

# Childhood allergy: How to manage and is it preventable?

At a symposium dedicated to allergy, part of the 1st APPS Annual Scientific Congress jointly held with the 18th HKSPRA Annual Scientific Meeting, leading specialists in their fields from Hong Kong and Taiwan shared important insight and data on the topics of skin and food allergy, from epidemiology and pathophysiology to management and prevention. Highlights are featured here.

## Is allergy preventable?



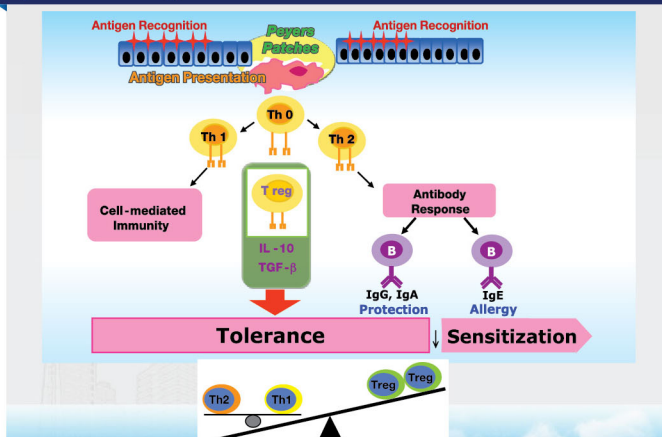
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### Pathogenesis of allergy

In the last few decades the prevalence of chronic diseases, including immune disorders such as asthma, has increased in Western countries and those undergoing economic and epidemiological transition, while infectious diseases have diminished.

Allergen type 1 helper T cells (Th1), allergen type 2 helper T cells (Th2) and regulatory T cells (Treg) play a pivotal role in the immunological pathogenesis of allergic diseases (**Figure 1**). As Prof Huang outlined, reduced microbial exposure in early life may shift the Th1/Th2 balance in the immune system towards the pre-allergic Th2 response. Th2 play a triggering role in the activation/recruitment of IgE antibody producing B cells, mast cells and eosinophils.

**Figure 1. Immunological pathogenesis of allergic diseases (Th1/Th2/Treg)**



Environmental factors leading to epigenetic regulation may also partly account for the increased predisposition to allergies in the

general population. Furthermore, among children, the hygiene hypothesis provides another possible explanation for the rise in allergic diseases.<sup>1</sup> This postulates that an environment with a high incidence of infectious diseases is *protective* against allergic and autoimmune diseases; conversely, surroundings that are too hygienic will increase the incidence of such disorders.<sup>1</sup> Very recent data in animal models appear to support this, showing that mice chronically exposed to low-dose endotoxin or farm dust were protected from developing house dust mite-induced asthma.<sup>2</sup>

### Primary prevention of allergy: Environmental control and nutritional interventions

Primary prevention strategies for allergy center upon reducing the Th2 reaction, adequately increasing the Th1 reaction and inducing immune tolerance (**Box 1**).

#### Box 1. Primary prevention strategies for allergy

##### Reduce Th2 reaction

- Avoid contact with allergens
  - Breast feeding
  - Food (milk, nut, egg, etc) – although early introduction is emerging as a therapeutic strategy
  - Inhalant allergens (pets, dust mite, etc)
- Decrease allergenicity
  - Hydrolyzed formula (partial, extensive)
  - Amino acid formula

##### Adequately increase Th1 reaction

- Probiotics, prebiotics, etc – possibly; role is unclear

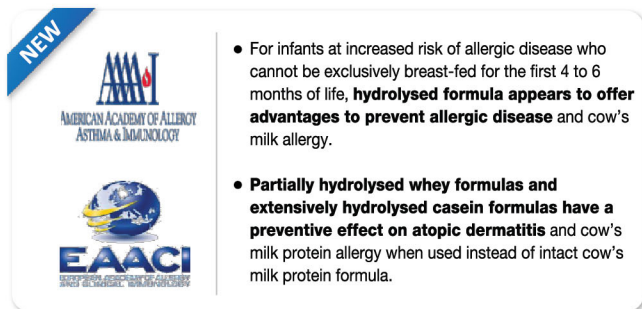
##### Induce immune tolerance

In terms of environmental control, smoking avoidance is most impactful, given that prenatal and passive smoking exposure is well documented to increase the risk of asthma and wheezing.<sup>3</sup> Very recent evidence has also demonstrated an association between tobacco smoke exposure and IgE sensitization to particular allergens.<sup>4</sup>

In terms of nutritional intervention, maternal avoidance of food allergens – either during pregnancy or breast feeding – is an ineffective strategy for reducing the risk of allergic disease. Exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age, and may reduce the incidence of atopic dermatitis in children younger than 2 years, early-onset wheezing (but not asthma) before 4 years and the incidence of cow's milk allergy (but

not all food allergy) in the first 2 years of life. Nevertheless, the effects of breastfeeding on allergic diseases remain inconclusive at this time. When infant formula is used, selection of the type of formula can make a difference in the primary prevention of allergic disease, as specified in the new recommendations of the American Academy of Allergy, Asthma & Immunology, and the European Academy of Allergy and Clinical Immunology (**Figure 2**).<sup>5,6</sup>

**Figure 2. Selection of infant formula for primary prevention of allergic disease in children** <sup>5,6</sup>



Finally, complementary foods should be introduced for the primary prevention of allergic disease in children. Optimal timing for introducing these foods ranges from 4 to 6 months, depending on the guideline followed.

## Food allergy treatment and prevention in 2015



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### Food allergy: The second wave of allergy epidemic after asthma

Food allergy is the leading cause of anaphylaxis presenting in emergency departments in many countries.<sup>7-9</sup> In Hong Kong, the prevalence of “probable food allergy” (defined by reaction within 2 hours of consumption of the allergen plus positive skin prick test or blood allergen-specific IgE level) is 2.8%, with major culprits being shellfish, egg, peanut and cow’s milk.

### Management strategies for food allergy

For many decades, the mainstay of management has been food avoidance. However, in recent years, novel immunomodulatory treatments such as anti-IgE and herbal medicines have demonstrated some benefits in clinical studies.<sup>10-12</sup> Furthermore, oral and sublingual immunotherapy may possibly be effective against foods

such as peanut, egg and cow’s milk, although these investigations remain confined to the research setting at present.<sup>13-16</sup>

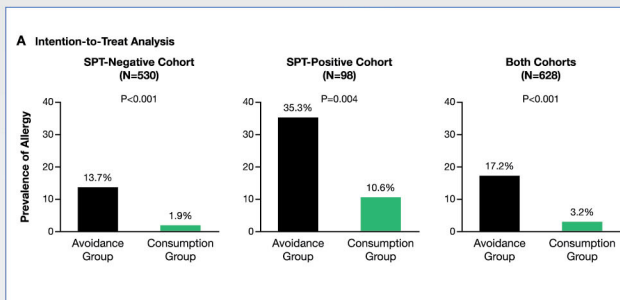
### What about prevention?

Breastfeeding is the best way to provide young infants with the nutrients they need for healthy growth and development. With respect to food allergy prevention, however, the evidence base is somewhat controversial. A recent systematic review of 11 published studies showed that breastfeeding generally had a protective benefit for high-risk infants.<sup>17</sup> Nevertheless, two cohort studies included in the same review found an opposite effect – there was no benefit with breastfeeding – and exclusive breastfeeding might even increase the risk of food allergy. This controversy carries through to the normal risk or unselected infant population, with the systematic review finding some data to indicate that breastfeeding reduced the risk of sensitization or food allergy whereas other cohort studies suggested an increased risk or no association. Despite its controversial benefit for food allergy prevention, breastfeeding remains the recommended method for delivering nutrients to infants because of its other unequivocal benefits, such as enhanced immunity and mother-baby bonding.

In terms of primary prevention of allergy and food intolerance with infant formula, two Cochrane Collaboration reviews – one of soy formula and the other of hydrolyzed cow’s milk formula – have been published.<sup>18,19</sup> For the former review, the authors concluded that “feeding with a soy formula cannot be recommended for prevention of allergy or food intolerance in infants at high risk of allergy or food intolerance”.<sup>18</sup> The review on hydrolyzed formula however revealed evidence for the effectiveness in preventing cow’s milk allergy: “In high risk infants who are unable to be completely breast fed, there is limited evidence that prolonged feeding with a hydrolyzed formula compared to a cow’s milk formula reduces infant and childhood allergy and infant cow’s milk allergy.”<sup>19</sup>

There is no evidence to support the use of prebiotics or probiotics for food allergy prevention.<sup>20</sup> In peanut allergy, a recent randomized clinical trial found that early peanut introduction may prevent the development of this allergy by 60 months in high-risk infants (**Figure 3**).<sup>21,22</sup>

**Figure 3. Peanut consumption in infants at risk for peanut allergy** <sup>22</sup>



• Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P=0.004).

Extracted from Du Toit G, et al.<sup>22</sup>

# Recent advances in the understanding and treatment of skin allergies, from eczema to urticaria



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The healthy skin barrier may be represented by the well-known ‘bricks and mortar’ model, in which the cornified layer of individual corneocytes (the bricks) are stuck together with the space-filling mortar, the inter-corneocyte lipids.<sup>23</sup> Barrier function of the normal epidermis depends on the quality of its bricks and mortar.

The initial event of atopic dermatitis (AD) is the breakdown of the skin barrier. This arises primarily due to genetic factors, although a minority of cases results from environmental factors.<sup>23</sup> Loss-of-function mutations within the filaggrin gene represents the most significant genetic factor predisposing AD.<sup>23</sup> Impairment of the tight junctions residing immediately below the stratum corneum, which regulate selective permeability of the paracellular pathway, also contributes to barrier dysfunction and immune dysregulation.<sup>24</sup>

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## What are the therapeutic implications?

### Preventive therapy for AD

Emollients soften the skin through supplying exogenous lipids and providing an occlusive layer to prevent water loss, and they are the mainstay preventive treatment in AD. They need to be used frequently enough (at least twice a day; around 250–500 g/week), and all over the body after bathing. Moreover, emollient use should be tailored to the phase of AD, with less oily lotions preferred in the acute phase, while oilier emollients are indicated in the chronic phase.

### Acute lesions of AD and acute flare-up

For acute AD lesions, topical steroids are first-line treatment and are classed as mild, moderate or potent. In general, fourth-generation topical steroids have an improved tolerability profile with fewer side effects than older generation drugs. Potent steroids should be used selectively and for short periods only in children.

Acute flare-up may also result from infection, most commonly by *Staphylococcus aureus*. Infective flare can be readily treated with topical or systemic antibiotics together with a step-up regimen of steroids.

### Chronic maintenance in AD

A proactive treatment approach for chronic maintenance therapy of AD, involving the intermittent use of steroids even in the absence of a flare-up, is now favored. The stratum corneum pH should be preserved in the chronic maintenance phase and triggers, such as food allergens, should be avoided. Food allergens can occasionally be the main trigger source in infants, but less so in adolescents. A thorough medical history is most important for the identification of potential triggers.

Other drugs with efficacy in this setting are cyclosporine, azathioprine, mycophenolate mofetil and methotrexate.

### Urticaria

Acute urticaria persists for less than 6 weeks, beyond which it is classed as chronic urticaria. In infants, major causes of acute urticaria include cow’s milk, and both immune and non-immune mechanisms are at play (**Box 2**). In older people, infections or drugs are more likely causes. The pathophysiology of chronic urticaria is not well understood; it involves non-specific histamine release but with no association with atopy, and serum IgE levels remain normal. The cornerstone of treatment for urticaria is antihistamines, and careful attention to past medical history may provide useful information on possible causes.

#### Box 2. Food as a cause of urticaria

- 7–10% of chronic urticaria
  - Immune: Nuts, fish, eggs
  - Non-immune: Shellfish
- 5 major foods in children
  - Eggs, peanuts, cow’s milk, fish and mustard
- Time of onset
  - Immediate: Fish, berries, nuts, eggs
  - Delayed for several hours: Cereals, milk, chocolate, vegetables

## Management of allergy – the Taiwan experience: Interview with Prof Huang

In Taiwan, the diagnosis and management of childhood allergic diseases – largely undertaken by pediatricians and sometimes by family practitioners – has dramatically improved in recent years. What is the secret of their success? We interviewed Prof Jing-long Huang to find out more.



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### Q: Which key factors have contributed to the improved diagnosis and management of childhood allergic diseases in Taiwan?

**Prof Huang:** The diagnosis and management has improved, but not the epidemiology. I think it is mainly due to greater awareness of allergic diseases among doctors, nurses, patients' parents and the general population. We have increased awareness via more education for the general population and parents, as well as for medical professionals, particularly pediatricians and nurses. Most importantly, we want parents to know the difference between the clinical manifestations of allergic rhinitis, bronchial asthma and atopic dermatitis – the most common allergic diseases – and viral infections. The differential diagnoses of these diseases are also important for doctors to understand.

We use Web media, group education and individualized education – you have to find every possible method to educate different populations. Recently we have also developed APPs in Taiwan for allergic disease management. These APPs allow patients to enter PEF data, outpatient data, daily temperature, humidity, exposure to potential triggers, compliance with medication and other personal information, which can be retrieved by their doctor. Allergic disease is also taught quite thoroughly at medical school in Taiwan.

### Q: What has the impact of lifestyle and diet been on allergic diseases in Taiwan?

**Prof Huang:** If we talk about lifestyle, the hygiene hypothesis may be important. Taiwan, like Hong Kong, now has a more Westernized lifestyle. Economic growth and gross domestic product have increased, which interestingly is associated with increased prevalence of allergic diseases. According to the hygiene hypothesis, improved hygiene in the home, more complete vaccination coverage among children, has increased the prevalence of allergic disorders.

If we want to reduce this prevalence, we may have to let our kids be more exposed to microbes and endotoxins – live on the farm!

### Q: In terms of long-term health outcomes why is it important to prevent allergy early?

**Prof Huang:** We do not cure our patients of allergic diseases but as they grow older some will improve while others will develop more severe symptoms. Unfortunately, right now, we do not know – we cannot predict – which patients will get worse and which will improve. This is why it is important to prevent and treat early. For the treatment strategy, in bronchial asthma and rhinitis we try to treat aggressively, but it is probably more important to prevent exposure to allergens and irritants. Prevention is of course better than cure but it is difficult to prevent allergies, including sensitization, and to prevent the clinical phenotype from developing.

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