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AN UPDATE ON PROBIOTIC RESEARCH: EXPLORING A POTENTIAL BENEFIT FOR NEW PATIENT GROUPS

A re-examination of the probiotic category

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At a meeting organised by the Food and Agriculture Organisation of the United Nations and the World Health Organisation in 2001, a definition for probiotics was decided. Twelve years later, this time on behalf of the International Scientific Association for Probiotics and Prebiotics (www.isapp.net), an expert panel met to re-examine the probiotic category, and reinforced the original definition of probiotics (with a minor grammatical correction) as: 'Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (1).

A distribution of probiotic mechanisms was proposed: some that are widespread (e.g. colonisation resistance; production of short chain fatty acids; regulation of intestinal transit; normalisation of gut dysbiosis), some that could be species-specific (e.g. vitamin synthesis; bile salt metabolism; gut barrier reinforcement) and some that are rare and strain-specific (e.g. neurological, immunological and endocrinological effects).

Reviewing the multiple uses, targets and products of probiotics, the following categories were considered as falling within the definition: probiotic drugs, medical foods, foods, dietary supplements, infant formula and animal feeds, non-oral probiotics and defined microbial consortia. Fermented foods with undefined microbial content (i.e. live starter cultures with no evidence of health benefit that are used to prepare fermented foods) and undefined microbial consortia (such as in person-to-person faecal microbiota transplants) were not considered to be probiotic.

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It was stressed that evidence of health benefit is required for any product to be considered probiotic; in addition, strains must be safe for human consumption and clearly identified to either species or strain level depending on the claim for the product.

EXPLORING PROBIOTIC BENEFITS IN A WIDER RANGE OF PATIENTS

1. Insulin-resistance/Type 2 diabetes

The implications of obesity on health (and the NHS) have been widely reported. In 2012, Public Health England estimated that 62 percent of adults were overweight or obese - a major concern because obesity is the strongest risk factor for Type 2 diabetes (T2D) (2, 3).

Characterised by insulin resistance and low-grade chronic systemic inflammation, T2D is also associated with compositional changes in the intestinal microbiota (4, 5). One study, for example, found patients had significantly lower levels of Firmicutes (Gram-positive bacteria) and a higher proportion of Bacteroidetes and Proteobacteria (Gram-negative bacteria) compared to non-diabetic patients (5, 6). However, no correlation with BMI was found, highlighting that further research is needed.

Changes in the gut microbiota composition have been associated with metabolic endotoxemia (the presence of endotoxins in the blood), which drives inflammation and triggers insulin resistance and weight-gain (7-9). Endotoxaemia is a consequence of impaired gut permeability, which increases bacterial translocation from the gut, causing a rise in plasma levels of endotoxic lipopolysaccharide (LPS: a major component of the outer membrane of Gram-negative bacteria) (9). Interestingly, it has even been hypothesised that some individuals may be predisposed to obesity based on their gut microbiota and its promotion of metabolic disease (10, 11).

There are emerging indications that probiotics could, through their ability to modulate the gut microbiota, help to prevent high-fat diet-induced insulin resistance. For example, in a study on T2D patients given a yoghurt containing *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12, the intervention was associated with reduced fasting blood glucose concentrations and glycosylated haemoglobin levels (12). A recent trial also showed that *Lactobacillus casei* Shirota helped maintain glucose sensitivity in healthy adults after a short period of overfeeding on a high fat/high calorie diet, which caused insulin resistance in the group not given the probiotic (13).

2. Patients infected with Human Immunodeficiency Virus (HIV)

The gut, where most of the immune system is located, is also the site of major HIV virus replication early in infection. This results in the destruction of CD4+ T helper lymphocytes, as well as changes to the gut microbiota and barrier function, causing microbial translocation from the gut to the bloodstream (14). The weakening of the immune system means that people living with HIV are vulnerable to opportunistic infections, which can be fatal. All of this explains why researchers have turned their attention to the gut microbiota as a possible therapeutic target (15). Not all probiotic studies have shown benefit for HIV-infected patients, but there have been several positive findings, mainly relating to improvements in immune and/or gastrointestinal function. Studies in Canada and Africa with yoghurt containing *Lactobacillus rhamnosus* GR-1 +/- *Lactobacillus reuteri* RC-14 (16-18) showed a range of associated effects, including an increase in CD4 cells, an increase in energy and ability to perform tasks and improved gut function. A trial involving the same strains in capsule form, however, did not show benefit in women naïve to anti-retroviral treatment (19). Improved CD4+ cell count has also been shown with the probiotics *L. casei* Shirota (20) and *Bacillus coagulans* GBI-30 (21). Use of the yeast *Saccharomyces boulardii* in HIV patients with long-term viral suppression was associated with decreased gut-derived bacterial LPS and inflammation (IL-6) (22). Infant formula supplemented with a B. lactis strain has been linked to improved weight gain for infants born to HIV-positive mothers (23). Consumption of commercial probiotic yoghurt also resulted in less vaginal fungal colonisation in HIV-infected women (24).

None of the studies showed any safety problems regarding probiotic use in these immunocompromised patients. Although there are not enough safety studies and adverse events are

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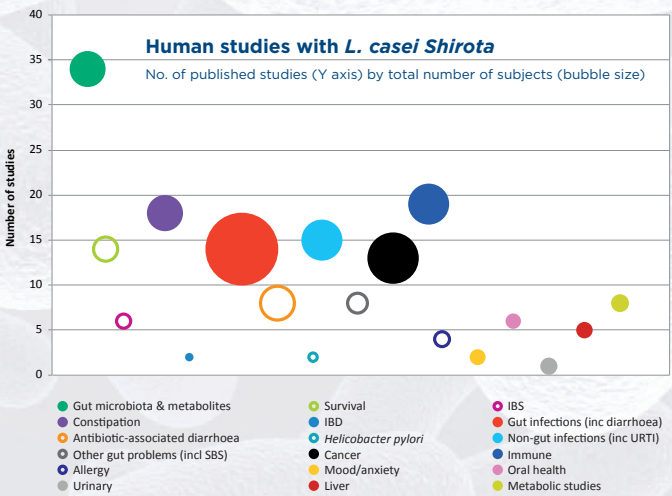
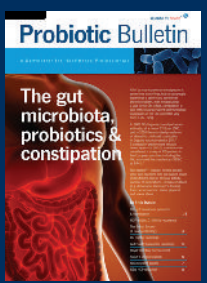
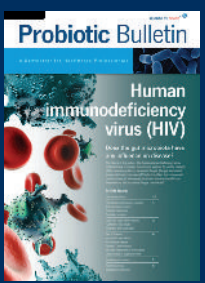
- **Gut disorders,** e.g. constipation, IBS, IBD
- **Infections,** e.g. *Clostridium difficile*-associated diarrhoea (and antibiotic-associated diarrhoea), norovirus, nosocomial, upper respiratory tract
- **Emerging areas,** e.g. cancer, metabolic diseases and liver disease







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The impact of antibiotics on the balance of the gut microbiota can be profound, with as many as 30 percent of patients suffering from varying severities of diarrhoea

poorly reported, probiotics generally appear to be safe for this patient group (25).

3. Antibiotic-resistant pathogens

No one can have missed newspaper headlines highlighting the global concern about multi-drug-resistant pathogens. The World Health Organisation report in 2014 chillingly pointed out that it is now a real possibility that antibiotics will no longer work, so that even common infections and minor injuries could be fatal (26). There is emerging but still very limited data on the use of probiotics to modulate the commensal microbiota and thus reduce colonisation by multi drug-resistant bacteria in the gut (27) and on the skin (28).

In a pilot study in the USA, 48 subjects with a history of methicillin-resistant *Staphylococcus aureus* (MRSA), many of whom were immunocompromised with multiple comorbidities, were given either a probiotic (*L. rhamnosus* HN001) or placebo for four weeks. The probiotic was well tolerated and three patients who were initially positive for vancomycin-resistant enterococci (VRE) became negative after the intervention (29). Clearance of intestinal VRE colonisation in four very sick patients has also been reported, with a strategy of environmental disinfection, patient isolation, bowel washout and antibiotics (linezolid and daptomycin) followed by the probiotic *L. rhamnosus* GG (30). The same probiotic has also been used successfully to eliminate VRE from colonised hospitalised children (31).

A few case reports also suggest the potential of probiotics. A case report of a geriatric surgical patient with persistent diarrhoea and heavy intestinal colonisation with MRSA described how treatment with oral vancomycin and topical mupirocin as well as oral *S. boulardii* resolved the diarrhoea and eliminated faecal MRSA (32). In another study, a hospital dietitian was credited with suggesting a commercial probiotic (*L. casei* Shirota) for an ICU patient colonised with an extremely drug resistant *Pseudomonas aeruginosa*; the presence of the pathogen was linked to a lack of healing and the breakdown of the patient's burn wounds. After two weeks of taking the probiotic, the pathogen was no longer detected and the wounds eventually healed (33).

4. Spinal cord injury (SCI) patients

The impact of antibiotics on the balance of the gut microbiota can be profound, with as many as 30 percent of patients suffering from varying severities of diarrhoea (34, 35). Antibiotic-associated diarrhoea (AAD) is not just debilitating for sufferers, it can also compromise other medical treatment (36). SCI patients are at particular risk for AAD, as well as *Clostridium difficile* infection (a spore-forming pathogen that produces toxins causing diarrhoea and more serious illness). This has prompted probiotic research: a recent study at the National Spinal Injuries Centre (Stoke Mandeville) demonstrated a significant risk reduction ($P<0.001$) in AAD for patients given a *L. casei* Shirota fermented milk drink (37). Poor appetite and no use of probiotics were identified as independent risk factors for AAD with these patients.

Chronic recurrent cystitis may be promoted by the severe acute inflammatory response that occurs early in infections by UTI-causing pathogens (which are usually Gram-negative Enterobacteriaceae bacteria). Even though the majority of SCI patients are men, chronic urinary tract infections (UTIs) are common and can cause serious problems in SCI patients (40). Probiotics may have potential benefit for UTI sufferers (41, 42) and studies have now been conducted in SCI patients. An implant of an avirulent *Escherichia coli* strain into the bladder of SCI patients was shown to reduce their risk of colonisation by urinary pathogens (43), while a two-case study of SCI patients showed that intake of probiotics *L. rhamnosus* GR-1 and *L. reuteri* RC-14 reduced pathogenic load on the urinary tract (44).

5. Patients with Parkinson's disease

Parkinson's disease (PD) is a progressive neurological condition, characterised by dopamine loss and impairment of voluntary movements. Non-motor symptoms are also significant aspects of the disease's clinical spectrum: these include sleep disturbances, bladder problems, sexual problems and depression, as well as gastrointestinal problems (e.g. a prevalence of 28 to 61 percent for constipation) (45-47). Interestingly, several studies have shown that constipation can precede the onset of PD; constipation has also been associated with an elevated risk of the disease. This highlights the importance of the role of the gut in both disease progression and maintenance (45, 46). A complex bidirectional communication system exists between the GI tract and the central nervous system (CNS), otherwise known as the gut-brain axis (48).

Dietary modifications, fibre supplements and laxatives are typical strategies used to alleviate constipation. It is only in the last few years that the use of probiotics to control constipation in PD patients has been explored. In a study of 40 PD patients with constipation, probiotic *L. casei* Shirota for five weeks was associated with a statistically significant increase in the number of days per week where stools were of normal consistency ($P<0.01$) (47). Significant improvements in bloating ($P<0.01$), abdominal pain ($P<0.01$) and sensation of incomplete emptying ($P<0.01$) were also reported.

6. Women's health

Recent research has highlighted the importance of a well-balanced gut microbiota during pregnancy, as vertical transmission of intestinal microbes has been demonstrated from mother to child (49). The range of potential benefits resulting from probiotic consumption by pregnant women include reduced risk of preeclampsia, gestational diabetes mellitus, vaginal infections, maternal and infant obesity, and allergic diseases (50, 51). Women are also at risk of becoming constipated or developing haemorrhoids after giving birth. A recent placebo-controlled study found that a probiotic *Lactobacillus*-fermented milk drink alleviated constipation-related symptoms, with some indications of benefit for haemorrhoids (52).

With regard to babies at high risk of developing allergies, recent guidelines from the World Allergy Organisation advise that, despite low quality evidence, there could be benefit in the mothers taking probiotics during pregnancy and whilst breastfeeding, and subsequently for the infants themselves to be given probiotics (50). A recent systematic review and meta-analysis, which identified 16 studies assessing 10 probiotics in 2,797 children, reported a statistically significant reduction in the incidence of eczema if children had been exposed to probiotics during infancy or *in utero* (53).

Another area of probiotic research specific to women is breast cancer. Positive indications from mechanistic studies have now been supported by a population based, case-control study comparing 306 women with breast cancer with 662 controls. Analysis of their diet, lifestyle and other risk factors found that regular consumption since adolescence of a probiotic *L. casei* strain or isoflavones was associated with a reduced risk of breast cancer (54). Interestingly, earlier studies in France and the Netherlands found a negative correlation between consumption of fermented milk products and breast cancer risk (55,56).

Finally, virtually all cases of cervical cancer are caused by human papillomavirus (HPV) infection. A study in Belgium of 54 women diagnosed with HPV-associated low-grade squamous intraepithelial lesion diagnosis from their PAP smear found that those who were given a daily probiotic drink for six months were twice as likely to have clearance of cytological abnormalities and were also more likely to have HPV clearance (57).

CONCLUSIONS

Clinicians and researchers continue to explore the benefits of probiotics in more types of patients, so it is always worth keeping up to date with probiotic research. Probiotics are relatively cheap, have many mechanisms of action and have a good safety record. Clinicians are advised to check the supporting evidence for any probiotic they are considering, particularly for the specific patient and their condition. With seriously ill patients, the potential benefits and risks of probiotic usage must be weighed (58).

For full references to this article, please click here…

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Questions relating to: *An update on probiotic research: exploring a potential benefit for new patient groups* Type your answers below and then **print for your records** or print and complete answers by hand.	
Q.1	What is the currently accepted scientific definition for probiotics?
A	
Q.2	Which of these are considered to be probiotic: a) A faecal microbiota transplantation from a relative or friend b) A fermented milk product made with a named strain of *Lactobacillus* with evidence of health benefit for humans. c) A yoghurt prepared in the home, by fermenting milk with a spoonful of live yoghurt. d) An animal feed containing a *Bacillus* species, with no evidence of health benefit. e) A multi-strain probiotic powder marketed as a drug, with evidence of health benefit.
A	
Q.3	What is the link between the gut microbiota and insulin resistance?
A	
Q.4	Why has there been probiotic research in HIV-infected patients?
A	
Q.5	What probiotics have been associated with increased counts of T cell (CD4+) lymphocytes in HIV-infected patients?
A	
Q.6	What probiotic mechanism of activity might help with the problem of nosocomial multi-drug pathogens?
A	
Q.7	What is the proposed mechanism for improvements seen in SCI patients who take probiotics?
A	
Q.8	Name two independent risk factors for AAD in spinal cord injury patients.
A	
Q.9	What probiotic benefits have been reported in studies with Parkinson's disease patients?
A	
Q.10	What potential benefits have been reported for women taking probiotics during pregnancy?
A	