

CONSENSUS STATEMENT

PRIMARY PREVENTION OF ALLERGY IN AT-RISK INFANTS

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**ACADEMY OF MEDICINE
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INTRODUCTION

In recent years, the approach to primary prevention of allergy (mainly to food allergy and eczema) has drastically changed, largely due to the influence of well-conducted studies, such as The LEAP study and The EAT study (1,2). This has resulted in major changes in various national and international guidelines on primary prevention of food allergy and eczema in USA, Europe and Australia (3 – 5).

Whilst in the past avoidance or late introduction of allergenic foods, such as egg and peanut, was generally recommended, a complete switch of attitude towards early introduction of allergenic foods is now generally advised.

Furthermore, it is now clear that eczema has a major association with food allergy in early life, as the highest prevalence of food allergy (especially to egg) is found in infants with moderate to severe eczema. A careful approach to food introduction for these group of infants is thus recommended (6).

Interventions of primary prevention of food allergy and eczema can be divided into interventions during pregnancy (antenatally) and intervention during early life (postnatally). Most existing studies address postnatal primary prevention, but more insights are becoming available on the role of primary prevention during pregnancy, for example, the role of the pregnant woman's microbiome on the offspring's immune system (7).

AIM

This document aims to provide guidelines on primary prevention of allergy, thereby decreasing the risk of allergy development (without guarantee) in at-risk infants e.g. infants with at least one allergic parent and/or infants with an allergic sibling. These guidelines are applicable to Singaporean children and to children who have immigrated to Singapore.

METHODS

An electronic search of the available evidence on this topic was performed, preferentially including systematic reviews on the subject. Where no systemic reviews could be found, randomized controlled trials (RCTs) and cohort studies on primary prevention of allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy) were included instead.

The data was then presented to a working group, consisting of currently practicing paediatricians with special interest in allergy in Singapore, and the evidence was critically appraised, through email and round-table discussion on September 28, 2019. A consensus was then reached regarding the recommendations to be made, including the level of evidence of the recommendations (see Table below). This guideline is the result of the electronic search and discussions that have taken place.

TABLE: LEVELS OF EVIDENCE – GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

LEVEL	TYPE OF EVIDENCE
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

LEVEL	TYPE OF EVIDENCE
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group

RECOMMENDATIONS

(1) During Pregnancy

Recommendation 1:

During pregnancy, smoking and alcohol consumption should be avoided.

Grade C, level 2

There is an association between pre- and post-natal tobacco exposure and recurrent wheezing in childhood as well as asthma (8 - 10). There is also evidence that alcohol intake in pregnant mothers is associated with the development of atopic dermatitis subsequently in the child (11). This is independent of the health risks of smoking and alcohol intake to the mother's health. Hence, this group recommends avoidance of smoking and alcohol intake in pregnant mothers.

Recommendation 2:

Pregnant mothers should consume a balanced healthy diet.

GPP

There is presently no evidence that avoidance of dietary allergens (such as egg, milk and other foods) during pregnancy may reduce the risk of allergic diseases. On the other hand, a restricted maternal diet may increase the risk of preterm birth and result in lower birth weight (low level of evidence). Therefore, pregnant mothers should consume a balanced diet as advocated by the Health Promotion Board (12 - 16), also referred to as a Mediterranean diet (15).

Recommendation 3:

Whilst strong evidence for primary prevention of allergy is weak, vitamin D supplementation is a safe intervention for those found to be vitamin D deficient.

GPP

There is at present no definitive evidence that vitamin D supplementation during pregnancy lowers the risk of allergic disease in the newborn, although some studies suggest potential benefit (17). In view of the low risk of the intervention, vitamin D supplementation may be considered in mothers who are found to be vitamin D deficient. Most experts agree that 1,000 to 2,000 international units per day of vitamin D during pregnancy is safe (18 - 22).

Recommendation 4:

Mothers of infants at risk of eczema (1st degree relative with a history of atopy) can consider probiotic intake during last trimester of pregnancy.

Grade C, level 1+

Although still a matter of intense debate, taking bacterial products (probiotics, prebiotics or synbiotics) during the last trimester of pregnancy, mainly *Lactobacillus* species, including *L. rhamnosus* GG, and *L. reuteri*, has been shown to reduce the risk of allergic disease (mainly of eczema) in children, although negative studies have been reported. It is noted however that long-term outcomes (after more than 15 years) have been disappointing (23, 24). More studies have been published regarding probiotics rather than prebiotics or synbiotics. Pregnant women with a personal or strong family history of allergies and atopy can consider taking probiotics during the last trimester of pregnancy (25 – 27).

Recommendation 5:

There is insufficient evidence to recommend fish oil supplementation in pregnant women for atopy prevention.

Grade B, level 2+

Current evidence for maternal n-3 PUFA supplementation with fish oil supplements during pregnancy on prevention of allergy remains conflicting (28 – 30). There is insufficient evidence to recommend fish oil supplementation in pregnant women for atopy prevention.

(2) During the first 6 months of life**Recommendation 1:**

Exclusive breastfeeding for 3-4 months and continued breastfeeding beyond that may help prevent eczema and wheezing in early life.

Grade B, level 1+

There is evidence that exclusive breastfeeding during the first 3-4 months reduces the incidence of eczema in the first 2 years of life. During breastfeeding the mother does not need to avoid any allergenic foods. In addition, non-exclusive breastfeeding beyond this duration has been shown to reduce incidence of wheezing in the first 2 years of life (31, 32).

Recommendation 2:

Mothers of infants at risk of eczema (1st degree relative with a history of atopy) should consider probiotic intake during breastfeeding.

Grade C, level 1+

There is evidence that maternal probiotic intake while breastfeeding reduces the risk of eczema in the child. Studies concluded that the best intervention with probiotics is to administer them both during the last trimester of pregnancy as well as during the first 6 months of breastfeeding. Hence, mothers with a family history or personal history of atopy should consider taking probiotic during the last trimester of pregnancy and in the first 6 months of breastfeeding (25 - 27).

Recommendation 3:

If breastfeeding is impossible within the first 6 months of life, mothers may consider supplementing with a partially hydrolyzed formula containing prebiotics or probiotics in infants with a family history of atopy

Grade C, level 1-

Breastfeeding remains the preferred modality of feeding in infants less than 6 months of age. However, should breastfeeding not be possible, there is limited evidence that supplementation with a partially hydrolyzed formula containing prebiotics or probiotics may reduce the incidence of eczema and possibly other types of allergic disease. This practice should be restricted to infants with a risk of atopy (i.e. a 1st degree relative with atopic disease) (33 – 36).

UNNECESSARY EARLY SUPPLEMENTATION with cow's milk protein formula should be avoided in babies who are exclusively breastfed to reduce the risk of cow's milk protein allergy.

Breastfed babies are still being put at significantly increased risk of cow's milk protein allergy (CMPA) by receiving supplemental formula in the beginning of life (mainly during the first days of postnatal life, and probably up to the age of one month). Mothers and healthcare providers should be educated on the benefits of exclusive breastfeeding and avoid unnecessary formula supplementation to reduce the risk of developing CMPA. The role of hydrolyzed formula as a supplement during early life to breast milk in preventing CMPA is unknown, but worthwhile studying (37).

Recommendation 4:

For babies with a family history of atopy or mild eczema, complementary foods, such as egg and peanut should be introduced EARLY, one at a time, no earlier than 4 months and up to 6 months once they are able to tolerate solids.

In infants with moderate to severe eczema, a pre-existing food allergy should be considered and might have to be excluded by allergy testing, such as specific IgE or skin prick test (SPT). If allergy tests are negative, egg and peanut can be introduced. If allergy testing is positive the food should be avoided, and the food allergy should be monitored by repeating allergy testing after at least 6 months. Alternatively, an oral provocation test under optimal safety conditions can be considered if results of allergy testing are borderline or only slightly positive.

GPP

Several key studies (LEAP, EAT, PETIT) have shown that early weaning with peanut and egg is beneficial in preventing allergy to peanut and egg respectively. Hence in recent years, there has been several key changes in international and national guidelines worldwide (1,2,38).

PEANUT: The LEAP trial performed on infants at high risk of peanut allergy (pre-existing eczema or egg allergy) demonstrated that early introduction of peanuts from 4-11 months reduced the risk of peanut allergy as compared to delayed introduction (1). It has yet to be determined if this result is applicable to Asian countries, including Singapore, which have a lower prevalence of peanut and food allergy, compared to European populations despite delayed peanut or allogeneic food introduction (39,40). Hence, early introduction of allergenic foods may not be necessary in populations with low prevalence of food allergy and thus infant feeding recommendations should be carefully tailored to individual populations. However, in view of potential benefit, early introduction (between 4 to 6 months, one at a time) of peanut in infants at risk of peanut allergy is recommended.

EGG: Whether early weaning of egg helps prevent egg allergy remains controversial. The PETIT study suggested that early weaning of cooked egg can prevent egg allergy (38, 41). Therefore, in view of the potential benefit, early introduction of cooked egg in infants at high risk of egg allergy (pre-existing severe eczema) is recommended.

In otherwise healthy infants, normal weaning (between 6 to 10 months) practices can be followed.

Example of peanut and egg introduction

Egg or peanut should be introduced in low doses and increased gradually over weeks or months and continued for a year of life. Daytime feedings are recommended, rather than evening feeds, to ensure that the caregiver can respond if the baby has an allergic reaction to the food.

PEANUT: should be in the form of smooth peanut butter, one to two teaspoons, two to three times per week. The peanut butter should be mixed with 2-3 teaspoons of warm water or mixed with vegetable puree to achieve consistency comfortable for the infant.

EGG: should be in the form of hard-boiled egg (no raw egg) pasted into your baby's usual food, such as vegetable puree, starting with 1/8 teaspoon, and gradually increased to 1/4 teaspoon on the next occasion if there are no allergic reactions.

Once egg or peanut are introduced, parents are advised to continue to give these foods to baby regularly (twice weekly) to maintain tolerance.

Till now, there are no published studies on early weaning of other allergenic food (such as seafood). However, it is generally recommended not to delay introducing any food in infants at risk for allergy.

Recommendation 5:

Consider assessing children with moderate to severe eczema for a pre-existing allergy to eggs and peanuts, as it has been shown that these infants have a higher incidence of food allergy.

Grade D, level 2+

Recommendation 6:

Moisturizers should be used from birth in infants with a family history of eczema.

Grade B, level 1

In two independent studies (from Japan and UK) it was shown that use of moisturizers early from birth (before eczema occurs) decreases the prevalence of infant eczema in infants with a family history of eczema (42, 43). Long-term studies on the subject are not available.

Recommendation 7:

Moisturizers should not contain food products.

GPP

Any commercial moisturizer may be used but it should not contain food proteins. Use of moisturizers containing peanut has been associated with peanut sensitization (44). There are also anecdotal information that moisturizers or soaps containing food proteins, such as oat, sesame, hydrolyzed wheat or coconut may lead to food sensitization.

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