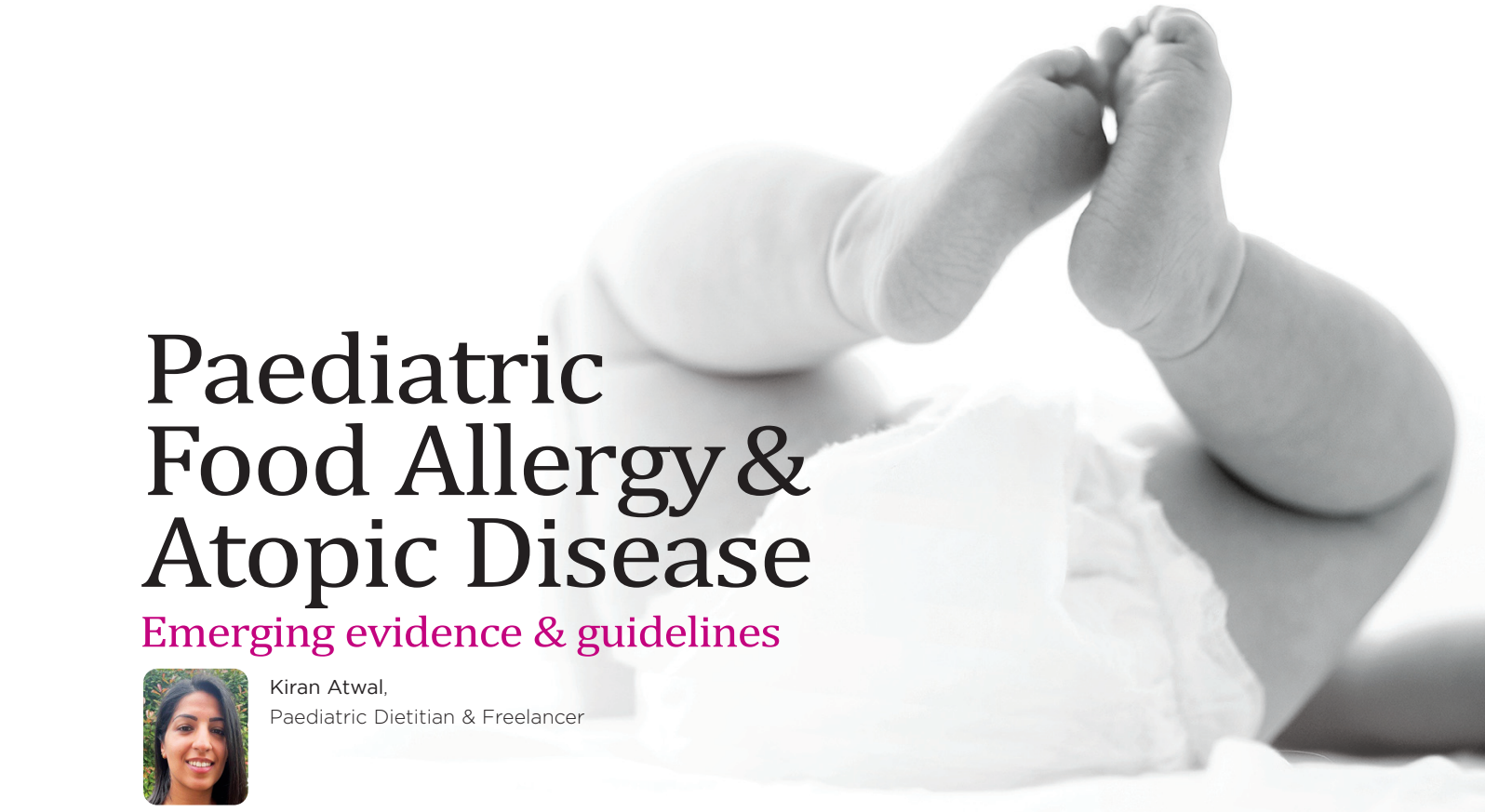

Paediatric Food Allergy & Atopic Disease

Emerging evidence & guidelines

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The evolution of food allergy (FA) management has allowed for improvement in the support of children living with FA or at high risk. Despite renewed understanding and progress over the years, demand for safer and effective care persists, particularly as paediatric FA service provision has increased.[1] This article discusses various insights from research and new guidelines on the prevention and management of FA in paediatrics, as well as the role of diet in the development of atopic disease.

Role of fibre & prebiotics in the development of atopic disease

It is well known that the fermentation of fibre by the gut microbiota leads to the secretion of bioactive compounds that may modulate the immune system and protect against atopic disease. A recently published narrative review on the role of fibre examined evidence from the past 5 years on respiratory outcomes, atopic dermatitis (AD) and risk of atopic disease.[2] There was a limited number of studies, most inadequately powered, but three studies in paediatrics included: one observational study in 639 mother-infant pairs (with family history of atopic disease) found that higher maternal intake of resistant starch was associated with reduced diagnosis of infant wheeze, but higher odds of eczema;[3] a small randomised-controlled trial (RCT) in 65 infants with AD randomised to prebiotic fibre (kestose) found that subsequent increases in specific bacterium were linked to significant improvement in the symptoms of AD;[4] a double-blind randomised controlled trial (DB-RCT) in 256 healthy young children supplemented with cows' milk fortified with prebiotics (polydextrose and galactooligosaccharide [GOS]) demonstrated fewer manifestations of atopic disease in the intervention than control group.[5] The review called for reclassification of fibre types based on their specific role in the mediation of the immune system (e.g. promotion of the epithelial barrier, induction of T-cells), as well as further research.[2]

Infant formula supplemented with 5 strains of prebiotics (2'fucosyllactose and 2',3-di-O-fucosyllactose, lacto-N-tetraose, 3'sialyllactose and 6'sialyllactose oligosaccharides) was investigated in a multicentre, DB-RCT in 693 formula-fed infants (compared to infants breastfed or on standard formula).[6] The authors found the test formula enabled the gut microbiota to develop similarly to that of breastfed infants, demonstrated by higher *bifidobacteria* and lower toxigenic *C. difficile* abundance. Furthermore, there was a significantly higher concentration of faecal secretory Immunoglobulin-A (marker of mucosal immunity in the gut) in the test group. Unfortunately, no long-term outcomes were measured.

Whilst these publications are in favour of fibre and prebiotics in allergy, there is conflict in the guidelines. The World Allergy Organization (WAO) guidelines, from 2016, recommend prebiotic supplementation in not exclusively breastfed infants; however, in newer guidelines by European Academy of Allergy and Clinical Immunology (EAACI) there is no recommendation due to a very low certainty of evidence.[7, 8] More longer-term, high-quality research is needed to develop the application of fibre and specific prebiotics in early life in the prevention atopic disease.

New guidelines on food allergy prevention – *'EAACI guideline: preventing the development of food allergy in infants and young children (update)'*

In 2021, the EAACI committee updated their 2014 guideline to reflect changes in recent evidence on the prevention of FA.[8] In summary, the guidelines do not recommend fish oil consumption during pregnancy to reduce the onset of FA (which was previously recommended). Of the new recommendations, avoidance of cows' milk formula supplemented alongside breastfeeding in the first week of life is recommended. Although this recommendation comes from a very small study – insufficiently powered and not without methodological limitation – which found an increased risk of cows' milk allergy (CMA), it aligns with the World Health Organization (WHO). The WHO warn that supplementation may be associated with reduced breastfeeding. The guideline does not suggest hypo-allergenic formula (nor soy-based) as an alternative, and highlights that the recommendation only relates to temporary supplementation as there is no evidence on the impact of prolonged use of cows' milk formula whilst breastfeeding. The update continues to support the introduction of cooked hens' eggs and peanuts between 4-6 months for the prevention of FA (which has a stronger recommendation grade). There was little other significant changes to the guidelines; an overview can be found by Marques-Maejias *et al.* (2022).[9]

Food allergy management: reintroduction with ladders

Developing tolerance to common food allergens, including mild-moderate cows' milk and egg allergies, can be determined by an oral food challenge (OFC) or the use of 'ladders', which allow stepwise introduction. A group of authors reviewed the 'ladders' available in the literature to examine their benefits, differences, and their use in immunoglobulin-E (IgE) and non-IgE-mediated FA.[10] Whilst many local versions of milk ladders exist, the review focused on the updated Milk Allergy in Primary Care (MAP) Guidelines for non-IgE CMA, which has been found to be the most common ladder used in the UK.[1, 11] Surveys have found that up to 70% of healthcare professionals (HCPs) use ladders to establish tolerance at home in non-IgE CMA and, interestingly, 60% also use a ladder approach in IgE-mediated allergies, particularly where there is no asthma or previous anaphylaxis.[1, 10] Studies have shown that ladders can be used safely in the management of IgE-mediated CMA and egg allergy.[12, 13] Ladders available through the British Dietetic Association Food Allergy Specialist Group (BDA FASG) for non-IgE egg, soy and wheat allergies have not been validated but were used in another study on children with non-IgE gastrointestinal FA. In this study, data from 131 patients using the ladders deemed them safe, and most developed tolerance to baked allergens.[14] The specific patient factors that denote favourable use of ladders in the management of FA have been summarised in **Table 1**.[10] This provides a helpful guide for HCPs as there is little navigation to suggest where ladders can be considered.

Table 1: Patient-specific factors for favourable use of food ladders[10]

- Non-IgE-mediated allergy (excluding FPIES)
- IgE-mediated with prior mild, non-anaphylactic reactions
- Non-asthmatic is ideal, with stable, treated asthmatics potentially suitable
- Willing and prepared patients and families with no language or comprehension barriers
- Families ideally have ready access to emergency services
- High previous reaction threshold
- Low or decreasing skin prick test wheal or serum specific-IgE levels
- Younger patients (e.g. preschool) are preferred, though not without risk, since older patients may be prone to persistence of allergy and suffer from co-existing allergies.

Vulnerable groups: adolescents

Adolescents have the highest rates of fatal food-induced anaphylaxis, according to the European Anaphylaxis Registry.[15] Authors from a recently published systematic review identified several important findings regarding adolescent beliefs around FA.[16] The family home was perceived the safest for navigating FA as opposed to different environments, including school, restaurants and holidays. Not eating the same as everyone else and scepticism of catering were documented as some of the biggest concerns when eating in different environments.

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Carrying and using adrenaline auto-injectors (AAI) was highlighted as a barrier in some studies due to inconvenience, difficulty of use (including fear of incorrect use) and perceived likelihood of allergen exposure. One study found that those with greater anger, anxiety or a belief they were more likely to have a reaction, were more likely to carry their AAI.[16] Across the studies, adolescents were both dismissive while yet expressed great fear of their FA and risk of anaphylaxis. Consumption of allergens was reportedly increased if peers consumed a food containing a potential allergen, which was linked to beliefs around independence, fitting in and gaining the trust of others. Some adolescents were more likely to eat a food with a potential allergen if parents were present (as they felt safer). Interestingly, some adolescents reported after disclosing their FA to classmates they experienced discrimination. Some adolescents only disclosed their FA to close friends and felt frustrated their FA was not taken seriously by others, including teachers. Where there was presence of other people with FA, adolescents felt more accepted. Some parents of children with FA reported hypervigilance and constant reminders of FA consequences, which led to parent-child conflict, whereas some adolescents recognised parental hypervigilance as a sign of care. For some adolescents FA was a big part of their identity. Maladaptive coping strategies reportedly included hand washing and isolation. Some viewed their FA as causing a burden to others by forcing them to adapt. One study found that those who were more likely to engage in risky behaviour were identified with a strong sense of self and increased confidence.[17] Overall, this systematic review highlighted an extensive range of behaviours and beliefs amongst adolescents living with FA that HCPs should be aware to prevent poor outcomes in this vulnerable group.[16]

Racial differences in atopic disease presentation

Emerging evidence from the US is uncovering greater understanding of allergic presentations amongst unrepresented populations. Children from various backgrounds in Ohio were studied prospectively from early-life, to identify differences in atopic disease presentation.[18] The authors found that white children were more likely to be sensitised to food allergens, and 3 times more likely to have FA or allergic rhinitis (AR) without asthma risk, whereas black children were >6 times likely to have high asthma risk without FA, sensitisation or AR. Black children had greater intact skin barrier (measured by filaggrin expression and trans-epidermal water loss in non-lesional skin), whereas white children had more dysfunctional skin barrier. Furthermore, there was more genetic inheritability identified for asthma amongst black children. In another retrospective review, black children with eosinophilic oesophagitis presented with more failure to thrive, poor growth and low treatment compliance than non-black children.[19] Racial inequalities and variation in environmental risk factors could explain some of the observed differences in this study from the US. UK-based studies are needed to better understand country-specific differences, as there are various nuances related to each country. It is also important studies support inclusion of patients where English may not be a first language, to ensure diversity and representation.

Diagnosing food allergy – *'EAACI guidelines on the diagnosis and management of IgE mediated food allergy (update)'*

Members of the EAACI FA guidelines expert group published a protocol which outlines a systematic review of latest evidence on the diagnosis of IgE-mediated FA.[20] Previous guidelines are outdated (released almost 10 years ago), and newer diagnostic procedures, such as component resolved diagnosis (CRD), which are becoming common, require critical analysis. The systematic review will compare evidence on the sensitivity and specificity of CRD versus OFC (open or DB-placebo controlled), as well as basophil and mast cell activation tests in diagnosing FA. Evidence from this systematic review will feed into updated guidelines, which may outline if services can offer more readily available diagnostics to better meet demand. Paediatric FA clinics in the UK have seen a four-fold increase (and seven-fold increase for new patient appointments) over the past 15 years.[1]

Improving national food allergy management – *'National Food Allergy Education Strategy: British Society for Allergy and Clinical Immunology (BSACI)'*

The need for education on FA management has been identified as there is currently a wide gap in the education provision across the UK. Earlier this year, the BSACI proposed a national education strategy to address the professional develop needs of HCPs working in FA.[21] The strategy aims to provide high quality, accessible education for differing types of HCPs working across community and secondary care, as well as better preparing undergraduate HCP programmes. HCP specific competencies are also under development, which will include considerations in allergy management across the life cycle, from early life, through to adolescence and adulthood. The BDA FASG are currently developing dietetic competencies and a network for shared learning. The BSACI invite departments to share local experiences, education programmes and ideas into the work to help implementation. For more information see: www.bsaci.org/education-and-events/bsaci-national-allergy-education-strategy/

Conclusion

This article focuses on an array of fascinating areas in FA that should be considered in the care of paediatric patients, but also highlights ever changing recommendations, vulnerabilities, gaps and research needs which need to be appropriately acknowledged and addressed.

References: **1.** Wells R, *et al.* (2022). National Survey of United Kingdom Paediatric Allergy Services. Clin Exp Allergy.; doi: 10.1111/cea.14198 [Online ahead of print]. **2.** Venter C, *et al.* (2022). Role of dietary fiber in promoting immune health - An EAACI position paper. Allergy.; doi: 10.1111/all.15430 [Online ahead of print]. **3.** Pretorius RA, *et al.* (2019). Maternal Fiber Dietary Intakes during Pregnancy and Infant Allergic Disease. Nutrients.; 11(8): 1767. **4.** Koga Y, *et al.* (2016). Age-associated effect of kestose on Faecalibacterium prausnitzii and symptoms in the atopic dermatitis infants. Pediatr Res.; 80(6): 844-851. **5.** Pontes MV, *et al.* (2016). Cow's milk-based beverage consumption in 1- to 4-year-olds and allergic manifestations: an RCT. Nutr J.; 15: 19. **6.** Bosheva M, *et al.* (2022). Infant Formula With a Specific Blend of Five Human Milk Oligosaccharides Drives the Gut Microbiota Development and Improves Gut Maturation Markers: A Randomized Controlled Trial. Front Nutr.; 9: 920362. **7.** Cuello-Garcia CA, *et al.* (2016). World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics. World Allergy Organ J.; 9: 10. **8.** Halken S, *et al.* (2021). EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update). Pediatr Allergy Immunol.; 32(5): 843-858. **9.** Marques-Mejias MA, *et al.* (2022). Translating research into practice: What's new in the 2021 EAACI food allergy prevention guidelines? Clin Exp Allergy.; 52(4): 476-80. **10.** Venter C, *et al.* (2022). Food allergen ladders: A need for standardization. Pediatr Allergy Immunol.; 33(1): e13714. **11.** Venter C, *et al.* (2017). Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP-an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. Clin Transl Allergy.; 7: 26. **12.** Ball HB, Luyt D (2019). Home-based cow's milk reintroduction using a milk ladder in children less than 3 years old with IgE-mediated cow's milk allergy. Clin Exp Allergy.; 49(6): 911-920. **13.** Leech SC, *et al.* (2021). BSACI 2021 guideline for the management of egg allergy. Clin Exp Allergy.; 51(10): 1262-1278. **14.** Meyer R, *et al.* (2021). The Challenge of Home Allergen Re-introductions Using the Ladder Approach in Children With Non-IgE Mediated Gastrointestinal Food Allergy. Front Allergy.; 2: 721686. **15.** Maris I, *et al.* (2021). Peanut-induced anaphylaxis in children and adolescents: Data from the European Anaphylaxis Registry. Allergy.; 76(5): 1517-1527. **16.** Newman KL, Chater A, Knibb RC (2022). Beliefs about food allergies in adolescents aged 11–19 years: A systematic review. Clin Transl Allergy.; 12(4): e12142. **17.** MacKenzie H, Roberts G, van Laar D, Dean T (2010). Teenagers' experiences of living with food hypersensitivity: a qualitative study. Pediatr Allergy Immunol.; 21(4 Pt 1): 595-602. **18.** Biagini JM, *et al.* (2022). Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. J Allergy Clin Immunol.; 149(5): 1702-10.e4. **19.** Edwards-Salmon S, *et al.* (2022). Comparing Eosinophilic Esophagitis (EoE) in a Black and Non-Black Pediatric Cohort. J Pediatr Gastroenterol Nutr.; doi: 10.1097/MPG.0000000000003552. Online ahead of print. **20.** Genuneit J, *et al.* (2022). Protocol for a systematic review of the diagnostic test accuracy of tests for IgE-mediated food allergy. Pediatr Allergy Immunol.; 33(1): e13684. **21.** Holloway JA, *et al.* (2022). BSACI national allergy education strategy for healthcare professionals. Clin Exp Allergy.; 52(4): 481-484.