SECTION OF PAEDIATRIC ALLERGY & IMMUNOLOGY, COLLEGE OF PAEDIATRICS & CHILD HEALTH, SINGAPORE,
COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS, SINGAPORE & ACADEMY OF MEDICINE, SINGAPORE

ADDENDUM GUIDELINES ON THE PRIMARY PREVENTION OF ALLERGY IN AT-RISK INFANTS

2 SEPTEMBER 2024

New published data, including systematic reviews and meta-analyses, have now provided high-level evidence for interventions for prevention of cow's milk protein allergy (i.e., Recommendation 3) and eczema (i.e., Recommendation 6), presented here in 2 addendums.

ADDENDUM 1 to Recommendation 3: on the role of partially hydrolyzed in the prevention of cow's milk protein allergy (CMPA).

> ***Recommendation 3:***
>
> ***There is insufficient evidence to recommend the use of extensively hydrolyzed formula (eHF) and partially hydrolyzed formula (pHF) for cow's milk allergy and eczema prevention."***
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> ***Grade A, level 1***

Breastfeeding remains the preferred modality of feeding in infants less than 6 months of age. New information has become available on the role of hydrolyzed formulas in the prevention of CMPA and eczema in infants at risk for developing CMPA.

Infants at risk to develop CMPA

A positive family history of atopy (i.e., a history of eczema, asthma or allergic rhinitis in a first-degree family member) is considered a risk factor for an IgE-mediated CMPA. Non-IgE-mediated CMPA remains a difficult issue because of lack of knowledge of its underlying mechanisms, and therefore, lack of a reliable diagnostic test, except for an oral food challenge.

Risk factors for non-IgE-mediated CMPA are also unknown and may be different from risk factors for IgE-mediated CMPA.

Role of hydrolyzed formulas

The recommendation for use of a hydrolyzed cow's milk formula for allergy prevention in the first year of life was based on older studies, such as the GINI study[1]. The results of this study were not reproducible in a recent multi-centre study[2]. Moreover, a recent Cochrane review (2017) and a meta-analysis (2016) were also unable to show any effect of hydrolyzed formulas on allergy prevention[3,4]. In 2021, EFSA (European Food Safety Authority) concluded that a cause-and-effect relationship was not established between the consumption of pHF and the reduction in the risk of developing atopic dermatitis in infants with a family history of allergy[5]. Since then, several professional societies have adopted strong positions on the insufficiency of evidence for hydrolyzed formulas for prevention of allergic diseases / atopic disease compared with regular cow milk formula or breast milk. The latest consensus from ESPGHAN (Feb 2024) stated that "For infants with a documented family history of

allergic disease who cannot be exclusively breastfed, there is insufficient evidence to recommend the routine use of pHF, eHF-Whey, eHF-Casein or AAF for preventing CMA."[6]

There is also insufficient evidence to recommend for or against the use of formulas containing bacterial products, such as probiotics and prebiotics for CMPA prevention. Furthermore, these formulas are composed of various hydrolyzed formulas, making it impossible to assess the separate contribution of bacterial products in preventing CMPA.[7,8]

Other interventions that are currently under investigation for CMPA prevention are the negative role of early substitution with a cow's milk formula during the first few days of life, and the age of introduction of cow's milk in fully breastfed infants. Isolated clinical trials suggest that the avoidance of early substitution and the early introduction and regular consumption of cow's milk from the age of 4 – 6 months might be useful for cow's milk allergy prevention. However larger studies and validation across different populations are needed before definite recommendations can be made.[9-12.]

CONCLUSION:

Usage of eHF and pHF seems to have no effect, and most guidelines now no longer recommend its usage in the prevention of CMPA.

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ADDENDUM 2 to Recommendation 6: on the role of early moisturizing for eczema prevention.

Recommendation 6a:

We recommend application of moisturizers from birth in high-risk infants with a family history of atopy (in a first-degree family member) to reduce the risk of eczema.
There is insufficient evidence at this time to recommend for or against this intervention for food allergy prevention.

Grade A, level 1

Skin barrier therapy for AD and FA prevention

Early-life skincare measures have been investigated as a preventive approach for eczema and food allergy (FA), aiming to mitigate transepidermal water loss (TEWL) and repair the skin barrier before the onset of these conditions. In 2014, two distinct randomized controlled trials (RCTs) conducted in the USA/UK and Japan were concurrently published, indicating that the application of moisturizers to high-risk infants with a family history of eczema within the initial two months of life reduced the risk of developing AD by the ages of 6 and 9 months.[1, 2] Horimukai et al. [1] found no significant disparities in egg sensitization at 32 weeks, while Simpson et al. [2] did not evaluate food sensitization or FA outcomes.

In 2020, two extensive randomized controlled trials carried out in Norway/Sweden (the Preventing Atopic Dermatitis and ALLergies in childhood - PreventADALL study) and the United Kingdom (the Barrier Enhancement for Eczema Prevention – BEEP study) similarly did not reveal any impact of skin emollient applications on atopic dermatitis development in both normal-risk (PreventADALL) and high-risk (BEEP) infants. [3, 4] PreventADALL also indicated no advantage of this intervention against food sensitization or FA by the age of 36 months. [5] On the other hand, the BEEP study observed a tendency towards increased FA in children who underwent the skin intervention, albeit without statistical significance. [4]

The PEBBLES (Prevention of Eczema By a Barrier Lipid Equilibrium Strategy) pilot study, employed a ceramide-dominant triple lipid moisturizer on high-risk infants (n=80) starting from the first 3 weeks of life for a duration of 6 months. The study reported a tendency towards a decreased occurrence of eczema and food sensitization by the age of 12 months. [6] Long-term follow-up is currently underway to evaluate the effect of this intervention on food allergy outcomes. [7]

The STOP AD (Short-term Topical Application to Prevent Atopic Dermatitis) trial discovered that the daily use of an emollient comprising ceramides, fatty acids, and oats during the initial 8 weeks of life decreased the prevalence of eczema at the ages of 6 and 12 months among high-risk infants, when compared to conventional skincare practices. [8] However, food sensitization rates between the two groups were not significantly different, although its effect on food allergy could not be evaluated due to limited sample size.

A Cochrane meta-analysis conducted by Kelleher et al. concluded that various early skin interventions, including the use of bath oils, bathing techniques, and emollients at any point within the first year of life, did not provide protection against the development of eczema and might even elevate the risk of skin infections. [9]

However, Zhong et al. specifically investigated the impact of emollients used solely within the initial 6 weeks of life on eczema development at any stage. They found that this intervention could potentially be effective in high-risk populations but not in those at normal risk. Furthermore, it might delay rather than entirely prevent the onset of eczema and showed benefits when continuously applied rather than with intervals between treatment cessation and assessment of eczema outcomes. [10] Both meta-analyses identified a similar tendency towards increased food sensitization, albeit mainly supported by data from the BEEP study at that point in time.

Recommendation 6b:

We recommend against the use of moisturizers containing food products, especially in infants with significant eczema.

Grade B, level 1

Evidence suggests that epicutaneous exposure to food allergens, particularly through an impaired skin barrier such as in eczema, induces a potent pro-allergic Th2 immune response through activation of antigen-presenting cells in the dermis resulting in specific IgE production to the implicated food allergens.[11, 12] This has been supported by observational studies which found associations between cutaneous exposure to environmental food allergens as well as through topical applications of food allergen-containing skin products, and the development of food sensitization and food allergy.[13-18] Based on these studies, it is recommended that topical moisturizers should not contain food products, particularly in infants with eczema, to avoid inducing food allergy.

Good practice point (GPP).

Ensure that hands are clean (i.e., simple hand washing and avoidance of application with dirty hands) before application of moisturizers to reduce the risk of skin transfer of food allergens or bacteria onto infants' skin.

Grade D

The BEEP study showed a trend towards increased FA in children who received the skin intervention, although this was statistically non-significant.[4] The Enquiring About Tolerance (EAT) study enrolled normal-risk infants at birth to examine the effect of early allergenic food introduction on food allergy outcomes.[19] A post-hoc analysis found that greater use of moisturizers at 3 months of age was associated with increased food sensitization and food allergy at 1 and 3 years of age, even in those with no visible eczema at baseline.[20] It was thus postulated that application of topical moisturizer could either increase skin exposure to food allergens from caregivers' hands; enhance the translocation of food allergens across the skin barrier or may have a direct deleterious effect on the skin barrier which promotes epicutaneous sensitization.

A Cochrane meta-analysis found that early skin interventions could also potentially increase the risk of skin infections, although no clear mechanisms were described in these trials.[9]

As transfer of food proteins or bacteria can also theoretically occur from contaminated hands to the inflamed skin of infants, thereby increasing the risk of food sensitization or skin infections, a good practice point recommendation is to ensure that caregivers' hands are clean before application of emollients onto infants' skin.

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