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**Title:** Skin and oral intervention for food allergy prevention based on the dual allergen exposure hypothesis

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Key words
Atopic dermatitis, food allergy, prevention, dual allergen exposure hypothesis, skin, immune tolerance, infant, nutrition, proactive therapy, sensitization

Key Message
For food allergy prevention in infants, we recommend a personalized approach of both skin intervention (eczema treatment to achieve early remission and well-controlled skin with no eczema to prevent percutaneous IgE sensitization) and oral intervention (early allergenic food introductions) to avoid adverse events based on the dual allergen exposure hypothesis.

Abstract
Early-onset atopic dermatitis increases the risk of food allergies, suggesting that transcutaneous sensitization may occur through inflamed skin. Regarding food allergy causation, the dual allergen exposure hypothesis proposes that oral-route allergen exposure leads to immune tolerance, whereas allergen exposure via the inflamed skin
causes food allergy. This hypothesis implies that it is important to induce oral immune
tolerance and prevent allergic food sensitization through the skin. In this review, we focus
on the breakthrough evidence based on the dual allergen exposure hypothesis—both skin
intervention and oral intervention for food allergy prevention.
Introduction

Food allergy and allergic diseases are widespread in Korea, Japan, and many countries. The emergence of the food allergy epidemic has been a global concern, and its psychosocial and economic toll has become a public health concern. Food allergies affect approximately 10% of children in the United States and Japan. The major allergens responsible for food allergy vary by country and ethnicity. Peanut allergy is the most common food allergy in North America and Europe, whereas hen’s egg allergy prevails in Australia and Asian countries. Recently, there has been increased interest in preventing IgE-mediated food allergies. Although the mechanisms of sensitization and the onset of food allergy are not fully understood, a major shift in preventive approaches to food allergy is underway. It has been suggested that environmental and genetic factors (including epigenetic changes) may also influence the development of allergies, such as food allergies. Factors reported influencing the risk of developing food allergy in childhood include genetic factors and environmental factors (family history, specific genes, atopic dermatitis, gut microbiota, sunlight, and vitamin D). Atopic dermatitis is a major contributing risk factor for the onset of food allergy. Food allergy prevention is defined as the primary prevention of sensitization (the production of specific IgE...
antibodies) and the secondary prevention of the development of food allergy in sensitized individuals. (16) Lack (17) proposed “the dual allergen exposure hypothesis,” which states that percutaneous exposure of infants with eczema to food antigens induces an allergenic immune system, which enhances the allergy, and that oral intake of food antigens induces immune tolerance by enhancing the immune system, which suppresses the allergy. To prevent the onset of food allergy, it is essential to prevent transdermal sensitization by controlling atopic dermatitis and to induce oral immune tolerance by starting oral intake at an early stage of infancy. (18)

We understand that various environmental factors, such as delivery mode, animal exposure, air pollution, smoking, medications, such as antibiotics, and harmful chemicals, might modify the mechanism of allergy. (19-22) In this review, we focus on the breakthrough evidence based on the dual allergen exposure hypothesis—both skin intervention and oral intervention for food allergy prevention, except for environmental interventions (see Figure 1).

**Atopic dermatitis is a significant risk factor for food allergy onset.**

Lack et al. (23) reported an association between eczema and peanut allergy, specifically severe dermatitis and skincare containing peanut oil as risk factors for the onset of peanut
disease, suggesting sensitization by percutaneous peanut allergen exposure. A cohort study in Australia reported that eczema in infancy increased the risk of developing peanut and hen’s egg allergies later in life. (24) We previously reported that the onset of eczema at 1.2 months of age was associated with the highest adjusted odds ratio (aOR 6.61, 95% CI 3.27–13.34), followed by 3.4 months of age (aOR 3.90, 95% CI 2.34–6.52) from a general birth cohort in Tokyo. (25) Additionally, we reported that persistent eczema was associated with food allergy at 3 years old from a national birth cohort in Japan. (13) A Canadian birth cohort study demonstrated that atopic dermatitis at 1 year of age was associated with a higher risk of food allergy at 3 years of age. (26) There were several phenotypes of atopic dermatitis. (27, 28) A European birth cohort showed that early-onset atopic dermatitis is a risk for the onset of food allergy. (28) According to these reports, atopic dermatitis is a major risk factor for the onset of food allergies. The earlier atopic dermatitis develops, the higher the risk of developing food allergy.

Food allergens in the environment

Food allergens have been found in the environment, including on tables, beds, hands, and dust. (29) In Japan, we detected hen’s egg allergens in all bed dust of children at 3 years of age and peanut and hen's egg proteins from pet fur. (30, 31) The concentration of hen’s...
egg protein in dust in the living rooms and bedrooms increased after consuming hen’s eggs at home. (32) In the United States, the levels of peanut protein in the dust were higher at school than at home. (33) In the United Kingdom, a study demonstrated a positive association between peanut antigen levels in dust and infant peanut sensitization and peanut allergy. (34) Peanut allergy was associated with a reaction of T cells expressing homing receptors to the skin with peanut antigens, suggesting a mechanism of percutaneous sensitization. (35) Food allergens in the environment are thought to contribute to food allergy via sensitization through inflamed skin, such as eczema in children.

**Early enhanced anti-inflammatory treatment of eczema and maintenance of remission**

For allergen exposure via the inflamed skin, an animal study demonstrated that when mice were exposed to peanut and ovalbumin allergens across disrupted skin, they developed a potent systemic immune response to these allergens. (36) As previously stated, several cohort studies and a systematic review indicated that early-onset eczema is one of the most important risk factors for the onset of food allergy. (25, 37-39) Recently, we identified infants at one month of age who already developed atopic dermatitis by mRNAs
in their sebum.\textsuperscript{(40)} For early interventions for preventing or treating atopic dermatitis, only emollients (moisturizers)\textsuperscript{(41, 42)} or pimecrolimus with reactive method did not prevent food allergy.\textsuperscript{(43)} Emollients and weak anti-inflammatory medication applied only to clinically affected skin lesions might be insufficient to prevent food allergies. Emollients (moisturizers) are not anti-inflammatory products, as we all know. In 2014, we conducted the first confirmatory randomized controlled trial (RCT)\textsuperscript{(44)} for an atopic dermatitis prevention study using moisturizer applications. We discovered that applying moisturizer to infants who had a family history of atopic dermatitis reduced the onset of atopic dermatitis, but we did now show the efficacy of the onset of food allergy. Guttman–Yassky et al.\textsuperscript{(445)} presented strong evidence that immune and barrier abnormalities exist in both clinically affected and unaffected skin lesions of AD, suggesting that sufficient anti-inflammatory treatment for the whole body, including clinical and subclinical lesions, is probably required for food allergy prevention through the skin route. Proactive treatment (see Figures 2, 3) is a long-term maintenance approach that uses low-dose intermittent anti-inflammatory topical agents, such as topical corticosteroids, to treat and prevent flare-ups of chronic subclinical skin inflammation in atopic dermatitis.\textsuperscript{(46-50)} We show the proactive treatment protocol on a daily basis in our allergy center (see the published supporting information \textsuperscript{(52)} and Figures 3, 4). Approximately 90\% of children
with severe AD were able to have well-controlled eczema (clear or mild AD) by proactive
treatment and education from our real-world data. Impaired skin barrier function and
inflamed skin, like atopic dermatitis, have been suggested as risk factors for percutaneous
sensitization to food allergens. A case-control study by Yamasaki et al. demonstrated
that infants with atopic dermatitis who started proactive therapy by 4 months of age had
a significantly lower incidence of hen’s egg allergy by 18 months of age compared to
infants who started proactive therapy after 5 months of age (9.1% versus 24.2%). We also
discovered a significantly lower prevalence of food allergy at 2 years of age in the group
with infant atopic dermatitis who started proactive therapy within 4 months of developing
atopic dermatitis compared to the infants who received delayed treatment for atopic
dermatitis (see Fig. 5). These results suggest that in children with atopic dermatitis,
starting enhanced therapy of remission induction as early as possible and maintaining
remission with well-controlled skin may reduce the risk of developing food sensitization
and food allergy by preventing percutaneous IgE sensitization to food allergens. Recently,
we completed the PACI Study, an early enhanced intervention for infantile atopic
dermatitis to prevent the onset of food allergy: a multicenter, investigator-blinded,
randomized, and parallel group-controlled trial. Enhanced proactive treatment for infant
atopic dermatitis reduces the risk of hen’s egg allergy, but with some concerns regarding
early growth. PACI study provides new and convincing proof of principle that enhanced treatment of early onset atopic dermatitis can reduce the risk of hen’s egg allergy onset based on the dual allergen exposure hypothesis. However, we do not recommend widespread use of our “same” protocol of enhanced atopic dermatitis care in the PACI Study for food allergy “prevention” in a real-world setting. In a real-world setting, we adopt a personalized staged approach to atopic dermatitis treatment according to each infant’s morphology, distribution, severity, and treatment response.

Not recommended maternal allergenic food eliminations

Although the Cochrane Review did not directly evaluate food allergy as an outcome of maternal allergenic food eliminations, it did find that maternal food eliminations during pregnancy and lactation did not affect preventing food allergen sensitization or the development of eczema and asthma. According to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines, maternal allergenic food eliminations during pregnancy and lactation are not recommended to prevent the onset of food allergy.

Breastfeeding and infant formula
Although breastfeeding has many benefits for both infants and mothers, Lodge et al. (57) found no association between the duration of breastfeeding and food allergy in a systematic review and meta-analysis of observational studies. Sakihara et al. (58) in an RCT, showed that consuming at least 10 mL of regular milk per day in addition to breast milk between 1 and 2 months of age reduced the onset of milk allergy. Boyle et al. (59) showed in a systematic review and meta-analysis that partially or fully hydrolyzed milk was not associated with the development of food allergy compared to regular milk. Urashima et al. (60) in an RCT, showed that adding fully breastfed or amino acid formula for 3 days after birth was associated with less cow’s milk allergy at 1 year of age than adding 5 mL or more of regular milk per day for 3 days after birth. WHO recommends that exclusively breastfeeding should be performed for at least 6 months after birth. WHO considers all children across the world including developed and developing countries. However, along with the evidence from clinical trials, we consider that avoidance of cow’s milk formula during the first few days after birth and implementation of a small amount of cow’s milk formula beginning at 1 month of age might be recommended for milk allergy prevention.

**Weaning food introduction in infants**
There is no evidence that delaying weaning foods prevents the onset of food allergies. Nwaru et al. (61) showed that delayed introduction of solid foods was associated with food allergen sensitization. Burgess et al. (62) in a systematic review, found that starting solid foods other than milk before 4 months of age was not associated with the development of food allergy compared to starting after 4 months of age. At the moment, different local guidelines recommend different times for solid food introduction for infants. (63) The Asia Pacific Academy of Pediatric Allergy, Respirology, and Immunology (APAPARI) recommends solids food introduction at 6 months of age, (64) while Canadian guidelines recommend solid food introduction around 6 months. In contrast, UK guidelines recommend solid food introduction at 4 months. (63) As we mentioned before, exclusive breastfed is suggested by WHO and the recommendation of 4-6 months for allergy prevention varies based on guidelines.

**Oral “single” allergen introduction—hen’s egg in infants**

The LEAP trial was the first to report that early peanut intake for high-risk infants prevents subsequent peanut allergy onset. (65) Based on this evidence, various guidelines for food allergy recommend early single-allergenic food intake to prevent food allergy. (56, 66-68) Similarly, regarding the early introduction of hen’s egg, we reported that a tiny dose of cooked hen’s eggs to infants with atopic dermatitis at 5-6
months of age significantly reduced the incidence of hen’s egg allergy compared to infants that avoid hen’s egg until 12 months of age. (PETIT Study). (69) In our trial, no adverse events related to the interventions were reported. We believe that the successful prevention point was that infants with eczema could have it under control through proactive therapy along with a tiny dose of hen’s egg. Four RCTs(70-73) evaluated the preventive effect of the early ingestion of hen’s egg as a single allergen using a large portion of raw eggs, and some children developed anaphylaxis. A tiny dose of allergenic foods has enough of a preventive effect. Recent observational study demonstrated that hen’s eggs consumption ≥2 times per week (not every day) in late infancy reduced a risk of consequent egg allergy later in children. (74) We believe that even if infants eat only tiny amounts of allergenic foods in safely while suffering from well-controlled eczema, they can prevent food allergies.

Oral “multiple” food allergen introductions in infants

In the EAT study(75) on fully breastfed infants who were not considered high-risk, the early induction group who started mixed allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; at least 2 g of each food protein per week) between 3 and 5 months of age did not reduce the onset of food allergy more than the standard group
who started after 6 months of age. Since the dropout rate from the protocol was high, no
large proportion of allergenic foods as weaning food introduction in infants was feasible.
Nishimura et al. (76) conducted an RCT on atopic dermatitis infants aged 3–4 months in
a high-risk trial. In this trial, the early introduction group received allergenic food powder
(containing tiny doses of hen's egg, milk, wheat, soybean, buckwheat, and peanuts
powders) from aged 3–4 months, while the control group received placebo powders. The
powder was gradually increased (2.5, 7.5, and 20 mg of each allergenic food protein)
throughout the trial, which lasted 12 weeks, and was combined with well-controlled
eczema. The early multiple allergenic food introduction group significantly reduced the
onset of later food allergies. Similar to our previous trial for egg allergy prevention,(18)
a tiny dose was sufficient to induce immune tolerance.
Quake et al. (77) conducted a pilot study on healthy infants with no current food allergy
to evaluate the preliminary safety of 10 food allergen proteins mixed. They tested the
early introduction of single foods (milk, egg, or peanut) vs. two foods (milk/egg,
egg/peanut, or milk/peanut) vs. multiple foods
(milk/egg/peanut/cashew/almond/shrimp/walnut/wheat/salmon/hazelnut at low,
medium, or high doses). Adherence was as high as 95%, with no cases of anaphylaxis.
Both safety and feasibility were satisfactory. These results indicate that even low doses
of the mixed powder were sufficient for preventive effect. Furthermore, mixed powder interventions outperformed single/two allergenic food interventions.

Recently, multiple allergenic food products have been commercially available as early allergen introduction foods. Many of these are marketed as aiding in the prevention of food allergies. However, there are concerns about the safety of infants in the absence of a medical assessment. There have been several reports of allergic reactions to commercial allergen food products. (78)

**Conclusion**

Although several studies have been conducted to investigate the preventive efficacy of supplements, such as vitamin D, prebiotics, and probiotics, via oral-route intervention, several guidelines have not recommended supplements, prebiotics, and probiotics for food allergy prevention due to low certainty of evidence. (56, 79, 80) We have been doing online parental preparation class during pregnancy to implement latest findings from various studies. (9) We believe that the major invaluable interventions for food allergy prevention are eczema management and early tiny dose of introduction allergenic foods. In our daily practice, we can almost completely prevent IgE-mediated food allergy (hen’s egg, milk, wheat, and soy) in infants with early-onset eczema. (81)
The New Nutrition Science has a holistic paradigm shift because it is informed based on integrating social (including cultural, economic, and political) dimensions with “classical” biological (biochemical, physiological, and medical) dimensions. (81) We should promote infant nutrition not only from a classical biological aspect but also from cultural, economic, and political aspects. We consider that the flow of food allergy prevention strategy (see Fig. 6) is recommended in daily practice based on the dual allergen exposure hypothesis—both skin intervention and oral intervention for food allergy prevention. To overcome the food allergy epidemic, pediatricians need to be specialists in atopic dermatitis treatment.

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Figure legends

Fig. 1
Breakthrough evidence based on the dual allergen exposure hypothesis - skin intervention and oral intervention for food allergy prevention

Fig. 2
Reactive treatment and proactive treatment

Fig. 3
Protocol of proactive treatment for atopic dermatitis

Fig. 4
A case of severe atopic dermatitis who treated with remission-induction therapy and maintenance therapy (proactive therapy)

Fig. 5
Delayed enhanced treatment for eczema increases the risk of developing food allergy

Fig. 6
Prevention strategy for food allergy in children
The timing for interventions might be modified based on each infant. It is difficult for specifying target populations for individual intervention. In a real-world setting, for food allergy prevention in infants, we recommend a personalized approach of both skin intervention (eczema treatment to achieve early remission and well-controlled skin with
no eczema to prevent percutaneous IgE sensitization) and oral intervention (early allergenic food introductions) to avoid adverse events based on the dual allergen exposure hypothesis.
Breakthrough evidence based on the dual allergen exposure hypothesis- skin intervention and oral intervention for food allergy prevention

Skin exposure

Allergen percutaneous exposure via inflamed skin
↓
Percutaneous IgE sensitization
↓
Allergy

Early skin (eczema) intervention

PACI Study (JACI, 2023)

Oral exposure

Allergen exposures via oral-route
↓
Oral immune tolerance
↓
Allergy remission

Early oral interventions

LEAP Study (NEJM, 2016)
PETIT study (Lancet, 2017)
SPADE Study (JACI, 2021)
Reactive treatment cannot control eczema for moderate and severe atopic dermatitis

**Reactive treatment**

- Only for visible eczema
- Similar with acute asthma attack treatment only
- Frequent flares
- Uncontrolled eczema

**Proactive treatment**

- Long-term maintenance approach that uses low-dose intermittent anti-inflammatory topical agents
- Prevent eczema flares
- Well-controlled eczema

Long-term controller like asthma as maintenance therapy to treat chronic inflammation and prevent eczema flares
Protocol of proactive treatment for atopic dermatitis (AD)

**Point 1!** AD education

**Point 2!** Skincare

**Point 3!** Personalized **proactive treatment** with topical anti-inflammatory drug (use appropriate potency) (decided based on patient's clinical history and examination)

- **Face:** mild steroids or other with topical anti-inflammatory drug
- **Body:** moderate or strong steroids other with topical anti-inflammatory drug

**Point 4!** Sufficient volume application

1 FUT (finger-tip unit)
4-year-old girl (severe AD)
Mother was a steroid phobia
Decreasing urine volume, Hypoproteinemia
Serum TARC 92,700 (2-19 years <743 pg/mL)

- **Education**
- **Skincare with washing body and emollients**
- **Proactive therapy with topical corticosteroids and topical tacrolimus without systemic agents**
Figure 5

Delayed enhanced treatment for eczema increases the risk of developing food allergy

Strategy for food allergy prevention in children

- **Pregnancy**: Mothers do not need to ensure unnecessary food eliminations during pregnancy and breastfeeding.
- **Birth**: A small amount of regular milk may be added to breast milk from the age of 1 month.
- **1 month**: Initiate skin treatment as soon as eczema develops. Promptly induce and maintain remission for eczema. Maintain eczema-free skin to prevent percutaneous sensitization.
- **Introducing Solid Foods**: Start weaning foods conventionally. Do not delay the introduction of allergenic foods in cases of well-controlled eczema. Continue consuming allergenic foods, even in small amounts, if available.
- **Good control of other allergic diseases such as asthma and allergic rhinitis.**

- **Oral interventions**: Let's go forward with both skin and oral interventions, at the right timing and in the right way!

- **Skin interventions**

- **Share information with pregnant mothers before birth.** “Please see a doctor as soon as possible after eczema onset.”

- **Treat eczema and wean your baby with “perfectly no eczema” skin!**

- **If there is a history of eczema, please test IgE for allergies before introducing weaning food.**

- **If the allergy tests are negative, we can keep the baby's skin clean and start weaning food.**