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Can we predict future allergies from our infant gut microbiota?

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The ability to predict allergic disease at an early age has many benefits to our society. From the time of the first cultured-based studies conducted in the 1990s, the gut microbial ecosystem during infancy continues to be interrogated to better understand what predisposes some but not other infants to develop allergic disease. This testing had been advanced by gene sequencing technologies that permit the detection of a broader range of microbes in the human body than culture methods. Hence, more complete assessment of gut microbial communities during infancy enhances our ability to identify gut microbiome biomarkers which can predict future allergic disease. Such biomarkers also have the potential to reduce the over-diagnosis of food allergy, and subsequent stress for the child and family.[1,2]

According to several small European cohort studies,[3,4] reduced gut microbial diversity and abundance of genus *Bacteroides* by 1 month of age are early prognostic indicators of atopic dermatitis. Lowered microbial diversity at this age and 1 year later in infants born to women with a history of asthma has also been associated with a higher risk of allergic sensitization by age 6.[5] In the KOALA birth cohort study of 1000 infants, colonization with *Clostridium difficile* at 1 month predicted atopic sensitization at age 2.[6] By 18 months of age, Nylund et al. also observed greater abundance of *Clostridium* clusters, as well as lowered *Bacteroides* spp. abundance in toddlers subsequently diagnosed with atopic dermatitis.[7] Two cross-sectional studies have observed gut dysbiosis in infants with confirmed food allergy. At the phylum level, Ling et al. reported higher Firmicutes (of which *Clostridium* are members) and lower Bacteroidetes abundance among 5-month-old infants with food allergy, yet no difference in overall microbiota diversity.[8] In the Thompson-Chagoyan et al. study, infants with confirmed cow's milk allergy were more frequently colonized with *Clostridium coccoides*, lactobacilli and other cultured anaerobes, but had lower counts of bifidobacteria and enterobacteria.[9,10] Especially among infants with cow's milk allergy, fecal lactate levels (produced by lactobacilli) were positively correlated with concentrations of bifidobacteria and negatively correlated with *C. coccoides*.

Two recent studies have contributed further evidence on the predictive value of the gut microbial composition of infants.[11,12] In a general population cohort study, Azad et al. also found that lower gut microbial species richness in 166 infants, determined from Illumina sequencing of the V4 region of the 16S ribosomal gene, predicted a positive skin prick test to milk, egg or peanut at age 1. Sensitization to food allergens is common during early life, affecting up to 28% of preschool children.[13] While 66–90% of infants outgrow their sensitization to egg and milk, respectively, and prevalence rates drop to around 2% by age 5,[14,15] food-sensitized infants are twice as likely to experience the "atopic march" to conditions such as atopic dermatitis, allergic rhinitis and asthma.[16] Thus, predicting food sensitization in 1-year-old children has clinical value. A necessary condition for utilizing gut biomarkers such as microbial species richness to predict atopic disease is their evaluation in the breast-fed as well as in the non-breast-fed infant. This is because the early gut microbiota of breast-fed infants is normally less diverse than formula-fed infants.[17] Indeed, lowered species

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richness at 3 months in the Azad et al. study also predicted food sensitization among breast-fed infants who had been vaginally delivered and were antibiotic free.[12]

Consistent with the allergy literature,[3,7,8] Azad et al. observed a reduction in the abundance of *Bacteroidaceae* in the gut of 3-month-old infants who developed food sensitization 9 months later.[12] Members of this family stimulate mucin production which is required to maintain an intact gut microbiota–mucin barrier.[18] As shown in a fecal transplantation experiment in mice, a gut microbiota abundant in *Bacteroides* spp. prevents the development of milk allergy.[19] In the Azad et al. study, food-sensitized infants had an elevated ratio of *Enterobacteriaceae/Bacteroidaceae* abundance both at 3 and at 12 months of age, and this association was independent of reduced microbial species richness.[12] The link between prior and concurrent elevations of the *Enterobacteriaceae* and food sensitization is a novel finding. Others have reported a similar association for atopic dermatitis among caesarean-delivered infants [20]; higher abundance of *Enterobacteriaceae* in gut microbiota has been observed among schoolchildren with various atopic conditions.[21] In contrast, Abrahamsson et al. and Ling et al. found Proteobacteria (the phylum containing *Enterobacteriaceae*) to be less abundant in atopic infants.[3,8] Contradictions such as these are likely a function of taxonomic resolution since both studies found specific genera within the Proteobacterial phylum, including the *Enterobacteriaceae* genus, *Escherichia/Shigella* and *Escherichia coli*, to be elevated in allergic disease.

Food sensitization is common in infants with atopic dermatitis.[22] While this may reflect genetic predisposition, impaired skin barrier function in atopic dermatitis is posited to increase cutaneous absorption of food allergens.[23] There is evidence for maternal–infant transmission of gut *E. coli*.[24] Infants of mothers with atopic dermatitis (who are at genetic risk for atopic dermatitis) are born with meconium that is enriched for *Enterobacteriaceae*.[25] It is conceivable then that the *Enterobacteriaceae* can be transmitted *in utero* and that higher abundance of gut *Enterobacteriaceae* soon after birth is an early biomarker for atopic dermatitis and subsequent food sensitization. Of note, the *Enterobacteriaceae/Bacteroidaceae* ratio in the Azad et al. study was elevated fourfold among 1-year-old infants with food sensitization,[12] making it a robust biomarker for future food allergy and the atopic march.

What is the predictive value for gut biomarkers in infants already at risk for allergic sensitization? The new publication of a high-risk (for allergy) cohort study by West et al. determined gut microbial composition and diversity with 454 pyrosequencing at ages 1 week, 1 month and 12 months in infants (n = 10) who developed IgE-associated eczema and in those who remained free of allergic symptoms at 2.5 years of age (n = 10).[11] While mothers whose infants developed IgE-associated eczema had lower diversity of Bacteroidetes ($p = 0.04$) in their fecal samples, this dysbiosis was not evident in their newborn infants. At 1 week of age, however, the relative abundance of gut *Ruminococcaceae* was lower among neonates who eventually developed IgE-associated eczema compared to controls ($p < 0.005$). Of note, a reduction in the abundance of *Ruminococcaceae* at age 1 was five times more likely among food-sensitized infants in the Azad et al. study, independent of birth method, breastfeeding and antibiotic exposure.[12] Like the *Bacteroidaceae* and bifidobacteria, the *Ruminococcaceae* are able to degrade fiber [26] and are present more often in weaned or formula-fed infants.[27] They are also readily detected in breast-fed infants, depending on the oligosaccharide content of breast milk.[28] Similar to the Thompson-Chagoyan findings, West et al. found the diversity of the phylum Actinobacteria (to which the bifidobacteria belong) to be lower in 1-year-old infants with IgE-associated eczema compared to controls.[11]

Are gut microbial associations with innate system responsiveness, namely the release of pro-inflammatory cytokines (such as IL-6 and TNF-α), a hallmark for future allergic disease? In parallel to that of the gut microbiota, the innate immune system and production of pro-inflammatory cytokines via Toll-like receptor (e.g., TLR-4) stimulation evolves from birth throughout infancy.[29] Gut microbiota modulate systemic innate immunity cytokines in infants [30]; associations between these two systems signal the degree of microbial-induced immune deviation toward an allergic profile. West et al. related gut microbiome profiles of neonates at 1 week and 1 month in relation to peripheral cytokine responses to TLR-2 and TLR-4 stimulation at 6 months of age.[11] One week after birth, the relative abundance of *Ruminococcus* was inversely correlated with TLR2-induced levels of serum IL-6 ($r = -0.567$, $p = 0.042$) and TNF-α ($r = -0.597$, $p = 0.032$); there was also an inverse association between the abundance of the Proteobacteria and TLR4-induced TNF-α levels ($r = -0.629$, $p = 0.024$). These relationships persisted at 1 month of age, with strong inverse associations between the relative abundance of *Enterobacteriaceae* and TLR4-induced TNF-α levels, and of *Enterobacteriaceae* abundance and serum IL-6.

The consequences of parent and physician decision-making regarding birth choices and infant feeding practices should not be underestimated regarding their impact on gut microbial development in the infant and future allergic disease. Deficiency of Bacteroidetes in gut microbiota soon after birth is a predictable outcome of caesarean delivery, which can persist throughout infancy.[31–33] Cessation of breastfeeding soon after birth deprives the infant of breast milk oligosaccharides, a favorite food source for bifidobacteria and *Bacteroides* species.[34] While human gut microbiome research holds much promise toward identifying biomarkers of disease, it is early days yet. A taxonomic marker that works well in Canada and Finland may not work well in Germany or the USA. Continued investigation is necessary to confirm which core "deviations" of infant gut microbial colonization and function are important to the development of food allergy and allergic disease, and which present novel targets for intervention.

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References

1. Peters RL, Allen KJ, Dharmage SC, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. J Allergy Clin Immunol. 2013;132(4):874–880.
2. Cummings AJ, Knibb RC, King RM, et al. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010;65(8):933–945.
3. Abrahamsson TR, Jakobsson HE, Andersson AF, et al. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol. 2012;129(2):434–440, 440.
4. Wang M, Karlsson C, Olsson C, et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema. J Allergy Clin Immunol. 2008;121 (1):129–134.
5. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011;128 (3):646–652.
6. Penders J, Thijs C, van den Brandt PA, et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. Gut. 2007;56(5):661–667.
7. Nylund L, Satokari R, Nikkilä J, et al. Microarray analysis reveals marked intestinal microbiota aberrancy in infants having eczema compared to healthy children in at-risk for atopic disease. BMC Microbiol. 2013;13(1):12.
8. Ling Z, Li Z, Liu X, et al. Altered fecal microbiota composition associated with food allergy in infants. Appl Environ Microbiol. 2014;80(8):2546–2554.
9. Thompson-Chagoyan OC, Fallani M, Maldonado J, et al. Faecal microbiota and short-chain fatty acid levels in faeces from infants with cow's milk protein allergy. Int Arch Allergy Immunol. 2011;156(3):325–332.
10. Thompson-Chagoyan OC, Vieites JM, Maldonado J, et al. Changes in faecal microbiota of infants with cow's milk protein allergy–a Spanish prospective case-control 6-month follow-up study. Pediatr Allergy Immunol. 2010;21(2 Pt 2):e394–e400.
11. West CE, Ryden P, Lundin D, et al. Gut microbiome and innate immune response patterns in IgE-associated eczema. Clin Exp Allergy. 2015;45:1419–1429.
12. Azad MB, Konya T, Guttman DS, et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clin Exp Allergy. 2015;45(3):632–643.
13. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol. 2010;126(4):798–806.
14. Soller L, Ben-Shoshan M, Harrington DW, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130(4):986–988.
15. Venter C, Arshad SH. Epidemiology of food allergy. Pediatr Clin North Am. 2011;58(2):327–349, ix.
16. Brockow I, Zutavern A, Hoffmann U, et al. Early allergic sensitizations and their relevance to atopic diseases in children aged 6 years: results of the GINI study. J Investig Allergol Clin Immunol. 2009;19(3): 180–187.
17. Azad MB, Becker AB, Guttman DS, et al. Gut microbiota diversity and atopic disease: does breast-feeding play a role? J Allergy Clin Immunol. 2013;131(1):247–248.
18. McGuckin MA, Linden SK, Sutton P, et al. Mucin dynamics and enteric pathogens. Nat Rev Microbiol. 2011;9 (4):265–278.
19. Rodriguez B, Prioult G, Hacini-Rachinel F, et al. Infant gut microbiota is protective against cow's milk allergy in mice despite immature ileal T-cell response. FEMS Microbiol Ecol. 2012;79(1):192–202.
20. Hong P-Y, Lee BW, Aw M, et al. Comparative analysis of fecal microbiota in infants with and without eczema. PLoS One. 2010;5(4):e9964.
21. Candela M, Rampelli S, Turroni S, et al. Unbalance of intestinal microbiota in atopic children. BMC Microbiol. 2012;12:95.
22. Hill DJ, Hosking CS, de Benedictis FM, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. Clin Exp Allergy. 2008;38(1):161–168.
23. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129(5):1187–1197.
24. de Muinck EJ, Oien T, Storro O, et al. Diversity, transmission and persistence of Escherichia coli in a cohort of mothers and their infants. Environ Microbiol Rep. 2011;3(3):352–359.
25. Gosalbes MJ, Llop S, Valles Y, et al. Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin Exp Allergy. 2013;43(2):198–211.
26. Shen Q, Zhao L, Tuohy KM. High-level dietary fibre up-regulates colonic fermentation and relative abundance of saccharolytic bacteria within the human faecal microbiota in vitro. Eur J Nutr. 2012;51 (6):693–705.
27. Tannock GW, Lawley B, Munro K, et al. Comparison of the compositions of the stool microbiotas of infants fed goat milk formula, cow milk-based formula, or breast milk. Appl Environ Microbiol. 2013;79(9):3040–3048.
28. Coppa GV, Gabrielli O, Zampini L, et al. Oligosaccharides in 4 different milk groups, Bifidobacteria, and Ruminococcus obeum. J Pediatr Gastroenterol Nutr. 2011;53(1):80–87.
29. Kollmann TR, Levy O, Montgomery RR, et al. Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. Immunity. 2012;37 (5):771–783.
30. Sjogren YM, Tomicic S, Lundberg A, et al. Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. Clin Exp Allergy. 2009;39(12):1842–1851.
31. Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by Caesarean section. Gut. 2014;63:559–566.

32. Azad MB, Konya T, Maughan H, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ. 2015;45:632–643.

33. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006;118 (2):511–521.

34. Marcobal A, Barboza M, Froehlich JW, et al. Consumption of human milk oligosaccharides by gut-related microbes. J Agric Food Chem. 2010;58(9):5334–5340.