The Role of the Microbiome in Childhood Diseases & Conditions

Alisa Morris, Highly Specialist Paediatric Dietitian, Great Ormond Street Hospital for Children, London

The gastrointestinal tract, predominantly the gut, plays home to an ecosystem of diverse microorganisms known as the microbiome.[1] These microbes often have a symbiotic relationship with their host, where in return for their residence in our gut, they can contribute towards our overall health.[2] The composition of the microbiome and balance of 'good' and 'bad' bacteria can be influenced by many factors, including medications, environment, birth method and most vitally, diet.[1, 2] Certain foods can be detrimental to the microbiome, such as processed foods,[3, 4] whereas some foods can be beneficial.

Prebiotics are substrates that are selectively utilised by host microorganisms conferring a health benefit.[5] In terms of the gut, prebiotics are usually carbohydrates that are fermented by gut bacteria to provide themselves with a food source, producing byproducts such as short chain fatty acids (SCFA) in the process, which are beneficial for human health.[6] Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host.[7] Foods or supplements containing probiotics or prebiotics can improve the diversity and abundance of beneficial intestinal bacteria.[8, 9] However, if the composition of the gut bacteria is negatively altered, known as dysbiosis, it can contribute towards poorer health outcomes.[2]

Childhood development

The gut microbiome can be a critical influence on childhood development, spanning the development of the brain, lungs and the immune and nervous systems via the gut-brain and gut-lung axes.[10, 11] Dysbiosis can cause different metabolites to be produced by the microbiome, which affects the function and integrity of the blood-brain barrier, central nervous system (CNS) inflammation and CNS communication.[10] Reduced cognitive performance in expressive and receptive language domains have been observed due to dysbiosis.[10]

Evidence suggests the microbiome, particularly in the first two years of life, can affect length and weight gain,[10] with dysbiosis noted in many children with faltering growth.[12] The mechanisms behind this include the microbiota regulating growth hormone signalling and energy yield from nutrients.[10, 13] Probiotic supplements can improve the absorption of calcium, zinc and B12, which may improve growth.[12]

Infections

In addition to the development of the immune system, the microbiome can help prevent infections. Beneficial gut bacteria compete against pathogenic bacteria for space in the gut and nutrients; therefore, if more beneficial bacteria are present, there is less space for pathogenic bacteria, reducing the likelihood of pathogen colonisation.[2, 14] Microbiota also produce antimicrobial substances.[2]

The consumption of prebiotics helps improve the integrity of the gut barrier by producing SCFA, which reduce bacterial translocation and the intestinal pH, making it less desirable for pathogenic growth.[10, 15, 16] SCFA reduce inflammation in the gut and regulate the production of cytokines, T-helper cells, and antibodies.[15, 17]

Bifidobacterium, in particular, is important in developing the immune system,[10, 18] with low abundance of *Bifidobacterium* associated with respiratory infections at one year old.[18] Interestingly, the gut microbiome strongly correlates with the lung microbiome via the lung-gut axis, with the composition of the gut bacteria influencing the composition in the lungs.[12]

Necrotising enterocolitis (NEC)

NEC is a serious illness caused by inflammation of the intestines, leading to infection and necrosis of the tissue.[19] It occurs predominantly in neonates.[19] Low microbial diversity and dysbiosis are significantly associated with an increased risk of developing NEC and increased rates of complications due to NEC, including sepsis.[12] Administration of probiotic supplements can reduce the risk of NEC and death caused by NEC.[12, 20] There is no consensus on what particular strains of probiotics can achieve these outcomes, yet the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have weak recommendations based on low grade evidence for the use of *Lactobacillus rhamnous* GG or combination of *Bifidobacterium infantis* and *Streptococcus thermophilus*.[21] However, concerns remain surrounding the safety of probiotics, especially in preterm babies who have immature immune systems.[12, 20]

Allergy & atopic conditions

The cause of atopic conditions is complex and multifactorial, and can be influenced by genetics, ethnicity and environment, to name a few.[22] Previously, it was thought atopic conditions developed due to over-sterile environments limiting the full development of the immune system,[23] whereas the updated 'microflora hypothesis' suggests the exposure to microbes is limited by overly hygienic environments, altering the composition of the infant gut microbiome and, therefore, the development of the immune system, resulting in atopy.[10] Dysbiosis has been observed in atopic conditions, including asthma, atopic dermatitis and food allergies.[10, 12] Multiple studies have shown low levels of the beneficial bacteria strains *Bifidobacterium, Faecalibacterium, Roseburia,* and *Ruminococcus* in infancy is correlated with development of asthma by 6 years old.[18] Additionally, infants colonised with pathogenic bacteria *Clostridium difficile* were at a higher risk of developing eczema, allergies and recurrent wheeze.[11]

In the hypoallergenic formula industry there is increasing interest in the effect of probiotic, prebiotic and symbiotic supplementation.[24, 25] Part of this is due to breastmilk proving to be a protective factor in developing food allergy, with prebiotic human milk oligosaccharides (HMO) thought to be one of the main mechanisms behind this.[16, 22, 24] HMO are utilised by beneficial *Bifidobacterium*, producing SCFA.[24] In one study, children who had higher stool SCFA levels at 1 year old had reduced sensitisation to food allergens at 3 to 6 years old, compared to children with lower stool SCFA levels.[23] Supplementation of hypoallergenic formula with HMO has been shown to increase faecal SCFA and the abundance of *Bifidobacterium*, whilst also decreasing the abundance of pathogenic strains, such as *Klebsiella pneumoniae*.[26] Conversely, extensively hydrolysed formula supplemented with *Lactobacillus rhamnosus* GG showed improved rates of milk allergy resolution 6 months after initiation, compared to infants receiving the formula without probiotics.[23]

Gastrointestinal conditions

Given where the gut microbiome is located, it is logical that its presence may affect gastrointestinal function. Bidirectional communication via the gut-brain axis results in brain signals affecting the sensory, motor and secretory functions of the gastrointestinal tract and, in return, the gastrointestinal tract signals influencing brain function.[11]

Despite multiple studies identifying different microbiome compositions between children with constipation compared to healthy children, there is no consensus on what bacterial strains are more or less prevalent in those with constipation.[27] A systematic review was unable to conclude if probiotic supplements improved the frequency of defaecation,[28] although probiotics are shown to help regulate intestinal transit.[7] The ESPGHAN position statement does not recommend the use of probiotics to improve functional constipation due to the lack of efficacy.[21] However, ESPGHAN do provide weak recommendations for the use of *L reuteri* DSM 17938 for children with functional abdominal pain disorders to reduce pain intensity or *L rhamnosus* GG for reducing pain intensity and frequency in children with irritable bowel syndrome.[21]

Studies show individuals with inflammatory bowel disease (IBD), including Crohn's and ulcerative colitis, have reduced microbial diversity compared to healthy individuals, with the difference even more significant when the gastrointestinal tissue is inflamed.[11] The functional capacity of the microbiome is reduced in those with IBD, resulting in decreased production of SCFA and metabolism of carbohydrates.[11] Despite the observed dysbiosis in IBD, there is no evidence that probiotics can induce or maintain remission of Crohn's.[20]

Chronic kidney disease (CKD)

Children with CKD experience rising serum urea levels as their kidney function declines, due to an increasing inability to excrete urea.[29] Urea promotes the overgrowth of proteolytic bacteria in the gut, which ferment amino acids to create uremic toxins.[12, 27] Uremic toxins cause a detrimental effect on the gut microbiome, by increasing the pH of the colon and disrupting the protective intestinal barrier,[27, 30] in turn promoting bacterial translocation.[15] These factors contribute towards systemic inflammation, which can worsen kidney and cardiovascular function,[27] with dysbiosis being observed in as early as CKD Stage 2.[31] Interestingly, in a study by Hsu, children with CKD who had abnormal blood pressures had a distinctly different microbiome, with lower abundance of certain bacterial strains, compared to children with CKD who had normal blood pressures.[31]

Higher levels of uremic toxins are inversely associated with kidney function, with uremic toxins shown to contribute to CKD progression.[27, 29] Uremic toxins are also hypothesised to decrease T and B cell memory, resulting in reduced immune function.[12]

Constipation is more prevalent in those with poorer kidney function. It is theorised that constipation may exacerbate the decline in kidney function due to gut dysbiosis associated with constipation, leading to a vicious cycle of worsening constipation affecting CKD progression and vice versa.[27] The recommended treatment for constipation for the general population is to increase dietary fibre and fluid intake.[32] Fibre intakes can often be low in CKD patients due to dietary potassium restrictions, where some fruits and vegetables are advised to be avoided due to their potassium content.[27] One study has found an inverse relationship between increased dietary fibre consumption and serum levels of uremic toxins, highlighting the importance of dietary fibre intake in this population.[15]

Childhood cancers & stem cell transplant

Children undergoing treatment for cancer or stem cell transplant (SCT) are exposed to many factors that can negatively affect the microbiome, including chemotherapy, antibiotics and infections,[33] with the effects of dysbiosis lasting for years after treatment and potentially playing a role in long-term health.[33] Reduced intestinal microbial diversity is also associated with increased gastrointestinal toxicity of chemotherapy and radiotherapy, increased risk of graft versus host disease (GvHD), serious bacterial infection and mortality.[33, 34]

Additionally, children undergoing SCT or chemotherapy are often advised to follow a neutropenic diet.[35] Although the exact dietary restrictions involved in a neutropenic diet varies nationally,[35] foods including unpeeled fruits and vegetables are often excluded, which are good sources of prebiotics.[36] Probiotics are currently not advised by 75% of paediatric oncology and SCT centres in the UK.[35] Preliminary evidence suggests it is feasible to administer probiotics to children and adolescents undergoing stem cell transplant.[37] Yet, the safety and efficacy of administering probiotics is yet to be established[38] and, currently, there is limited evidence that probiotics influence the microbiome during SCT and chemotherapy.[38, 39]

Neurodivergent conditions

Dysbiosis is frequently observed in children with autism spectrum disorder (ASD), due to overgrowth of pathogenic bacteria and reduced microbial diversity.[12] Dietary fibre intakes are lower in children with ASD,[40] which could be contributing towards dysbiosis.[41] Research has shown neurotransmitters, including serotonin and dopamine, can be produced and regulated by the microbiome.[10] These neurotransmitters play a part in sensory processing pathways, mood and behaviour.[40] Preliminary evidence shows probiotic and prebiotic supplementation can reduce ASD severity and ASD-associated behaviour, such as non-social behaviour.[42] Interestingly, one study found infants who were supplemented with probiotics showed a decreased likelihood of developing attention deficit hyperactivity disorder (ADHD) or ASD.[43] However, more studies are needed to establish if the development and severity of neurodivergent conditions is caused by gut dysbiosis.[44]

Similar to ASD, the microbiome may be atypical in children with ADHD with differences in bacterial diversity even observed between those taking stimulant medication for ADHD and those with ADHD who were not medicated.[45, 46] Unfortunately, there is limited evidence that probiotic supplementation improves ADHD symptoms.[47]

Conclusion

The microbiome is shown to affect a wide range of clinical conditions across childhood. However, the evidence for correcting dysbiosis to improve clinical outcomes by supplementing with prebiotics and probiotics is still limited.

References: **1.** Heintz-Buschart A, Wilmes P (2018). Human Gut Microbiome: Function Matters. Trends Microbiol.; 26(7): 563-574. **2.** Thursby E, Juge N (2017). Introduction to the human gut microbiota. Biochem J.; 474(11): 1823-1836. **3.** Zhou X, *et al.* (2023). The Impact of Food Additives on the Abundance and Composition of Gut Microbiota. Molecules.; 28(2): 631. **4.** Berding K, *et al.* (2021). Diet and the Microbiota-Gut-Brain Axis: Sowing the Seeds of Good Mental Health. Adv Nutr.; 12(4): 1239-1285. **5.** Gibson GR, *et al.* (2017). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol.; 14(8): 491-502. **6.** Holscher HD (2017). Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes.; 8(2): 172-184. **7.** Hill C, *et al.* (2014). Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol.; 11(8): 506-514. **8.** So D, *et al.* (2018). Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. Am J Clin Nutr.; 107(6): 965-983. **9.** Wang X, Zhang P, Zhang X (2021). Probiotics Regulate Gut Microbiota: An Effective Method to Improve Immunity. Molecules.; 26(19): 6076. **10.** Ronan V, Yeasin R, Claud EC (2021). Childhood Development and the Microbiome- The Intestinal Microbiota in Maintenance of Health and Development of Disease During Childhood Development. Gastroenterology.; 160(2): 495-506. **11.** Ihekweazu FD, Versalovic J (2018). Development of the Pediatric Gut Microbiome: Impact on Health and Disease. Am J Med Sci.; 356(5): 413-423. **12.** Saeed NK, *et al.* (2022). Gut microbiota in various childhood disorders: Implication and indications. World J Gastroenterol.; 28(18): 1875-1901. **13.** Robertson RC, *et al.* (2023). The gut microbiome and early-life growth in a population with high prevalence of stunting. Nat Commun.; 14(1): 654. **14.** Bäumler AJ, Sperandio V (2016). Interactions between the microbiota and pathogenic bacteria in the gut. Nature.; 535(7610): 85-93. **15.** Snauwaert E, *et al.* (2023). The benefits of dietary fiber: the gastrointestinal tract and beyond. Pediatr Nephrol.; 38(9): 2929-2938. **16.** Chen X (2015). Human Milk Oligosaccharides (HMOS): Structure, Function, and Enzyme-Catalyzed Synthesis. Adv Carbohydr Chem Biochem.; 72: 113-190. **17.** O'Connor G, *et al.* (2023). An open-label pilot single-subject study to monitor theimpact of a Food-Based enteral formula on faecal short-chain fatty acid concentrations in children admitted to intensive care with sepsis. Clin Nutr Open Sci.; 53: 1-10. **18.** Alcazar CG, *et al.* (2022). association between early-life gut microbiota and childhood respiratory diseases: a systematic review. Lancet Microbe.; 3(11): e867-e880. **19.** Ginglen JG, Butki N (2023). Necrotizing Enterocolitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. **20.** Guarner F, *et al.* (2024). World Gastroenterology Organisation Global Guidelines: Probiotics and Prebiotics. J Clin Gastroenterol.; 58(6): 533-553. **21.** Szajewska H, *et al;* ESPGHAN Special Interest Group on Gut Microbiota and Modifications (2023). Probiotics for the Management of Pediatric Gastrointestinal Disorders: Position Paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications. J Pediatr Gastroenterol Nutr.; 76(2): 232-247. **22.** Berni Canani R, *et al.* (2018). Gut microbiota composition and butyrate production in children affected by non-IgE-mediated cow's milk allergy. Sci Rep.; 8(1): 12500. **23.** Bunyavanich S, Berin MC (2019). Food allergy and the microbiome: Current understandings and future directions. J Allergy Clin Immunol.; 144(6): 1468-1477. **24.** Nowak-Wegrzyn A, *et al.* (2019). Confirmed Hypoallergenicity of a Novel Whey-Based Extensively Hydrolyzed Infant Formula Containing Two Human Milk Oligosaccharides. Nutrients.; 11(7): 1447. **25.** Lin M, Yanjun C (2024). Research progress on the mechanism of probiotics regulating cow milk allergy in early childhood and its application in hypoallergenic infant formula. Front Nutr.; 11: 1254979. **26.** Gold MS, *et al.* (2022). Effects of an Amino Acid-Based Formula Supplemented with Two Human Milk Oligosaccharides on Growth, Tolerability, Safety, and Gut Microbiome in Infants with Cow's Milk Protein Allergy. Nutrients.; 14(11): 2297. **27.** Wan M, *et al.* (2023). Gutted: constipation in children with chronic kidney disease and on dialysis. Pediatr Nephrol.; 38(11): 3581-3596. **28.** Wallace C, *et al.* (2022). Probiotics for treatment of chronic constipation in children. Cochrane Database Syst Rev.; 3(3): CD014257. **29.** Rosner MH, *et al.* (2021). Classification of Uremic Toxins and Their Role in Kidney Failure. Clin J Am Soc Nephrol.; 16(12): 1918-1928. **30.** Vanholder R, Gryp T, Glorieux G (2018). Urea and chronic kidney disease: the comeback of the century? (in uraemia research). Nephrol Dial Transplant.; 33(1): 4-12. **31.** Hsu C-N, *et al.* (2020). Association of trimethylamine, trimethylamine N-oxide, and dimethylamine with cardiovascular risk in children with chronic kidney disease. J Clin Med.; 9(2): 336. **32.** National Institute for Health and Care Excellence (NICE) (2024). Scenario: Management of constipation in children. NICE Clinical Knowledge Summary (CKS). Accessed online: https://cks.nice.org.uk/topics/constipation-in-children/management/management/ (Aug 2024). **33.** Bhuta R, *et al.* (2019). The Gut Microbiome and Pediatric Cancer: Current Research and Gaps in Knowledge. J Natl Cancer Inst Monogr.; 2019(54): 169-173. **34.** Ciernikova S, *et al.* (2021). Targeting the gut microbiome: An emerging trend in hematopoietic stem cell transplantation. Blood Rev.; 48: 100790. **35.** Morris A, O' Connor G, Renshaw G (2023). A Cross-sectional Survey to Review Food Safety Practices Within Pediatric Oncology and Stem Cell Transplant Centers in the United Kingdom. J Pediatr Hematol Oncol.; 45(4): e471-e478. **36.** Markowiak P, Śliżewska K (2017). Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. Nutrients.; 9(9): 1021. **37.** Ladas EJ, *et al.* (2016). The safety and feasibility of probiotics in children and adolescents undergoing hematopoietic cell transplantation. Bone Marrow Transplant.; 51(2): 262-266. **38.** Lovell AL, *et al.* (2024). The evolution of nutritional care in children and young people with acute lymphoblastic leukaemia: a narrative review. J Hum Nutr Diet.; doi: 10.1111/jhn.13273 [online ahead of print]. **39.** Henig I, Yehudai-Ofir D, Zuckerman T (2021). The clinical role of the gut microbiome and fecal microbiota transplantation in allogeneic stem cell transplantation. Haematologica.; 106(4): 933-946. **40.** Al-Beltagi M, *et al.* (2023) Role of gastrointestinal health in managing children with autism spectrum disorder. World J Clin Pediatr.; 12(4): 171-196. **41.** Hojsak I, *et al.* (2022). Benefits of dietary fibre for children in health and disease. Arch Dis Child.; 107(11): 973-979. **42.** Mitchell LK, Davies PSW (2022). Pre- and probiotics in the management of children with autism and gut issues: a review of the current evidence. Eur J Clin Nutr.; 76(7): 913-921. **43.** Pärtty A, *et al.* (2015). A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr Res.; 77(6): 823-828. **44.** Ligezka AN, *et al.* (2021). A systematic review of microbiome changes and impact of probiotic supplementation in children and adolescents with neuropsychiatric disorders. Prog Neuro- Psychopharmacol Biol Psychiatry.; 108:110187. **45.** Lawrence K, *et al.* (2023). Randomised controlled trial of the effects of kefir on behaviour, sleep and the microbiome in children with ADHD: a study protocol. BMJ Open.; 13(12): e071063. **46.** Stiernborg M, *et al.* (2023). Bacterial gut microbiome differences in adults with ADHD and in children with ADHD on psychostimulant medication. Brain Behav Immun.; 110: 310-321. **47.** Kalenik A, *et al.* (2021). Gut microbiota and probiotic therapy in ADHD: A review of current knowledge. Prog Neuro-Psychopharmacol Biol Psychiatry.; 110: 110277.