or septicaemia (for example, from urinary tract infection or pressure ulcers).[106] Sadly the leading cause of death is suicide for complete SCI patients, particularly younger adults. With such injury, there is complete loss of muscle control and sensation below the level of the lesion; this affects not just the limbs but also a wide range of systems and organs in the body.[107]

On average 44% of SCI patients are at risk of malnutrition. This risk is even greater for high cervical SCI patients (~60%) and those on ventilator support (56%).[108] Malnutrition may result from a range of issues that specifically affect these patients: their level of injury; pain; nausea/vomiting; constipation; swallowing difficulties; depression; confusion; medical treatment; ventilator use and co-morbidities. Other influencing factors include the eating environment, perhaps limited food choice, lack of suitable aids and the timings of meals. To overcome these difficulties, care pathways and guidelines are being developed and staff specifically educated about nutrition. Guidelines have to be very practical: for example, it can be difficult to measure the height and weight of paralysed patients; both data are needed to assess nutritional status. Audits[109] and research studies are also helping to assess current practice and investigate how malnutrition affects clinical outcome. The development and validation of the Spinal Nutrition Screening Tool has helped with these.[110]

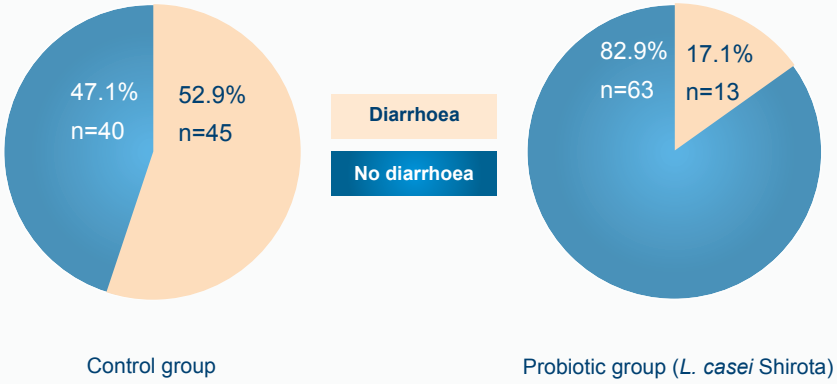
Certainly, undernutrition is associated with adverse clinical outcome. A small study by Wong *et al* in 2012 found undernourished patients remained significantly longer in hospital and had a higher mortality rate after 12 months.[111] Conversely, obesity is also a risk. This was demonstrated by the case history of a man who gained so much weight after his SCI (from 120 to 180.3 kg) that he underwent gastric bypass surgery, which caused weight loss and an improvement in

various health markers.[112] Vitamin D deficiency is a further risk; SCI patients may remain indoors for extended periods when first hospitalised.[113]

Improvement of patients' quality of life is a major aim of the SCI centres: patients are encouraged to participate in sport and supported into re-employment. Improving quality of life is also a focus of research. Dr Wong explained that use of catheters in these patients increases their risk of urinary tract infections. If diarrhoea develops as a result of the antibiotics they are prescribed, the patient's rehabilitation is delayed. Apart from the obvious impact on the patient, this also increases healthcare costs. This was why Dr Wong decided to conduct an exploratory study to investigate whether probiotics could help reduce the problem of antibiotic-associated diarrhoea.

The trial recruited 164 patients who had just been prescribed antibiotics and who had suffered their SCI in the preceding six months. The patients were randomly allocated to receive either no intervention or a daily probiotic fermented milk drink (*L. casei* Shirota) during the antibiotic course and for a further seven days after this finished. All the patients received the same routine care. The results showed that overall 65% of the patients were at risk of malnutrition. The probiotic *L. casei* Shirota was associated with significant reduction in antibiotic-associated diarrhoea (52.9% in the control group; 17.1% in the probiotic group; $P<0.0001$).[114] Whilst these results were very encouraging, there were limitations in the study design: the patients were not blind to the intervention and a placebo was not given. To confirm these findings, Dr Wong is currently conducting a larger placebo-controlled multi-centre study.

Antibiotic-associated diarrhoea in SCI patients: effect of *L. casei* Shirota probiotic



Nutritional care of spinal care injury patients: key messages from Dr Samford Wong

- The increasing life expectancy of SCI patients has focussed attention on improving quality of life and health care.
- Undernutrition can easily occur; this has a negative influence on clinical outcome.
- Other aspects of malnutrition are also risks: eg, overnutrition and vitamin D deficiency.
- Antibiotic-associated diarrhoea is a common problem for SCI patients: a recent trial showed benefit with the probiotic *L. casei* Shirota in reducing this risk.

7. Safety considerations for probiotic use in certain patients

The opening message of **Professor Kevin Whelan** was that, before giving a probiotic to a patient, particularly if they are seriously ill, clinicians should check that their probiotic of choice is safe and has potential benefit. Referring to the alarming newspaper headlines in 2008 questioning the safety of probiotics after publication of a study in patients with acute pancreatitis,[115] he explained that the study had nothing to do with normal probiotic consumption by the general public. The probiotics consumed widely are usually lactobacilli and bifidobacteria, which have a long history of safe use. He described a safety study in Finland that demonstrated there had been no increase in lactobacilli bacteraemia due to *Lactobacillus rhamnosus* GG (LGG) over a five-year period when there was a substantial increase in this probiotic's consumption by the general population.[116]

A clinician may consider a probiotic if there is convincing evidence of benefit for the particular type of patient, even if seriously ill. Professor Whelan gave examples of meta-analyses where probiotic benefit was concluded (for necrotising enterocolitis,[117] antibiotic-associated diarrhoea,[118] *Clostridium difficile*-associated diarrhoea[119] and post-operative infections[120]) as well as some randomised controlled trials (RCT): ventilator-associated pneumonia (LGG)[121] and enteral diarrhoea in an intensive care unit (ICU; *Saccharomyces boulardii)*.[122] He then outlined what the clinician should consider:

Probiotic-related

- Microbiological quality control
  - Does it contain the right strain and can you be sure there is no contamination?
  - Is the correct number of live microorganisms present (should be stated on the label)?
  - Does the product need to be stored in a fridge, and what is the shelf life?
- Virulence factors (should be low virulence).
- D-lactate production (a risk for D-lactate acidosis and short bowel syndrome).
- Antibiotic resistance transfer genes (rare for lactobacilli and bifidobacteria).

Administration-related

- Will delivery of the probiotic bypass the gastric acid in the stomach?[123]

Patient-related

- Is the patient malnourished or immunocompromised?
- Is there concomitant drug use?
- Is a central venous catheter in place?
- Could the patient have poor gastrointestinal permeability (ie, a 'leaky' gut)?

He advised that products bought from the chilled storage areas of supermarkets are of good quality but expressed concern about health food shop products, which are often poorly labelled.[124] With regard to the patients, he noted that there have been a few case reports of probiotic septicaemia in patients with central venous catheters,[125] which have been identified as a risk factor.[126] Following four cases of *Saccharomyces boulardii* fungaemia in patients with indwelling catheters, it was found that opening the packets or capsules of the probiotic was contaminating the air, environmental surfaces and hands of the operator.[127] Therefore, always open such products outside the patient's room, and use gloves.

Sepsis can result from bacteria translocating from the gut, particularly if there is increased gut permeability. This can lead to multi-organ failure.[128,129] The 2008 PROPATRIA study[115] (mentioned earlier) examined the effect of delivering a multi-strain bacterial mixture (Ecologic 641) or placebo via naso-jejunal tube to 296 patients with severe acute pancreatitis. Following unblinding, it was realised more patients had died in the test group. This was not due to infectious complications, however, but due to bowel ischaemia. Prof Whelan gave critical insights into this study. This was a novel 'probiotic' bacterial mix never tested in humans, which had been administered via naso-jejunal tube, thus bypassing the stomach - meaning high numbers of live bacteria were delivered to the colon.[130] Patients were also being given a prebiotic contained within their enteral feeding formula at the same time. Furthermore, at baseline there was a higher rate of organ failure in the bacterial group. Subsequent analysis showed that, for patients with organ failure, the bacterial intervention was associated with an increase in markers for bowel ischaemia and enterocyte damage.[131]

Prof Whelan recommended consulting a comprehensive safety review of probiotics published in 2011 (free to download), which covers trials in a range of patient groups. For ICU patients, for example, the relative risk of adverse event associated with probiotic use was estimated as 0.79 (95% CI 0.51 – 1.22; *P*=0.286).[132] Probiotic use in patients receiving nutritional support (eg, enteral or parenteral nutrition) has also been reviewed by Prof Whelan himself,[123] who identified the following risk factors for adverse events: central venous catheter; antibiotics; immune suppression and 'bacterial translocation'. Treatment of these complications included stopping the probiotic, removing the CVC, giving antibiotics (ampicillin; penicillin) or an antifungal (fluconazole). Both publications are useful reference sources for relevant studies with different probiotics.

Systematic review: clinical trials of probiotics in nutritional support[123]

- **52 papers reporting 53 trials:** probiotics (4,131 patients) *vs* placebo (3,643 patients)
  - Areas: ICU, premature infants, surgical, transplant, etc
  - Probiotics: lactobacilli, bifidobacteria, *S. boulardii*, mixtures (eg VSL#3)
  - Doses: 10^7 to 10^{12} cells per day
- **Safety trials (n=3)**
  - *Bifidobacterium breve*, *L. casei* Shirota, *Lactobacillus plantarum*
  - No adverse events; no bacterial colonisation
- **Non-safety trials (n=50)**
  - No significant increase in any negative outcome (n=47)
  - Significant increase in negative outcome (n=3). Generally 'non-infectious': liver transplant; neonatal ICU; pancreatitis (ischaemia; mortality)

'Clean' or 'neutropenic' diets are often advised for cancer patients on chemotherapy, despite a lack of evidence to support them.[133] A survey of UK dietitians in 2014 found that 4% of cancer units allow probiotics with these diets.[134] A recent systematic review of cancer patients reported no evidence of adverse events from nine RCTs but five case reports of probiotic-related adverse events.[135]

Prof Whelan concluded that, although there is little indication of probiotic risk for a range of patients, there are isolated examples of adverse events in trials and case reports. Risk could be better assessed if papers detail any adverse events in clinical trials. He recommended more trials specifically investigating probiotic safety, particularly for older people, long-term use, non-*Lactobacillus* products and the effect of the delivery vehicle.

The safety of probiotics for patients: key messages from Professor Kevin Whelan

- Probiotics can be used safely in a wide range of patients but always check published RCTs and case reports for both the probiotic and the particular patient's health problems.
- More probiotic safety studies should be conducted.
- Adverse events should always be fully reported in clinical trials.
- Always consider: (i) the quality and safety of the particular probiotic; (ii) how it will be administered and (iii) the patient's condition.
- Then assess the risks and benefits of giving a probiotic. In many cases, the potential benefit will outweigh any risk.

Professor Paul O'Toole, with chairperson Professor Christine Norton, answering questions from delegates.

The speakers and chairpersons at the study day

Dr Nathan Davies is a Senior Lecturer at the Institute for Liver and Digestive Health in University College London's Medical School. His work explores the processes related to inflammation and their effects on the body's systems during disease processes. Current research is investigating whether altering the gut microbiota can reduce potential sources of inflammation in the liver and benefit patients' health.

Dr Ailsa Hart is currently Lead of St Mark's Hospital Inflammatory Bowel Disease Unit and Senior Clinical Lecturer at Imperial College London. Her clinical work covers the spectrum of GI diseases, with particular interest in the pathogenesis of inflammatory intestinal disorders. Among her many responsibilities, she heads the Gut Microbiota for Health expert panel of the British Society of Gastroenterology.

Dr Gill Jenkins (chairperson) has over 30 years' medical experience, including 24 years in general practice. She is experienced in family planning, emergency medicine, the management of lifestyle and its medical sequelae, air ambulance/aeromedical repatriation and travel medicine. She now splits her time between general practice in Bristol, including being LTC Clinical Lead on the Bristol CCG Board, media work and medical repatriation.

Dr Julian Marchesi is a Reader at Cardiff University and Imperial College London. His research is currently focussed on investigating the effect of the gut microbiota on the health and function of the gut and the body as a whole. He uses a variety of "omic" approaches, such as metagenomics, metatranscriptomics and molecular ecology in this work.

Yvonne McKenzie is a Registered Dietitian and Clinical Lead in IBS for the Gastroenterology Specialist Group of the British Dietetic Association. She is the lead author in their guidelines for the dietary management of IBS in adults, a recognised national Allied Health Professions clinical expert in IBS, and is currently working with NICE to update their clinical practice guidelines for IBS.

Dr John O'Malley has been a GP for over 22 years. He worked as a hospital practitioner, specialising in gastroenterology, at the Wirral University Hospital Trust for over 20 years. He currently works as the Organisational Medical Director of an NHS Social Enterprise and is also head of Clinical and Information Governance, training and medicines management.

Christine Norton (chairperson) is the Florence Nightingale Professor of Clinical Nursing Research at King's College London and Imperial College Healthcare NHS Trust. She has spent the last 35 years working to help incontinent people, by setting up and running clinical services, teaching programmes and research programmes. Her current research is about helping people to better manage chronic gut symptoms and improving nursing care of hospital inpatients.

Paul O'Toole is a Professor of Microbial Genomics at University College Cork. His main research theme is the genomics and metagenomics of GI bacteria with emphasis on human-associated species and host interaction, particularly commensal lactobacilli. He is currently investigating links between the gut microbiota, diet, health, ageing and well-being.

Dr Nick Read is a registered gastroenterologist, nutritionist and psychotherapist. During a long academic career, he held university chairs in gastrointestinal physiology, human nutrition and integrated medicine. He now writes, lectures and maintains a private practice in psychotherapy but devotes most of his time to The IBS Network, a national charity for people with IBS.

Kevin Whelan is Professor of Dietetics in the Diabetes and Nutritional Sciences Division at King's College London where he leads a research programme exploring the interaction between diet, the gastrointestinal microbiota and disease. He has also investigated the microbiota in patients with IBD, IBS, and patients receiving artificial nutrition, and dietary means to modify these.

Dr Samford Wong is Lead Dietitian for Spinal Injuries and Research at the National Spinal Injuries Centre, Stoke Mandeville, and an Honorary Fellow at City University, London. He is currently investigating probiotics for prevention of antibiotic-associated diarrhoea, the role of nutrition supplements in pressure ulcer healing, and the prevention of osteoporosis and obesity management after spinal cord injury.

Parveen Yaqoob is Professor of Nutritional Physiology at the University of Reading, where she is School Director of Research for Chemistry, Food & Pharmacy and Deputy Head of Food and Nutritional Sciences. She is also a registered nutritionist. Her key areas of expertise include diet, healthy ageing and immune function/inflammation.

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

For further information, please contact the science team on **020 8842 7600** or **science@yakult.co.uk**