The gut microbiome

1. The gut microbiome

> I have a gut feeling that most of us have been exposed to the gut health revolution. It seems like everyone and anyone is talking about it – professionals and the lay public alike. But what actually is it? And with so many ultra-processed foods in the shops labelled with 'good for your gut', how can we tell the facts through the noise? This article will give it a bash!

Let's start with some definitions.

Microbiome: the total genetic material of all microorganisms in a particular environment.

Microbiota: the specific community of microorganisms present in a given environment. The average human has 10–100 trillion microorganisms (primarily bacteria) in the gut (Nature 2007;449:804). It is important to

note that we have a microbiota in our mouth, vagina and skin!

Microorganisms are predominantly comprised of bacteria, but also viruses, fungi and parasites. Each host as a different blend based on factors such as lifestyle, age, gender, genetics and environment.

Prebiotic

Plant fibre that acts as food for the good bacteria and stimulates its growth

Examples include:

- Vegetables: onions, leeks, dandelion greens, peas, Jerusalem artichoke
- Fruits: apples, bananas, kiwi
- Carbohydrates: lentils, oat bran
- Seeds and herbs: garlic, chicory, seaweed, burdock root

Probiotic

The organisms themselves:
beneficial microorganisms to add to your existing microbiome

Examples include:

- Sauerkraut, miso soup, kimchi, kombucha, kefir (dairy and non-diary), pickled vegetables, ultra-processed products such as Yakult and Actimel

Most probiotic products contain 7 core genera: Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia and Bacillus
A systematic review found that, in most cases, single probiotic strains demonstrated comparable effectiveness to blended mixtures (Dig Dis Sci 2021;66:694)

Postbiotic

Dead fragments and metabolites of probiotics that are beneficial to health (also referred to as parabiotics or paraprobiotics)

Can be achieved by consuming probiotics (examples above) because a significant proportion will die during the digestion process and become postbiotic (Nat Rev Gastroenterol Hepatol 2021;18:649, Nutrients 2020;12:389)

Synbiotic

Prebiotics and probiotics combined

The theory is that this selectively favours the probiotic 'live organism' you aim to supply, thus improving the survivability compared with introducing the probiotic in isolation (Nutrients 2010;2:611)

1.1. What does a healthy gut vs. an unhealthy gut microbiome look like?

There are a few definitions of what a healthy gut microbiome is, and it is harder to determine than you might think, but here is the most widely accepted definition:

"A healthy gut microbiome is one which successfully maintains long term stability, resists invasive infections, provides its host with essential nutrients, such as vitamins and fermentation byproducts, and aids in maintaining host metabolic and immunological homoeostasis." (Gut Microbes 2021;13:1-20)

An unhealthy gut microbiome is defined as dysbiosis:

"Dysbiosis is an imbalance in bacterial composition, changes in bacterial metabolic activities, or changes in bacterial distribution within the gut. The three types of dysbiosis are:

1) Loss of beneficial bacteria.

2) Overgrowth of potentially pathogenic bacteria.

3) Loss of overall bacterial diversity."

(Inflamm Bowel Dis. 2016;22:1137)

So, gut microbiome has been found to impact a lot, and the list is growing. Let's explore in more detail.

1.2. Why does the gut microbiome matter?

- The gut microbiome is fundamental to human existence, contributing to the evolution of complex species by aiding in tasks such as nutrient absorption, organ function and immune defence (BMJ. 2018;361:k2179).
- A key role is the fermentation of non-digestible plant fibre and intestinal mucus; this eventually leads to the production of short chain fatty acids, including butyrate.
- Butyrate (a product of prebiotic digestion by the gut microbiome) is a primary energy source for our gut cells, stimulates gluconeogenesis in the gut and even promotes apoptosis of colon cancer cells (Cell 2014;156:84).
- Over the past three decades, we have seen greater understanding in how the gut communicates with various organs through signalling controlled by gut hormones, and microbial metabolites forming various networks throughout the body (gut–brain axis, gut–liver axis, gut–kidney axis and gut–lung axis). Despite this progress, many regulatory mechanisms in this complex process remain unclear (Int J Mol Sci. 2023; 24:4089).
- When dysbiosis is present, it is associated with the development of various diseases and symptoms, with the list growing as our understanding improves.

1.3. How the gut microbiome affects health

Both the **composition** of the gut microbiome and its **diversity** have been shown to influence health.

Disruption or imbalance in the **composition** (dysbiosis), along with impaired gut structure and function, and immune imbalance, can lead to various intestinal diseases such as inflammatory bowel disease, irritable bowel

syndrome and colorectal cancer, as well as systemic diseases such as obesity and type 2 diabetes (Integr Med (Encinitas). 2014;13:17, Inflamm Bowel Dis. 2016;22:1137).

Gut microbiome **diversity** has been shown to vary significantly between individuals. A modern western diet and lifestyle is associated reduced diversity (Nature. 2012;489:220, Nutrients. 2018;10:365). A lack of gut microbiome **diversity** has been associated with numerous long-term conditions:

- Type 1 and 2 diabetes (Diabetes 2013;62:1238, J Diabetes Obes2015;2:1).
- Atopic eczema (J Allergy Clin Immunol2008;121:129).
- Inflammatory bowel disease (Gut 2006;55:205).
- Coeliac disease (BMC Microbiol 2010;10:175).
- Psoriatic arthritis (Arthritis Rheumatol2 015;67:128).
- Obesity (Nature 2009;457:480).

Obesity

It has been postulated that the composition of the gut microbiome may have an impact on obesity.

Obese individuals may be prone to weight gain due to changes in their microbiota, impacting energy absorption or affecting the gut–brain axis, and leading to reduced energy expenditure and altered satiety signals (Gastroenterology 2015;149:223).

The human gut microbiota is 90% composed of two dominant bacterial phyla: Firmicutes and Bacteroidetes.

- Firmicutes are associated with a tendency to gain weight.
- Bacteroidetes are more often found in lean people.

This is association rather than causation, and may relate to the different kinds of food consumed supporting the growth of different bacteria.

Most of the research has been done in animal models. One study found that conventionally-reared mice have a 40% higher body fat content than germ-free mice (mice raised in a sterile environment and with no microorganisms in their gut), even though they consume less food than their germ-free counterparts. Moreover, when the distal gut microbiota of the normal mice was introduced into germ-free mice, there was a notable 60% increase in body fat within just two weeks; this occurred without any observable rise in food consumption or evident differences in energy expenditure. This suggests that the gut microbiota has an impact on the host's obesity-related traits (Proc. Natl. Acad. Sci USA. 2004;101:15718). However, although this study has been replicated in other animal models, there have also been studies that have challenged this. It remains an area that needs further research (Acta Physiol (Oxf). 2021;231:e13581).

A small double-blind, randomised controlled study undertook faecal transplants between lean people (as donors) into people with obesity; this demonstrated some impact on insulin sensitivity, microbial diversity and weight change (Gastroenterology 2012;143:913). At present, there are no active practical applications of the research that has been done in humans. People are not queuing up for faecal transplants!

1.4. Can we manipulate our gut microbiome to improve health outcomes?

Because both the composition and diversity of the gut microbiome has been

shown to influence health outcomes, many have explored interventions to influence and manipulate them.

There has been extensive research on prebiotic, synbiotic or probiotic supplementation, and on dietary interventions targeting the gut microbiome, with a focus on improving cardiometabolic outcomes. A review article in the BMJ explored over 200 studies involving over 16 000 participants (BMJ 2023;383:e075180):

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- 72.5% of studies showed significant improvements in one or more cardiometabolic traits in those who had an intervention to try and change the gut microbiome (paucity of trials from South Asia and Africa).
    - The table below subdivides this based on the intervention used.
- The majority of studies were focused on assessing the impact on obesity and metabolic syndrome.

Intervention	Efficacy at changing the gut microbiome composition	Efficacy at improving host clinical outcomes
Probiotic supplementation	37%	70%
Prebiotic supplementation	82%	63%
Diet alone	70%	76%
Diet with another intervention	62%	87%
Synbiotic supplementation (pre and probiotics)	59%	70%

Effectiveness of Interventions

The review also identified a very small number of studies looking at faecal matter transplantation and physical activity. It found that they were both highly effective at achieving a change in gut microbiome composition (in fact, 100% of the time!). But is this a surprise? Physical activity has several direct functions on the gut, including increased gut motility (Exercise Immunology Review. 2015;21:70) and reduced inflammatory infiltrates, which can damage the gut lining and the environment for our microbiome (PLoS ONE. 2016;11(3):1–17). With respect to faecal matter transplantation, it is not surprising that you see a detectable change in composition – you are directly injecting them in!

The clinical outcomes in the trials selected for the BMJ review varied greatly – some were more clinically impactful than others! One explored the effect of a faecal matter transplant on blood pressure. I've highlighted this because, unlike physical activity and diet, any change in clinical markers is less likely to be influenced by other physiology outcomes of the intervention. It found that the intervention resulted in a systolic drop of: 5.09 ± 15.51, P = 0.009, and a diastolic reduction of: 7.74 ± 10.42, P < 0.001 (Front Cell Infect Microbiol. 2021;11:679624).

So, probiotic interventions appear to be less effective at improving the microbiome than broader interventions such as dietary changes or prebiotics. One hypothesis put forward by the authors of this trial is that new 'therapeutic' strains may struggle to survive in the host's microbiome if the gut conditions are not favourable. They suggest, therefore, that probiotics from the host gut microbiome, e.g. Akkermansia muciniphila, may be more promising.

The BMJ noted:

- A lack of consistency in outcomes and study designs.
- The need for consensus on mechanistic markers, including microbial metabolites linked to cardiometabolic risk.
- A need for well-designed large-scale studies with robust biomarkers, uniform protocols and integrated data-driven approaches.
- An urgent need for guidelines based on comprehensive research for practical applications.

The overall conclusion from the BMJ evaluation? Despite some contradictions, there was evidence for a number of effective interventions targeting the gut microbiome for disorders such as metabolic syndrome, obesity and type 2 diabetes.

Intermittent fasting and the gut microbiome

An increasing number of people are exploring intermittent fasting for the purported health benefits, including improved gut microbiome diversity.

A study looking at a group partaking in Ramadan fasts showed some improvements in gut diversity, but it was the types of foods consumed that made the greater difference (Front Microbiol. 2023;14:1203205).

In a 3-week study of intermittent fasting using the 5:2 approach, changes to the participants' microbiota were evident. There were also improvements in parameters related to obesity and atherosclerotic cardiovascular disease (NPJ Biofilms Microbiomes 2023;9:19).

It is not clear if intermittent fasting results in a change in gut microbiome that is clinically significant because there are mixed results from studies. If it is effective, this is likely a late effect after a prolonged adaptation to these dietary changes (NEJM 2019;381:26).

1.5. Potential practical applications

Diagnosis of diseases

Some of the microbes and/or metabolites in disease pathologies are being identified, opening the potential for future biomarkers for disease identification.

Several studies have looked at possible diagnostic disease biomarkers in the gut microbiome. These could include signalling metabolites (metabolites released by gut bacteria which trigger changes in host physiology) or

microbial genetic material. Conditions currently being explored include:

- Colorectal cancer (Int. J. Mol. Sci. 2019;20:4155).
- Breast cancer (J. Breast Cancer. 2020;23:579).
- Oesophageal cancer (Theranostics. 2017;7:4313).
- Inflammatory bowel disease (Inflamm. Bowel Dis. 2020;26:1463).

Identifying risk of future disease

Research shows the potential to predict the risk of developing several conditions, including gestational diabetes (Microb Biotechnol. 2022;15:129), coeliac disease (Proc Natl Acad Sci 2021;118: e2020322118) and cardiovascular disease (J Agric Food Chem 2020;68:3548).

1.6. Treatment

Possible uses of probiotics	Evidence	Reference
Prophylaxis of antibiotic-associated diarrhoea.	Probiotics may help prevent antibiotic-associated diarrhoea, although research on efficacy and optimal dosage is ongoing.	Antibiotics (Basel). 2017;126:21 Epidemiol Health.2018;40:e2018043
Prevention of traveller's diarrhoea.	One meta-analysis found statistically significant efficacy in the prevention of traveller's diarrhoea.	Epidemiol Health. 2018;40:e2018043

Prevention of *Clostridium difficile* diarrhoea.	There is some evidence that it may be beneficial here, but it is NOT included in the UK Health Security Agency guidance.	Cochrane Database Syst Rev. 2017; 1912:CD006095
Remission in inflammatory bowel disease.	Despite some interest and suspicion of potential application here, there is not yet evidence to support it.	Cochrane Database Syst Rev. 2019;3011:CD001176
Irritable bowel syndrome.	There is some evidence of potential benefit here. NICE states that if the patient wants to trial a probiotic, this must be done following the manufacturer's instructions and be for a minimum of 4 weeks. The more recent British Society of Gastroenterology guidelines differ by recommending 12 weeks. They both agree that there is no evidence to recommend a specific strain.	World Gastroenterology Organisation, February 2023 NICE 2017 IBS in adults CG61 Gut. 2021;70:1214
Eradication of *Helicobacter pylori*.	A meta-analysis found that kefir (fermented milk) increased eradication rates compared with standard therapy.	World J Gastroenterol. 2015;721:10644
Necrotising enterocolitis.	There is low to moderate evidence of the benefits of treating this condition seen in premature babies.	Cochrane Database Syst Rev. 2023;267:CD005496

Faecal microbiota transplant has been trialled for conditions such as obesity and irritable bowel syndrome, with mixed results (BMJ Open 2023;13:e073242).

Adjuvant therapy to increase efficacy of melanoma treatment

Use of the Bifidobacterium species alongside anti-programmed cell death ligand-1 therapy increased efficacy in mice. In fact, even when given in isolation, a positive response was seen (Science 2015;350:1084).

Tool to assess drug efficacy

Treatments targeted at the gut microbiome could potentially be used to assess candidacy for treatments in both human and animal studies (Microbiome. 2019;7(1):154), and to help reduce unwanted adverse effects from medicines (Microb Biotechnol. 2022;15:129).

1.7. How to use our knowledge of gut health now?!

Now we know that specific gut compositions and increased diversity can lead to positive health outcomes, we can start to assess our patients' gut health and promote healthy lifestyles to support this.

Commercial assessment

There are currently several commercial tests patients can request directly.

These generally explore 3 things:

- Gut microbial composition and diversity.
- Microbial metabolite levels (such as butyrate).
- Gut transit time.

Gut transit time is essentially the time it takes for food that you eat to come out the other end! This is measured by getting the patient to eat a blue-dyed food and waiting to see it in the toilet. Transit time has been shown to influence gut microbial composition, with longer and shorter transit times considered indicators of dysbiosis (J Neurogastroenterol Motil. 2017 Jan; 23(1): 124–134, Gut 2023;72:180-191).

There are, however, no standardised timings to interpret the results of these commercial tests (Gut 2021;70:1665-1674). Using these assessments in clinical practice is therefore problematic.

"It should be questioned whether current scientific knowledge is at a stage that can support these tests, reports and dietary advice." (British Dietetic Association)

So, what can we do?!

We are increasingly going to be handed a list of tests we have not ordered, the results of which have no standardised way of being interpreted! It is important we focus on what WE DO KNOW helps the gut microbiome, and share honestly with patients WHAT WE DON'T KNOW. Here are some key lifestyle tips that can help promote a healthy gut microbiome:

- Consume a wide range of plant-based foods (fruit, vegetables, nuts, seeds and spices).
- Aim for >30 different types of food across a week (mSystems 2018;3:10.1128); this is likely to improve nutrition generally!

- Look to add natural probiotics in the form of fermented foods.
- Literally feed the bugs (prebiotics).
- Limit ultra-processed food (Nutrients. 2019;11:2287).
- Encourage regular physical activity (see our article *Physical activity: effective consultations*).
- Promote good hydration (J Nutr. 2022;152(1):171).
- Be mindful of using medications such as antibiotics and those that can negatively impact the gut flora.

1.8. Cautions around use of commercial probiotics

(Microb Biotechnol. 2022;15:129)

- There are a wide variety of probiotics; some are extensively studied, while others lack research.
- There is a concern about the impact probiotics can have on weakened immune systems, and the theoretical risk of illness.
- Probiotics are considered dietary supplements, not drugs, and their content and manufacturing are therefore not closely monitored.
- This leads to uncertainty around the quality of products in pharmacies and health-food stores.
    - There is lack of clarity on whether products contain the listed probiotic bacteria.
    - There is the potential for lower-quality products to not match their label information.
- Our knowledge of the gut microbiome is still in its infancy. The exact

> mechanisms for any benefits remain unclear. Gut microbiome testing, in particular direct-to-consumer testing which is now widely available, should be used with caution.

This is an exciting area. Our understanding is improving rapidly. But we don't know all the answers or fully understand any risks that may be associated.

1.9. What is causing the exponential growth in interest?

> Money, money, money (ABBA)

Research around gut health has grown, with more than £1.35 billion being spent in the past ten years (Nature. 2019;569:623). This has piqued the interest of investors into the 'microbiome market', and new products and supplements are cashing in on the craze.

However, the human market is dwarfed by the huge investment in agronomy, where it is hoped environmental microbiomes will replace toxic chemicals (Discov Food 2022;2:9). By 2027, it is predicted this market will be worth £9.55 billion (Fortune Business Insights, 2021).

There is money to be made, and it may be our role to help patients navigate this market to get the benefits of a healthy gut without an empty wallet – and without inadvertently worsening the quality of their nutrition just because a product says 'gut health' on it!

The gut microbiome

- The gut microbiome is a crucial component of the body, communicating with various organs to control numerous functions.
- Our understanding has improved massively over the past 2 decades, but there is far more to discover.
- Practical applications are growing; we can expect these to start to become commonplace clinical practice over the next 10 years.
- There is a large market for products that are targeted at our gut health. Efficacy of these products is not clear.
- Unsurprisingly, a natural whole food diet, regular physical activity and good quality sleep have been shown to outperform supplementation.

Useful resources:

Articles (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- Microbiota in health and diseases Sig Transduct Target Ther 2022;7:135

Podcasts

- Microbiome Medics

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