Infant & Young Child Feeding n Nutrition in Perspective
透視嬰幼兒餵哺與營養
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Updates on the Primary Prevention of Food Allergy

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Food Allergy and the Atopic March

Food allergy (FA) has emerged over the recent decade as a "second wave" of the allergy epidemic, following the peak of respiratory allergies 20+ years ago.[1] Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.[19] Food sensitisation, on the other hand, refers to the process by which a person develops detectable IgE antibodies to a specific allergen (allergen-specific IgE). The HealthNuts Study in Australia reported the highest FA prevalence to date, with 1 in 10 infants suffering from confirmed FA through oral food challenges.[2] The same study team followed up their subjects until 6 years of age.[3] At age 6 years, children were invited for a health assessment that included skin prick testing for ten foods and eight aeroallergens, oral food challenges, and lung function testing by spirometry. Children with both food allergies and food sensitisation at age 1 were linked to a higher risk of developing asthma by the age of 6. Additionally, the findings indicated that only children with FA, but not children with food sensitisation but clinical tolerance to the food allergen, had worse lung function as measured by FEV1 and FVC at age 6. It is therefore imperative to implement preventive measures in order to prevent the onset of FA.

The Link between Atopic Dermatitis and Food Allergy

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with a complex interplay of factors including dysfunctional skin barrier, immune dysregulation, microbiome dysbiosis, genetic and environmental factors. Evidence suggests AD predisposes to FA, while food allergens are believed to trigger AD exacerbations.

Atopic dermatitis is a major risk factor for food sensitisation and IgE-mediated FA, with studies showing a higher likelihood of food sensitisation in patients with AD compared to healthy controls. Among patients with severe AD, food sensitisation and FA were found in 66% and 81% of individuals, respectively.[4] Infants with AD are six times more likely to have egg and peanut allergies by 12 months than those without AD.[22] However, recent data is not confirmatory due to different study designs and disease severity.

Skin barrier mutations, Langerhans cells, Interleukin-33 (IL-33), and thymic stromal lymphopoietin (TSLP) have been implicated in skin-based allergic sensitisation in food allergies.[5] Experimental models have shown that epicutaneous exposure to food allergens induces a potent allergic type 2 immune response, leading to systemic food-allergic reactions, including anaphylaxis, on subsequent oral exposure.[6] Mechanical skin injury alone not only promotes cutaneous sensitisation to foods but also expands and activates intestinal mast cells, thus promoting anaphylaxis in mouse models.[7] Inflammation from skin barrier disruption alone can worsen symptoms of FA even when exposure to the allergen is removed.[8]

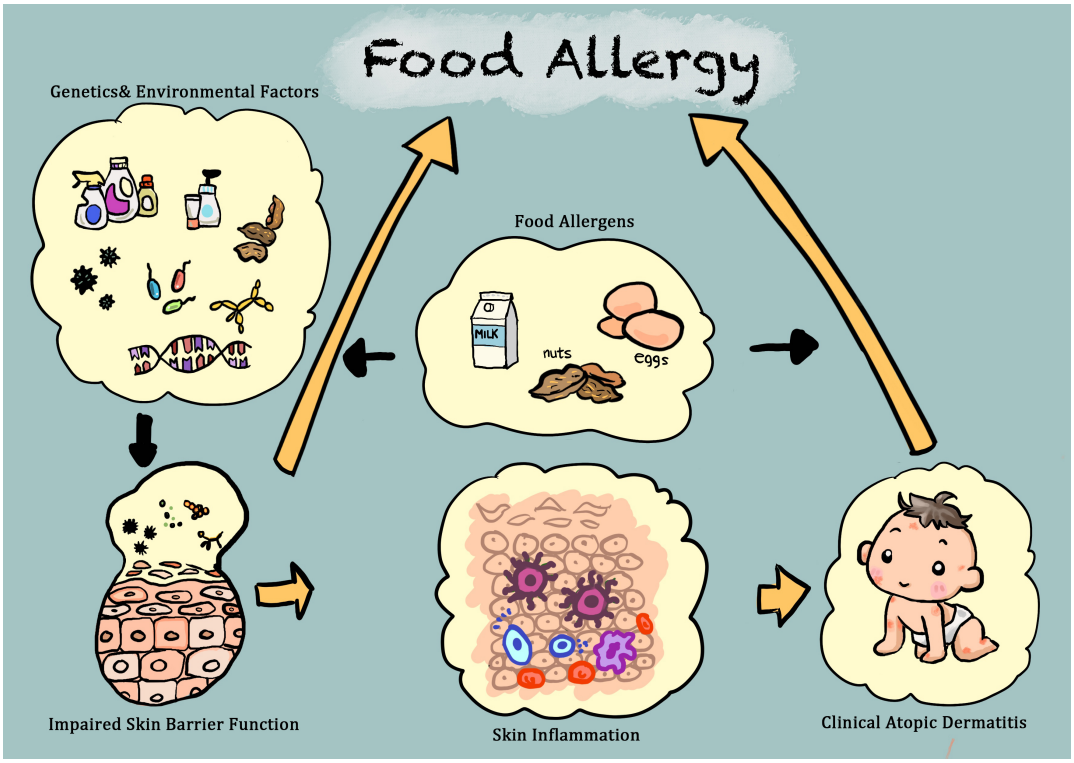

Diagram 1: Pathway from skin barrier dysfunction to food allergen sensitisation and food allergy [Adapted from Figure 2 - Ref. 5]

Role of Skin Care on Food Allergy Prevention

Restoring skin barrier and preventing AD could potentially prevent related allergic diseases, particularly food sensitisation and FA. Factors influencing success include the type of emollient, skin inflammation management, and primary and secondary prevention methods.

Emollients have been shown to reduce the incidence of AD and FA in infants. Pilot studies showed that standard petroleum-based moisturizers could reduce AD by up to 50% by enhancing skin hydration.[9,10] However, larger randomised controlled trials (RCTs) found no significant reduction in AD incidence, and in the Barrier Enhancement for Eczema Prevention (BEEP) study, there was an increased rate of infections and a trend toward increased FA.[11,12] A randomised trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitisation (the PEBBLES pilot study) used a ceramide-containing tri-lipid cream for 6 months, demonstrating a reduction in AD and food sensitisation at 6 and 12 months of age.[13] Proactive topical steroid treatment commenced by 4 months of age was associated with an almost twofold reduction in FA by 24 months. Numerous emollient studies for preventing atopic diseases are ongoing, but results have not been published.

Two large preventative emollient RCTs, the BEEP study and the Preventing Atopic Dermatitis and ALLergies in childhood (PreventADALL) study, have been disappointingly negative for several reasons. These include the age at which emollients were first applied, the rate of adherence with the study intervention, the properties of emollients on skin hydration, pH, restoration of the skin barrier, and immune function, and the potential disconnect between AD and FA development.

In addition, a study had sought to ascertain if proactive therapy of AD to both affected and unaffected skin is superior to reactive treatment in preventing hen's egg allergy.[14] The study involved 650 infants aged 7-13 weeks with AD and randomly assigned them to either enhanced early skin treatment or conventional reactive treatment using topical corticosteroids. The results showed that enhanced treatment significantly reduced hen's egg allergy compared to conventional treatment, with the caveat of lowering body weight and height at 28 weeks. The study suggests that well-controlled AD management could be a successful prevention strategy.

Role of Diet on Primary Food Allergy Prevention

The role of early solid introduction in FA prevention has been a topic of significant interest and research in recent years. Historically, it was believed that delaying the introduction of certain allergenic foods to infants could help prevent the development of food allergies. However, more recent studies have challenged this notion and suggested that early exposure to allergenic foods may be beneficial in reducing the risk of food allergies.

Several large-scale clinical trials, such as the Learning Early About Peanut Allergy (LEAP) study and the Enquiring About Tolerance (EAT) study, have provided important insights into the role of early solid introduction.[15,16] These studies focused on introducing peanuts and common allergenic foods, respectively.

The LEAP study found that early introduction of peanuts to infants at high risk of peanut allergy significantly reduced the development of peanut allergy by up to 86%. This landmark study led to a paradigm shift in guidelines for peanut introduction, with many professional organisations recommending early introduction of peanuts to infants to prevent peanut allergies.

Similarly, the EAT study investigated the introduction of multiple allergenic foods, including peanuts, eggs, milk, sesame, fish, and wheat, to infants. A secondary intention-to-treat analysis of this study showed that among infants with sensitisation to one or more foods at enrollment, the early introduction group developed significantly less FA than the standard introduction group.[23] This efficacy occurred despite low adherence to the early introduction regimen, which has implications for emerging infant feeding recommendations. Overall findings highlight the importance of early introduction of allergenic solids in preventing infant FA.

Furthermore, the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study investigated the early introduction of cooked eggs in infants. The study found that introducing cooked eggs at 6 months of age, alongside breastfeeding, reduced the risk of egg allergy development by 79% compared to delayed

introduction.[17] Similarly, the Beating Egg Allergy Trial (BEAT) investigated the effect of early egg introduction in infants with eczema.[18] The study found that introducing eggs from 4 to 6 months of age, alongside continued breastfeeding, reduced the prevalence of egg allergy at 1 year of age in infants with eczema.

Based on these findings, and findings from other randomised controlled trials, in regions where the baseline FA prevalence is high, guidelines have been revised to promoting early introduction of allergenic foods starting from 4-6 months, including peanuts and eggs.[20] Currently, non-delayed introduction of allergenic solids, i.e., before 12 months of age, is recommended in regions where FA prevalence is not high, including Hong Kong, until further research is conducted.[21,24] If infants are at risk of developing food allergies (e.g., healthy infants with a family history of allergies), allergenic solids can be gradually introduced when weaning has begun in a reasonable manner. In high-risk infants (e.g., with severe eczema), parents should seek advice from an allergy specialist for proper management of his/her eczema and consideration of allergy testing and supervised oral challenges.

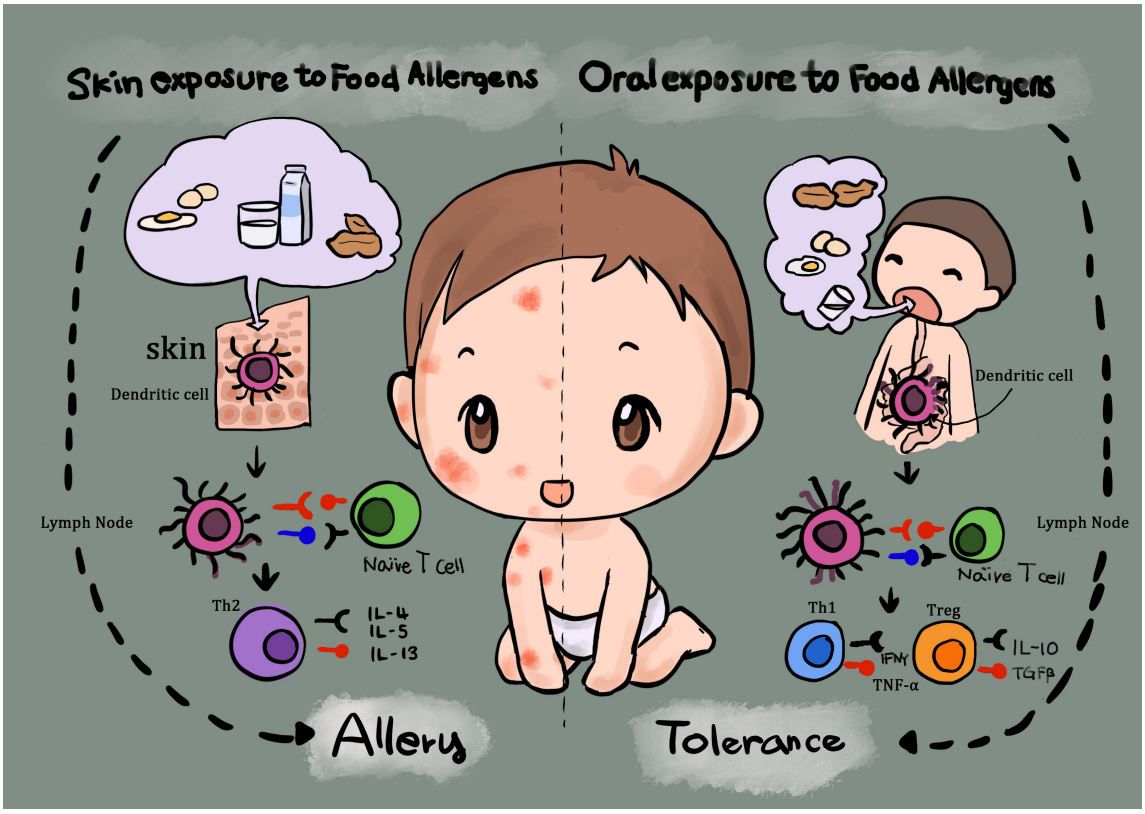

Diagram 2: Dual-allergen Exposure Hypothesis: Early life allergen exposure via the skin results in food allergy, while early oral exposure results in tolerance [Adapted from Figure 3 - Ref. 5]

Conclusion

Food allergies are a growing public health issue. Oral tolerance induction through early introduction of allergenic foods, particularly peanuts and eggs, offers a new strategy for FA prevention. On another front, research indicates that disrupted skin barriers contribute to food sensitisation and allergies. Interest in restoring the skin barrier to prevent AD and FA has grown. However, large RCTs using preventative emollient therapy have had initial negative results, and other studies are ongoing. Despite these challenges, these studies will inform the research on preventing FA and reducing the duration and severity of AD.

Key Messages:

- One of the main risk factors for IgE-mediated food allergy and food sensitisation is atopic dermatitis.
  由IgE介導的食物過敏的主要風險因素之一是異位性皮膚炎。

- Restoring the integrity of the skin barrier and proactive control of atopic dermatitis are promising strategies for primary and secondary prevention of food allergy.
  恢復完整的皮膚屏障和積極主動控制異位性皮膚炎，都有望成為預防食物過敏的有效策略。

- Research has demonstrated that introducing peanuts and eggs to high-risk infants at an early age can prevent the development of allergies to peanuts and eggs, respectively.
  研究顯示，讓有食物過敏高風險的嬰兒提早食用花生和雞蛋可以預防對花生和雞蛋過敏。

- Recently, recommendations have been changed to encouraging the early introduction (at 4 – 6 months) of allergenic foods, such as eggs and peanuts, in all infants in areas with a high baseline prevalence of food allergy.
  最近，在食物過敏流行的地區，已修訂建議為鼓勵所有嬰兒儘早（在 4 - 6個月大時）引入過敏食物，例如雞蛋和花生。

- In regions where the prevalence of food allergy is not high, including Hong Kong, allergenic solids should be introduced without delay (<12 months old), in healthy at-risk infants (with family history). However, if infants already develop severe eczema, early advice from allergy specialists would be warranted.
  在食物過敏較不普遍的地區，包括香港，則建議健康但有高風險（有家族史）的嬰兒不應延遲（應於12 個月大前）引入致敏的固體食物。 然而，若嬰兒已經出現嚴重的濕疹，便需及早向過敏專家查詢。

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