Session I Interactions of the host-microbiome system

In this guide

In this guide

Session I Interactions of the host-microbiome system

Food additive emulsifiers and their impact on gut microbiome, permeability, and inflammation: Mechanistic insights into inflammatory bowel disease metabolomic and gut microbiome

profiles & Maternal and early child health, women's health and the gut microbiome as a modifiable factor with nutrition to improve health outcomes

28. **Dr Federica Amati (Imperial College London and ZOE)** introduced the microbiome as an ecosystem / garden which helps keep the body healthy but can also contribute to illness as well as impact health outcomes. The speaker then presented on why the microbiome is important including effects on mood; appetite; food choices; influences on the immune system; impacts on the menopause and bone health; it breaks down fibre and polyphenols and produces postbiotics (enzymes, vitamins, fatty acids) (Valdes et al., 2018). Some preliminary studies have shown that modulating the microbiome can improve health outcomes.

29. The speaker then stated that the relationship between our microbes and food are complicated, complex subjects. In inflammatory bowel disease (IBD, which includes Crohn's and ulcerative colitis) gut permeability increases. allowing bacteria and toxins to cross the gut barrier which triggers an immune response. This immune response promotes chronic inflammation and results in worsening symptoms.

30. Gut dysbiosis is an imbalance of beneficial vs harmful bacteria and plays a significant role in IBD by weakening the gut barrier. This increases the permeability of the gut barrier and exacerbates inflammation. A reduction in the number of beneficial bacteria like *lactobacillus* and *bifidobacterium* is common.

31. Research has shown that IBD patients have distinct gut microbiome profiles with lower diversity and fewer beneficial bacteria. Pathobionts (harmful bacteria that thrive in dysbiosis), such as *Enterobacteriaceae* and *Fusobacterium*, are often elevated in IBD, driving inflammation. Tight junction dysregulation is a situation where the structures maintaining gut barrier integrity become compromised in IBD leading to a "leaky gut". Proteins like occludin and zonulin regulate these junctions. In IBD, pro-inflammatory cytokines are overproduced due to a dysfunctional immune response to gut bacteria. These cytokines disrupt the gut barrier perpetuating inflammation and gut permeability.

32. Gut bacteria produce various metabolites such as short chain fatty acids (SCFAs) and bile acids. SCFAs strengthen the gut barrier and regulate inflammation. Disruption of these metabolites in IBD and other gut disorders leads to impaired gut function. Metabolic analysis of IBD patients shows reduced production of SCFAs especially butyrate, which normally helps maintain gut

integrity. Butyrate deficiency contributes to increased gut permeability and inflammation.

33. Studies indicate that the western diet (high in protein, ultra processed foods (UPF) and sugar) has led to a 50% decrease in the diversity of the microbiome. This was determined by a comparison with the African Hadza tribe whose microbiome is more diverse than the western population. It was noted that further investigation of the microbial diversity of the microbiomes of other cultures is needed.

34. When considering the impact of emulsifiers and food additives on the gut microbiome the entire dietary pattern needs to be considered. In the UK, greater than 50% of the average person’s diet is made up of UPFs. People are consuming significant amounts of novel foods containing combinations of chemicals which humans have not evolved to consume. Food additives and emulsifiers should be considered as a mixture and not stand-alone components. As a result, there is a lot of information, and unknowns to take into account when assessing the risk they pose.

35. Studies have shown when comparing high to low UPF diets there is a trend towards reduction in gut microbiome diversity and negative metabolic health effects in high UPF diets. Less healthy food patterns gave rise to a less healthy gut microbiome, and this was associated with adverse metabolic effects. When considering artificial sweeteners, the science is varied and whilst it is widely accepted that they don’t enter the blood stream they do have local effects on the microbiome; in addition, food colourants have been linked to gut dysbiosis.

36. There is evidence to suggest that emulsifiers can lead to inflammation and that diets lower in emulsifiers are linked with fewer irritable bowel symptoms in humans. Emulsifiers have been shown to disrupt the lumen of the gut wall leading to leaky gut. This allows the movement of the components within the gut lumen to “leak” out.

37. Furthermore, there is some evidence that people who wash dishes and don’t rinse off the soap (which is an emulsifier) have a higher incidence of colon cancer due to gut microbiome disruption.

The maternal and infant microbiome

38. The second topic of discussion presented was that of maternal and early child health, women's health and the gut microbiome as a modifiable factor, using nutrition to improve health outcomes (Leeming et al., 2019).

39. During pregnancy, the gut microbiota shifts to support fetal growth. Dysbiosis in pregnant women is linked to adverse outcomes like gestational diabetes, preeclampsia, and preterm birth. A healthy maternal microbiome supports optimal pregnancy outcomes.

40. The maternal microbiome strongly influences the infant’s gut microbiome, especially during vaginal delivery and breastfeeding.

41. It is recognised that the gut microbiome is very malleable in the first 3 years of life, and early gut colonisation shapes the child’s immune system, digestion, and risk of developing allergies or chronic diseases later in life.

42. Research is being undertaken with a view to improve the microbiome of babies who are formula fed.

43. Gut and vaginal microbiome dysbiosis can have a negative effect on fertility and pregnancy outcomes. Tests are now available to diagnose vaginal dysbiosis and to predict the likelihood of preterm birth.

44. Observational studies have shown a relationship between babies growing up in spaces with pets and green spaces to have an improved microbiome and fewer allergies in later life.

45. Increasingly children in the UK are being diagnosed with poor health outcomes, including early adiposity, poor mental health and increased respiratory issues, which was correlated with UPFs (Oliviera et al., 2022).

46. The gut microbiota affects key aspects of women’s health including hormonal balance (e.g. oestrogen metabolism) and conditions including polycystic ovary syndrome, endometriosis and menopause. Dysbiosis can worsen these conditions by influencing inflammation and hormone regulation.

47. It has been suggested that the microbiome plays a role in the menopause transition and health. Studies on pre, peri and post-menopausal women have shown marked differences in responses and evidence shows that the markers measured were mediated by the gut microbiome composition. The marker levels measured in these women were more similar to those seen in men. A higher quality diet (which was considered to be one high in whole foods and mostly plant based) led to a lower prevalence of menopausal symptoms. Diet quality is associated with menopause symptoms. There was also a marked difference in the aspects of the gut microbiome that were measured due to this diet.

48. The Gut-Immune axis was introduced, with the speaker stating that the trillions of microbes in the gut train and educate the immune system, building defences, keeping the peace and ensuring optimal function. Therefore, looking after gut health is one of the easiest ways to look after immune health. This was followed up with evidence that increasing fibre intake by 5 grams per day could reduce unwanted inflammation (Shivakoti et al., 2022).

49. Finally, the speaker also discussed a concept called “proprietary gut microbiome scoring” which uses metagenomic gunshot sequencing integrated with MetaPhlAn4 (a computational tool for profiling the composition of microbial communities) to allow the comparison of microbiomes. The aim is to link certain microbial strains with specific health outcomes. Preliminary data shows that there is a significant difference in the microbiomes of US and UK cohorts when using this scoring method.

Antimicrobials in livestock and the potential impact on gut microbiota and colonisation by zoonotic pathogens

50. **Professor Rob Kingsley (Quadram Institute)** firstly described how antimicrobials are given to animals in agriculture to treat infections or as growth promoters.

51. The talk then focused on how the gut microbiota prevent pathogen invasion and how disruptions to the microbiota lead to pathogenic bacteria growing to high levels in the intestines of livestock.

52 .The speaker then explained colonisation resistance during homeostasis (Rogers et al., 2021). *Bacteroida* and *Clostridia* are important for the colonisation resistance of the gut from pathogens. They produce SCFAs such as propionate, acetate and butyrate, which can inhibit *Enterobacteriales*. Butyrate drives oxidative phosphorylation in epithelial cells, which are the main entry route for xenobiotics in the gut. Oxidative phosphorylation consumes oxygen and drives epithelial cell hypoxia and creates an anaerobic environment (anaerobiosis). The anaerobiosis maintains homeostasis and the abundance of obligate anaerobes, such as *Clostridia* and *Bacteroida,* and low levels of *Enterobacteriales*.

53. The speaker then discussed the impact of antibiotics on gut bacteria. Antibiotic use leads to depletion of *Bacteroida* and *Clostridia* in turn leading to depletion of SCFA and butyrate levels. Depletion of butyrate results in a switch to aerobic glycolysis which in turn causes oxygenation of the mucosal surface; inhibition of obligate anaerobes and expansion of *Enterobacteriales* (Rivera-Chávez et al., 2017). This is further compounded by the increase in carbon

sources such as sialic acid, fructose, galactarate, which can be used by *Enterobacteriales*. AMR is another problem in this situation as *Enterobacteriales* can become resistant to the antibiotics and further outcompete any commensals.

54. The speaker then discussed some of the work on a high copper diet in post-weaning piglets. Piglets are fed these diets as copper is used as a growth promoter and it reduces post-weaning diarrhoea. There is concern that pathogens are becoming adapted to the copper and there is co-selection for AMR. There are further concerns that co-resistance in pathogens as a result of copper use can lead to microbiome modifications as it could allow pathogens to become adapted to a different niche, normally occupied by commensals.

55. Epidemiology work identified the emergence of *Salmonella typhimurium* ST34 copper resistant strain (Branchu et al., 2018). This is one of the main foodborne pathogens. This resistant strain is thought to have emerged due to adaptations to the changing environment of the host. Resistance genes in this bacterium increase the minimal inhibitory concentration (MIC) of copper, especially in anaerobic conditions.

56. A farm study conducted in piglets that were fed high and low copper diets showed small changes to the microbiome with increased abundance of 4 species and decreased abundance of 10 species in response to the high copper diet. In the metabolome, 11 out of 67 metabolites were altered by copper. Butyrate, propionate and acetate levels were unchanged in the high copper diet, but formate had increased.

57. Therefore, the effect of a high-copper diet on colonisation resistance showed no significant reduction in *Clostridia* and *Bacteroida* and no reduction in short chain fatty acid production. The increase in formate, was a cause for concern with respect to the potential expansion of *Salmonella*. In addition, the decreased relative abundance of commensal *Enterobacteriales* might decrease the competition for *Salmonella*.

Effects of oral iron supplementation on the gut microbiota / different responses between the sexes to increased dietary protein on the gut microbiota using pig models

58. **Dr Marie Lewis (University of Reading)** presented a talk on the effects of oral iron supplementation on the gut microbiota, and the different responses between the sexes to increased dietary protein on the gut microbiota, using pig models.

59. The speaker discussed two research projects:

- Do high-protein diets have the potential to reduce gut barrier function in a sex-dependent manner?
- The effects of iron supplementation during infancy.

60. The first project looked at the sex-dependent effects of high protein diets on gut barrier function (James et al., 2024). The speaker noted that there is currently considerable promotion of high dietary intakes of protein and increased availability of high protein bars and foods. Also, higher protein intakes are encouraged in older age but are not effective without fibre consumption and exercise.

61. The speaker noted that it was previously thought that protein was completely absorbed from the gut but, around 10% reaches the colon, where it can be utilised by gut bacteria. The gut bacteria utilise oligosaccharides and fibre, and when the gut bacteria utilise protein, there is a shift in their metabolic profile. This metabolic shift increases the amount of negative microbial end products, such as ammonia, p-cresole and indole. These end products have been associated with reduced tight cell junction proteins which can potentially cause a leaky gut. The higher amounts of microbial derived end products enter the bloodstream and can lead to inflammatory responses. Therefore, the speaker indicated, there is a theoretical link between high protein diets and long term chronic inflammatory conditions such as coronary heart disease.

62. It was highlighted that the gut microbiota and the immune system are different between males and females. Therefore, it is logical to assume that the effect of different substances on the gut microbiota will vary between sexes.

63. The research project was initiated with a screening process using *in vitro* gut models. Types of animal protein analysed included: whey, milk, fish and eggs. It was noted that a lot of other research in this area uses very concentrated hydrolysed proteins. However, the issue with using hydrolysed proteins is that they are almost completely absorbed in the small intestine. Therefore, use of gut model systems would be artificial as the protein would not reach the colon. To prevent this occurrence in the study, the research group extracted only 70% of proteins so the substrates they were testing contained other substances that individuals would consume if they had a high protein diet.

64. The main observation from this study was a change in the gut microbiota, with some populations of bacteria being affected whereas others were not. Additional observations were that the type of protein influenced the type of

microbial end products produced. Therefore, the speaker suggested, advice on increasing protein in the diet should specify the type of protein. The speaker found that analysing the output of the microbiota (i.e. the end products) is more important than the composition of the microbiota.

65. Further results from the study were that there were sex differences in response to different types of proteins. Therefore, future advice on dietary protein intakes may have to vary between males and females. The latter part of this research on the effects of high protein diets on gut barrier function utilised a pig model. The speaker explained that the pig model was selected due to issues with translating results from rodent models to humans. Rodents live in a high hygiene facility, which alters their microbiome and leads to an unusual development of their immune system and metabolism. However, pigs are more similar to humans in terms of their gut physiology and microbiome and their inter-interindividual microbiome variation.

66. Both male and female piglets received either a low protein diet or a high protein diet (i.e. 28% protein) totalling four treatment groups. Results were that groups fed the higher protein diet grew faster, although there was no difference in growth rates between males and females between weaning and 12 weeks of age. Other findings were that the same differences in metabolic profile observed in the former part of the study were also observed in the latter study with piglets. The speaker concluded that the study provided direct evidence that high protein diets reduce the expression of gut barrier-function proteins in a sex-dependent manner (James et al., 2024).

67. The speaker then discussed the project on iron supplementation during infancy, which was conducted as infants fed on formula milk are receiving high amounts of iron. The speaker acknowledged that iron deficiency in infants is a potential concern but noted that, similarly to protein, high amounts of iron in the colon occurring due to lack of absorption from the gut can cause a shift in the metabolic profile of microbiota.

68. The speaker explained that piglets were received at one day of age and were not bottle fed but received formula milk from trays. It was noted that if piglets do not consume iron, they will develop anaemia in 2-3 weeks however, rodent models require a longer period before they develop anaemia.

69. The initial findings were that all types of iron supplementation were able to prevent anaemia. However, the control group were the only piglets that grew normally, and the groups receiving oral iron had a reduced growth rate similar to that of anaemic piglets. These findings implied that administering formula milk

containing iron could be reducing the growth rate of infants. Additional findings were that there were no differences in host metabolites between any of the iron treated groups. Furthermore, administration of oral iron had an impact on the composition of the microbiota. The speaker highlighted the associations found between weight gain and different members of the gut microbiota. The researchers were able to identify bacteria associated with increased weight and bacteria associated with decreased weight.

70. In the oral iron group, bacteria present in the microbiome had negative associations with weight gain (i.e. decreased weight gain). Final results indicated a direct link between specific components of the gut microbiota and lack of weight gain in infant piglets as a result of iron supplementation.

71. The main conclusions were that for the first time, in an animal model that is reflective of humans, protein was shown to directly impact gut barrier function in a sex-dependent manner. Also, females may be more prone to reduced gut barrier function following high protein diets compared to males. Furthermore, different types of protein have different effects on the composition of the gut microbiota and metabolic profiles of microbial-derived end-products. Finally, iron supplementation resulting in reduced weight-gain was associated with specific components of the microbiota that are less abundant.