Clinical Commentary Review

Prospects for Prevention of Food Allergy

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A rise in both prevalence and public awareness of food allergy in developed countries means that clinicians and researchers are frequently asked to explain reasons for the increase in food allergy, and families are eager to know whether they can take steps to prevent food allergy in their children. In this review, we outline leading theories on risk factors for early life food allergy. We summarize the leading hypotheses to explain the increase in food allergy as "the 5 Ds": dry skin, diet, dogs, dribble (shared microbial exposure), and vitamin D. We discuss currently available evidence for these theories and how these can be translated into clinical recommendations. With the exception of dietary intervention studies, evidence for each of these theories is observational, and we describe the implications of this for explaining risk to families. Current infant feeding recommendations are that infants should be introduced to solids around the age of 4 to 6 months irrespective of family history risk and that allergenic solids do not need to be avoided, either by infants at the time of solid food introduction or by mothers whilst pregnant or lactating. Additional potential strategies currently being explored include optimization of early life skin barrier function through a decrease in drying soaps and detergents and an increase in the use of nonallergenic moisturizers. The investigation of the role of microbiota and vitamin D is ongoing and cannot yet be translated into clinical recommendations. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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WHY IS FOOD ALLERGY ON THE RISE?

The rise in food allergy in developed countries is an intriguing phenomenon that has captured the attention of both the medical research community and the media. Although we need to be circumspect about the extent to which it has risen and which countries are most affected, there is little doubt that IgE-mediated food allergy and anaphylaxis were rarely reported 50 years ago but are now commonly described. The drivers for this modern-day epidemic are poorly understood, and indeed it is not clear whether this phenomenon is part of a second wave of allergy epidemic[1] following on from the general rise in allergic disease that was noted around the world at the end of the 21st century or whether the new food allergy epidemic is due to a new set of unique factors.

The possibility remains that this second wave of allergy epidemic has its roots in events that occurred when the parents of current children were *in utero*, and we are witnessing the expression of an epigenetic effect that has been transmitted through to the next generation—through a heritable epigenetic mechanism. Against this hypothesis is emerging evidence that postnatal factors, which are both common and modifiable, are associated with an increased risk of food allergy. If these factors that we describe in detail below are found to be causal, they will provide an important underpinning of new public health guidelines. However, evidence of causality needs to be generated through carefully controlled randomized trials or through elucidation of biological mechanisms that point to plausibility of such hypotheses, and as such there is currently insufficient data for informed public health guidelines for several of these factors.

In the meantime, as allergy clinicians and researchers, we are routinely asked whether food allergy is on the rise and why. Families are eager to know whether there are factors under their control that may have contributed to the development of food allergy in their children. They are also keen to know what steps they can take to prevent food allergy in subsequent children. Below we outline the emerging evidence for risk factors of early life food allergy. With the exception of the Learning Early about Peanut Allergy study,[2] evidence to date is primarily epidemiological or ecological. As such a word of caution is required in explaining risk to families. Careful adjustment for confounding is central to good quality epidemiological studies. For instance, families at high risk of allergic disease are more likely to breastfeed because guidelines inform them that breastfeeding may be protective. If researchers do not adjust their analysis for family history risk of allergy (the real reason why offspring are likely to be more allergic), it can appear that breastfeeding actually increases the risk of allergic disease that is of course spurious. This is called "reverse causation" and is one of the reasons why randomized controlled trials (RCTs) are required to provide level 1 evidence that a factor is indeed a risk factor. Even with the best intention, observational studies can be undermined by unmeasured confounders and as such clear high-quality data for a risk

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Abbreviations used
EAT- Early introduction of allergenic foods to induce tolerance in infants
EHF- Extensively hydrolyzed formula
GINI- German Infant Nutritional Intervention
PHF- Partially hydrolyzed formula
RCT- Randomized controlled trial

factor must be evident before recommendations are incorporated into public health guidelines. With these qualifications in mind, clinicians can still provide carefully framed information to individual patients about emerging evidence and allow families to decide for themselves whether to act on the information or not.

When asked by a curious member of the public why food allergy is on the rise, we often find we have long-winded academic responses. So we have summarized our response to this question with an overview of the emerging hypotheses in an easily digestible way. This overview is not meant to be exhaustive but provides information for consumers that helps to explain that there is a rapidly emerging body of research attempting to elucidate the cause of food allergy. It is not yet clear whether there is one main hypothesis that accounts for the epidemic or whether a number of factors act in concert. Alternatively, there may be multiple pathways to disease.

In the next sections, we outline 5 current leading hypotheses (dubbed the "5 Ds": dry skin, diet, dogs, dribble, and vitamin D) for the rise in food allergy and then conclude with an interesting and perhaps illuminating observation that offspring of migrants moving from developing to developed countries have the highest risk of food allergy if the offspring are born in the developed country. We conclude with some simple recommendations that families might consider whilst waiting for level 1 evidence to emerge to inform the construction of updated public health guidelines (Table I).

DRY SKIN

Clinicians have recognized for many years a strong association between eczema and food allergy. Not only are infants with eczema 5 times more likely to develop IgE-mediated food allergy but also more than half of those with moderately severe early-onset eczema (defined as onset before age 3 months and requiring treatment with topical corticosteroids) will develop challenge-proven food allergy by age 1 year.[3] This association led researchers to investigate whether the filaggrin gene (which is strongly associated with an increased risk of eczema) independently increases the risk of food allergy. Although some studies suggested that this is the case,[4] others have found that the real risk that filaggrin confers is probably an increased risk of food sensitization rather than food allergy itself.[5] The presence of a filaggrin gene mutation does not appear to distinguish between those who are sensitized to foods but clinically tolerant and those who are both sensitized and allergic.

In 2008, Gideon Lack proposed a mechanism to explain the role of skin barrier function in the development of food allergy that he termed the "dual allergen hypothesis"—often now referred to as the "Lack" hypothesis.[6] The Lack hypothesis proposes that allergic sensitization to foods may occur through exposure to low doses of allergen through the skin because of food allergens absorbed through a damaged skin barrier (such as in eczema or presence of filaggrin loss-of-function mutations). A second aspect of this hypothesis suggests that oral exposure to these allergens through the consumption of allergenic foods early in infancy can abrogate the development of sensitization and instead result in the development of oral tolerance and prevention of the development of food allergy. Mechanistic evidence supporting this hypothesis comes from mouse models showing that sensitization can be induced following the application of allergen to damaged skin, and that this can be reduced by prior high-dose oral allergen exposure.[7] Further support of this hypothesis comes from a recent study demonstrating that higher exposure to environmental peanut antigens found in households increases the risk of peanut allergy in children with either filaggrin loss-of-function mutations[8] or atopic dermatitis.[9]

Two exciting new studies were recently published that both undertook RCTs of daily moisturizing from birth in an attempt to reduce infantile eczema and potentially sensitization to foods. The first demonstrated an impressive 50% reduction in eczema but unfortunately did not examine the protective effect on the development of food allergy.[10] The second assessed both eczema and egg sensitization, and although it also showed a decrease in eczema prevalence in those applying topical moisturizers, it did not appear to have the power to show a statistically significant decrease in food sensitization.[11] A number of larger trials are in progress to pursue this concept and inform public health guidelines.

DIET

Allergen exposure

The Lack hypothesis was first promulgated after the publication of a paper by Du Toit et al[12] that found a 5-fold higher prevalence of peanut allergy in Jewish children in the UK versus Jewish children in Israel. Although the dietary history of children in this observational study was not ascertained, the authors reported a significant difference in dietary patterns between the 2 populations. At the time, it was common practice in Israel to introduce a peanut snack (Bomba) as a weaning food into the diet of infants around the age of 4 to 6 months. By contrast, UK guidelines at the time recommended avoidance of peanut until after the age of 3 years. Lack and colleagues[2] subsequently embarked on a large and ambitious RCT to formally assess whether the early introduction of peanut prevented the development of peanut allergy at age 5 years. The results of this landmark trial were recently published and are the first level 1 evidence to show that the early introduction of peanut (between 4 and 11 months) is protective against peanut allergy in infants who are at high risk (as defined by early-onset eczema or coexistent egg allergy).[2] A note of caution has been sounded however, as an earlier RCT by Palmer et al[13] that assessed the role of the early introduction of egg in a similar high-risk group of infants was abandoned because of adverse events at study entry point during egg challenges. This suggests that care needs to be taken at the time of introduction in high-risk infants, and this sentiment is reflected in recently published interim international consensus guidelines.[14] These emerging trials add weight to previous observational studies that delayed timing of introduction of egg,[15] cow's milk,[16] and wheat[17] is associated with an increased risk of those respective food allergies. Of course, the interplay between the timing of introduction of one allergenic solid and another is difficult to tease out both observationally and