CME

Managing Pediatric Atopic Dermatitis and Concomitant IgE-Mediated Food Allergies

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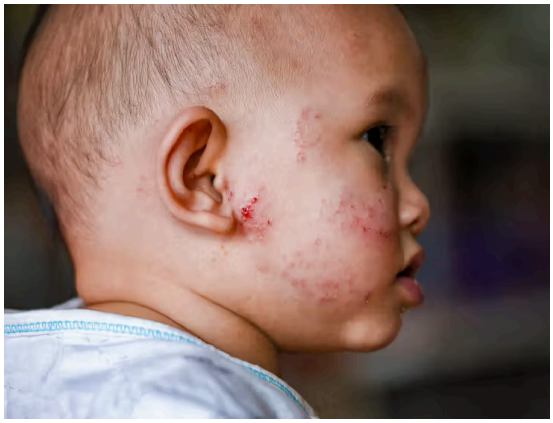
ABSTRACT

Atopic dermatitis is a type of eczema and is the most common inflammatory skin disease[1]. The condition is caused by a mutation that results in defects and lack of moisture in the skin's barrier leaving it vulnerable to infections and allergens [1]. People with AD often also have IgE related food allergies or will have them in the future [2]. IgE related food allergies can be serious and lead to death so any advancements in management or treatment are vital [2]. Potential ways to prevent serious allergies in pediatric patients with AD have been found and have influenced changes to national guidelines on allergy testing and early allergen exposure. New research has shown that the signaling pathways between atopic dermatitis and food allergies are the same, so biologic treatment for AD is being suggested as a possible treatment for patients with concomitant IgE-mediated allergic diseases as well [3].

Key words: Atopic dermatitis, food allergies, atopic march, atopic triad, "dual-allergen-exposure", pediatrics, dupilumab

Learning Objectives

- Review the etiology, presentation, diagnosis, treatment, and prognosis of atopic dermatitis and IgE-mediated food allergies.
- Describe the relationship between atopic dermatitis and IgE-mediated food allergies.
- Outline guidelines on testing for food allergies and early food allergen exposure.
- Explain the mechanism of dupilumab and how it can be used to treat both atopic dermatitis and IgE-mediated food allergies.



INTRODUCTION

9.6 million children in the US and 20 percent of all children worldwide are affected by atopic dermatitis (AD), a form of eczema [4,5]. This itchy dry rash is the most common chronic inflammatory skin disease with a prevalence that has been increasing over the past few decades [1]. Of the 20 percent of children worldwide with AD, 30 percent also have food allergies [6]. Food allergies in kids can be very serious and lead to complications such as anaphylactic shock and even death [2]. Unfortunately, childhood hospitalizations for food allergies have tripled between the late 1990s and the mid-2000s [7].

With these staggering statistics in mind, this article aims to educate on the basics of AD and IgE-mediated food allergies as well as clearly explain the relationship between the two conditions. Additionally, this research will provide pediatricians with patient education topics and updates on new management guidelines for both conditions. Lastly, for patients that are already diagnosed with AD and food allergies, this article will present a newer treatment regimen used for managing both diagnoses at the same time.

Key Points

- Children with uncontrolled atopic dermatitis are at an increased risk for developing severe food allergies.
- New guidelines support the introduction of allergens through food as early as 4 months in children with severe eczema.
- Atopic dermatitis and IgE-mediated food allergies can be managed simultaneously with dupilumab.

BASICS OF ATOPIC DERMATITIS

AD, also known as allergic eczema, is an inflammatory skin condition that falls under the broader category of eczema[1]. The condition is also part of the **atopic triad** which is composed of AD, asthma, and allergic rhinoconjunctivitis [4]. Commonly patients with one of these diagnoses also have another or all three parts of the triad because of a defective barrier of the skin, upper respiratory, and lower respiratory tract which leads to their symptoms [1].

The cause of AD is genetic and is often triggered by environmental factors. If one parent is atopic, meaning that they have AD, asthma or allergies, there is more than a 50% chance that their child will also develop atopic symptoms [1]. If both parents are affected, the chance increases to 80% [1]. On a genetic level, people with atopic symptoms have high levels of Th2 cytokines which downregulate the expression of a gene called filaggrin. This loss of function mutation in filaggrin decreases the body's natural moisturizing factors and therefore the skin's integrity, leading to atopic dermatitis (**Figure 1**) [4].

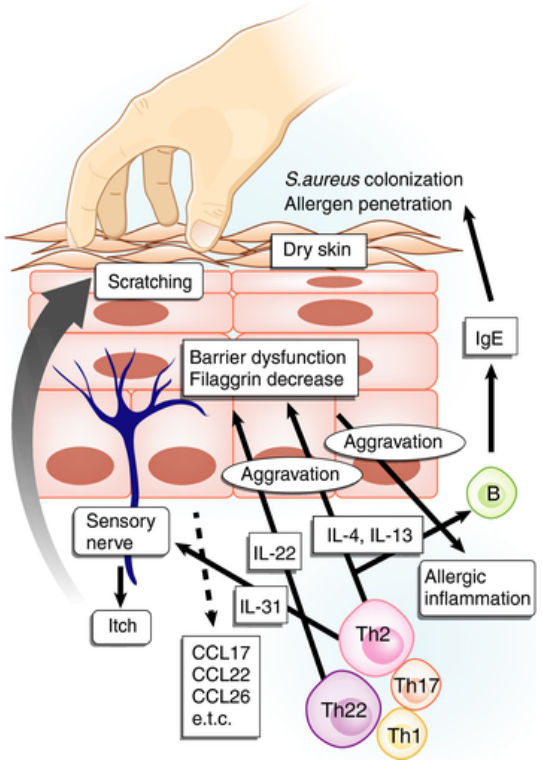


Figure 1: Pathogenesis of atopic dermatitis (AD) showing skin barrier dysfunction caused by genetic mutations of filaggrin (FLG) and Th2/Th22 cytokines inducing atopic dry skin and itching which accelerates penetration of allergens and increases the risk of Staphylococcus aureus colonization [8].

Children presenting with AD commonly have areas of very dry, scaly, and itchy skin[1]. The itchiness of the rash varies between patients however some patients experience extreme discomfort that may even disrupt a child's sleep[1]. If scratched hard enough, skin can break and increase the risk for secondary infections [1]. The most common secondary infection is a staphylococcus aureus colonization which is seen in more than 90% of AD patients [4].

Diagnosis of this condition is often made clinically, based on the presentation of the rash, the location of the dry patches, associated symptoms, as well as other comorbid conditions. Treatment of AD may involve a combination of nonpharmacologic and pharmacologic interventions [5]. Nonpharmacologic options for more mild cases include using skin moisturizers with ceramides after bathing, switching to hypoallergenic and

fragrance free soaps and detergents, wet-wrap therapy, increasing sun exposure, and using bleach baths to decrease rates of the secondary infections that were previously mentioned [1,4]. Pharmacologic options are often offered in a stepwise fashion after nonpharmacologic remedies have failed starting with topical corticosteroids, then moving to topical calcineurin inhibitors, systemic immunomodulating medications, and lastly biologics such as Dupilumab, Tralokinumab-ldrm, Abrocitinib, Upadacitinib, and Ruxolitinib [5]. Providers may also offer artificial phototherapy as well as antihistamines for itching and antimicrobials for infections [4,5].

A long-term study that evaluated patients with AD indicates that mild to moderate symptoms often persist for a decade or more[1]. With that said, AD may not be life-threatening, but it can seriously affect the patient's quality of life. It requires continued maintenance, significant lifestyle changes to avoid triggers, and patience as providers work with insurance companies to provide the treatment that works best for each patient. The most pivotal thing providers can do is start with education of the patient and/or parents of the chronic nature of the disease and importance of maintenance therapy, which improves the epidermal barrier and prevents sensitization to allergens[1].

BASICS OF IGE-MEDIATED FOOD ALLERGIES

In general, a food allergy is a medical condition in which exposure to a food triggers a harmful immune response called an allergic reaction. This allergic reaction occurs because the immune system attacks proteins in the food that are normally harmless but in these patients are labeled as harmful. The proteins that trigger the reaction are called allergens [7].

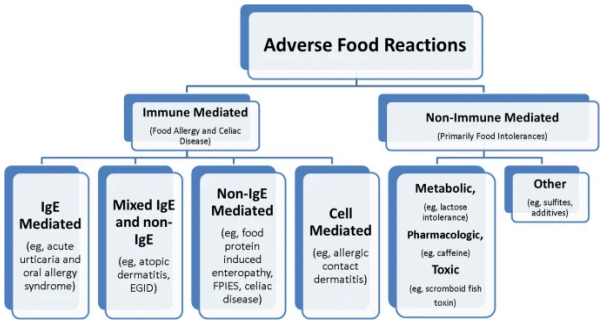


Figure 2: Classification of adverse reactions to food [9].

There are two types of immune mediated reactions to ingested food proteins; either immunoglobulin (Ig)E-mediated or non-IgE-mediated [2] (**Figure 2**). IgE-mediated food-allergies occur on the Th2 signaling pathway and result in a rapid type I hypersensitivity reaction (**Figure 3**). Patients with this type of food allergy complain of symptoms such as hives, angioedema, or anaphylaxis [9]. Common causes of IgE-mediated food allergies include peanuts, tree nuts, and shellfish [2]. In contrast, non-IgE-mediated food reactions are more delayed and present with symptoms such as abdominal discomfort, vomiting and diarrhea. Celiac disease, or an immune reaction to gluten proteins, is an example of a non-IgE-mediated food reaction [9].

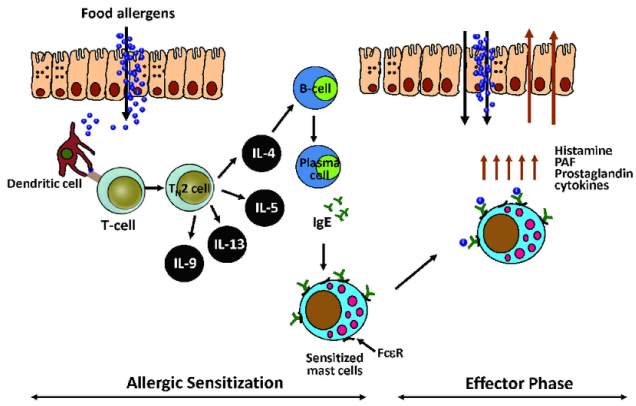


Figure 3: Classic immune mechanism of IgE-mediated food allergy. Naive CD4 T cells differentiate into Th2 cells and produce type-2 cytokines like IL-4, IL-5, IL-13, and IL-9. These type-2 cytokines promote B cells differentiation into IgE-producing plasma cells. Food allergen-specific IgE is distributed systemically and, after sensitization, induces degranulation of mast cells and release of several kinds of mediators causing a type I allergic reaction.

When diagnosing a patient with any food allergy the first step is always a careful history, in hopes of recognizing the triggers and patterns of different systemic reactions [2]. Next, a physical exam may help if the patient has associated conditions such as asthma or AD but is not always the most beneficial unless the patient is currently having an allergic reaction [2]. If a history and physical exam does not provide ample evidence for a diagnosis, allergy testing needs to be completed [2]. Tests include skin prick tests, quantitative serum IgE tests, or food elimination and challenges [2].

There is no cure for food allergies [7]. When diagnosing a patient with a food allergy the most important thing a provider can offer the patient and/or parents is extensive education. Topics that pediatricians or allergists may cover includes specific instruction on understanding food labels, restaurant meals, and risky behaviors that may lead to unexpected reactions [2]. For patients who are being diagnosed with an IgE-mediated allergy with the potential for anaphylactic reactions, the provider will prescribe self-injectable epinephrine and a written emergency plan for treatment of an unintentional ingestion [2]. These patients will most likely never grow out of their allergy and will have to carry a prescription epi-pen with them for the rest of their lives [2]. However, patients with non IgE-mediated allergies often grow out of their allergies or become tolerant around school age and often do not need to have prescriptions medications [2].

RELATIONSHIP BETWEEN ATOPIC DERMATITIS AND IGE-MEDIATED FOOD ALLERGIES

The correlation between allergies and eczema has been researched and proven for decades [4]. The connection that allergic reactions to food can make previously existing eczema flare up and that patients often have both conditions simultaneously is widely known around the medical community [2]. In fact, one study found that egg allergies are 6 times more common in infants with eczema than infants without. Additionally, peanut allergies were 11 times more common in infants with eczema than infants without eczema [10].

More recently, there have been advancements that may not only support this connection but also show causation. In addition to the atopic triad that was previously discussed, providers also need to be aware of the **atopic march**. The atopic march refers to how different types of allergic diseases develop throughout childhood and suggests that the presence of one allergic condition increases the risk for the development of others, resulting in an additive effect [11]. Common parts of the atopic march include AD, asthma, allergic rhinitis, and food allergies [11]. This theory was proven in a systematic review published in the Lancet in 2017. Within the study population, eczema appeared to precede the development of food allergy, suggesting that the former somehow triggered the latter [12].

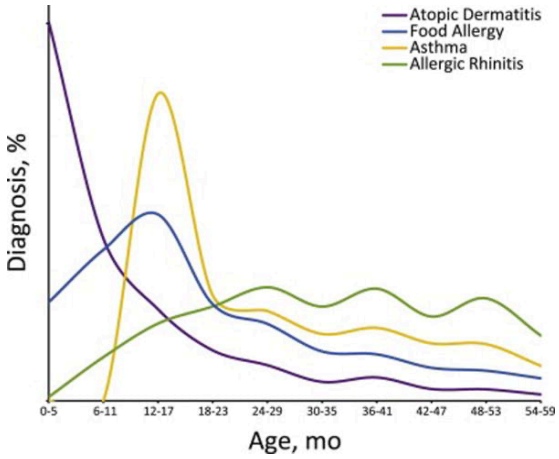


Figure 4: Age at diagnosis of common allergic conditions [11]

In efforts to explain this potential causal relationship, immunologists hypothesized that food allergens may reach immune cells more easily through a dysfunctional skin barrier affected by AD [6]. As the structure of skin cells collapses, it causes a loss of moisture and allows allergens and irritants to penetrate the vulnerable tissues thereby setting off biological processes that result in inflammation [4,6]. This exposure can hypersensitize the immune system

to the various allergens it encounters on the skin, causing an exaggerated response when those allergens are later eaten or inhaled (**Figure 5**). Interestingly enough, this new research further supports previous findings that kitchen workers with eczema are more likely to develop food allergies than people with eczema who have different jobs [13].

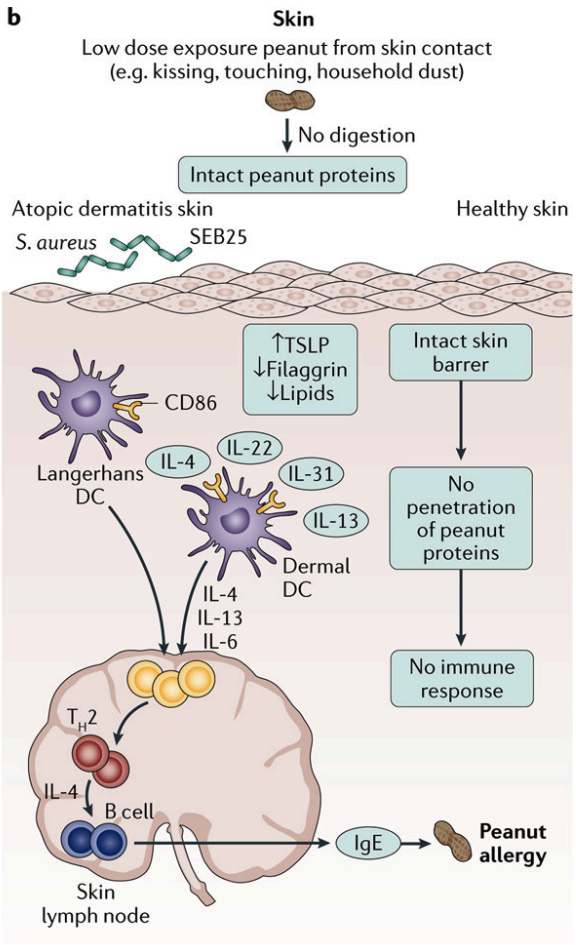


Figure 5: Food allergens entering through skin with atopic dermatitis setting off an IgE-mediated immune response causing a future peanut allergy when later ingested or inhaled.

A UNIQUE SUBTYPE OF ATOPIC DERMATITIS

After immunologists started to recognize that AD may lead to food allergies, many concluded that "eczema associated with food allergies may, in fact, be an entirely unique subtype of AD" [6]. This suggests that not all patients with eczema have an increased risk of food allergies but understanding the relationship may provide the 30 percent that will develop food allergies with ways to catch them early or prevent them completely [6]. Research has found that there are significant differences in molecular composition and structure between the healthy appearing skin of children with both AD and food allergies compared to children with AD alone [6]. To get a closer look, researchers used a minimally invasive technique to collect skin samples using small, clear tape strips (**Figure 6**). The scientists concluded that non-lesional skin from children with AD and food allergy was more prone to water loss, had an increased number of Staphylococcus aureus, and had gene expression typical of an immature skin barrier [6]. This research shows that not only is the skin barrier less sufficient within the lesions of AD, but so is the healthy skin near the lesions of patients with both diagnoses.

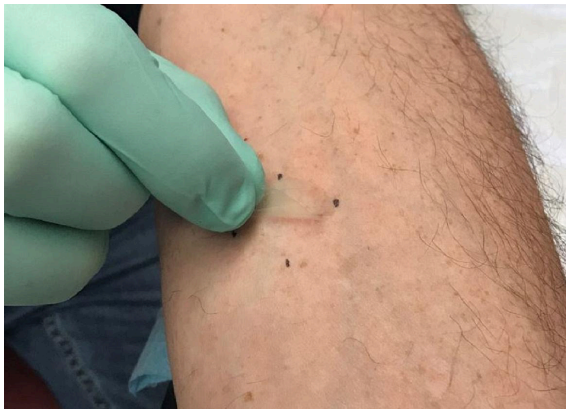


Figure 6: A researcher demonstrates the minimally invasive collection of skin samples using small, clear tape strips. In this study, scientists analyzed the outermost layer of the skin, the stratum cornea. [6]

PREVENTION OF SEVERE FOOD ALLERGIES IN PATIENTS WITH ATOPIC DERMATITIS

The first step in preventing severe food allergies in children with AD is by building back their skin barrier quickly and efficiently. According to NIAID Director Anthony S. Fauci, M.D. "Children and families affected by food allergies must constantly guard against an accidental exposure to foods that could cause life-threatening allergic reactions. Eczema is a risk factor for developing food allergies, and thus early

intervention to protect the skin may be one key to preventing food allergy" [6]. Children with refractory cases of eczema should be seen by a pediatric dermatologist. In addition, the American Academy of Dermatology, suggests that providers should be recommending food allergy testing for children younger than 5 years old whose eczema is not being controlled with treatment, as it is possible that allergens have already been sensitized through the skin [14].

Other than repairing the skin barrier and early allergy testing, providers should also educate the parents of patients with AD on early food allergen exposure. New research suggests that exposure to food antigens through the skin is more likely to lead to an allergy compared to early oral consumption, which is more likely to lead to tolerance. This phenomenon is called **"dual-allergen-exposure"** and has led the American Academy of Pediatrics to change its guidelines [15]. The guideline now recommends exclusive breastfeeding for six months, followed by breastfeeding in combination with the introduction of common allergic foods until the child is at least 12 months of age [15]. This includes the early introduction of peanut protein to reduce the risk of peanut allergy [15].

Patients who already have AD will benefit greatly from this as they have an increased risk for the dual-allergen-exposure phenomenon due to their insufficient skin barrier. In fact, an addendum to guidelines of allergen exposure by the National Institute of Allergy and Infectious Diseases was created in 2017 which specifies children with mild to moderate eczema should be introduced to peanut protein starting as early as 6 months [16] (**Figure 7**). In addition, children with severe eczema should be introduced to peanut protein as early as 4 months depending on allergy testing results [16]. These new guidelines need to be implemented by providers in efforts to decrease the number of severe and sometimes fatal allergic reactions in children. Unfortunately, a study completed in 2020 that was published in The Journal of the American Medical Association found that less than one-third of pediatricians fully implement the most up to date guidelines [17].

SUMMARY OF 2017 NIAID ADDENDUM GUIDELINES

Infant Criteria	Recommendations	Earliest Age of Peanut Introduction
Severe eczema, egg allergy, or both	Strongly consider evaluation with peanut-specific IgE and/or skin prick test and, if necessary, an oral food challenge. Based on results, introduce peanut-containing foods.	4 - 6 months
Mild to moderate eczema	Introduce peanut-containing food.	Around 6 months
No eczema or any food allergy	Introduce peanut-containing food.	Age- appropriate and in accordance with family preferences and cultural practices

Figure 7: Summary of addendum guidelines with 3 different categories based on the child's risk level and when to introduce peanuts to their diet [17].

TREATING BOTH CONDITIONS SIMULTANEOUSLY

Both AD and IgE-mediated food allergies are chronic conditions and therefore cannot be cured [1,2]. Fortunately, some children slowly grow out of these diseases however most of them do not [1,2]. If a patient is already diagnosed with both diseases the list of medications and lifestyle modifications necessary for correct management is extremely long and expensive which can lead to patient non-compliance.

In efforts to combat these barriers one medicine in particular, **dupilumab**, was found to have a positive effect on both diseases [3]. Dupilumab, also known for its brand name

Dupixent, is the first biological medication developed for atopic dermatitis and works by blocking the signaling pathway of Type 2 (Th2)-related cytokines, IL-4 and IL-13 [3]. Because food allergies also take place on the same pathway with the same cytokines, this medication has been shown to decrease the severity of food allergies and other Th2-related conditions [3]. The first case study to ever show this potential widespread IgE treatment was published in 2020 in *JAAD Case Reports*, the Journal of the American Academy of Dermatology. The report showed a pediatric AD patient with multiple comorbid allergic conditions, including food allergies, who experienced objective improvements in all of his conditions with dupilumab treatment [18].

Currently, Dupixent is only FDA approved to treat atopic dermatitis (ages 6 + months), asthma (ages 6 + years), chronic rhinosinusitis with nasal polyposis (ages 18 + years), eosinophilic esophagitis (12 + years, weighing at least 40 kg), and prurigo nodularis (ages 18 + years) [19]. However, since the case report 3 years ago, scientists have been working hard to provide ample evidence of Dupixent's effect on IgE-mediated food allergies. For example, one study completed in 2022 found that dupilumab treatment of food-allergic patients with moderate to severe AD, produced a sustained decrease in serum IgE levels, resulting in an estimated decrease of at least 80% for all food allergens after 3 years of treatment [3] (**Figure 8**). Additionally, 33 of 40 patients, who accidentally ingested foods during dupilumab treatment, reported a decrease in severity of food-allergic symptoms [3].

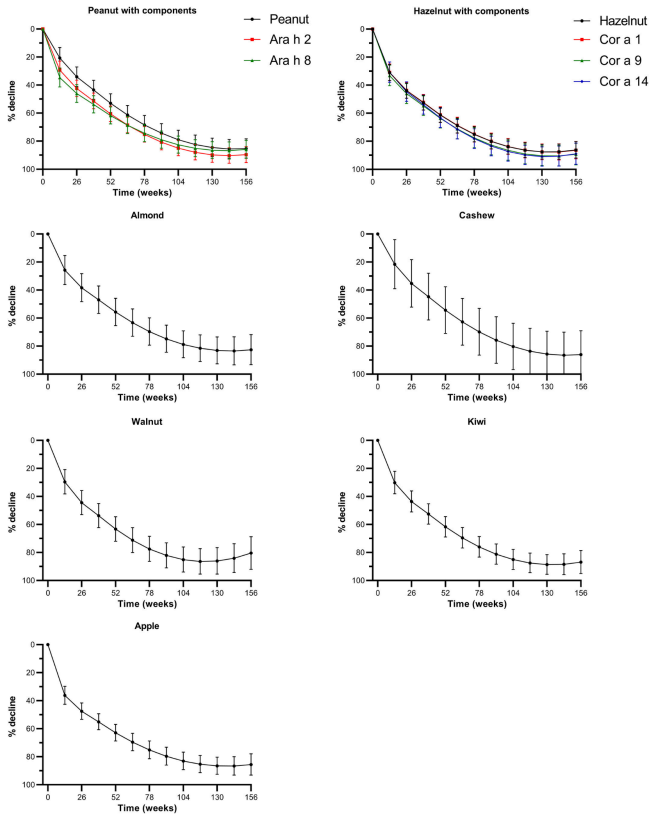


Figure 8: Estimated percentage decrease of sIgE levels during dupilumab treatment in patients with AD over the course of 3 years. The food allergens tested included peanuts, hazelnuts, almonds, cashews, walnuts, kiwis, and apples. Error bars indicate the 95% confidence interval [3].

CONCLUSION

The increase in prevalence of both AD and food allergies in children globally over the recent decades is critically relevant to public health. Quality of life is significantly hindered when diagnosed with either one but especially both conditions. Recent research on their relationship, the atopic march, and the dual-allergen-exposure phenomenon has helped to direct changes to national management guidelines and show new opportunities in prevention and treatment of both diseases. Further research using food challenges rather than accidental exposures would help to objectify whether dupilumab is an effective treatment for food allergies. Additionally, finding other conditions that may be a part of the atopic march would be beneficial in expanding what the current AD biologics are capable of treating.

MULTIPLE CHOICE QUESTIONS

1. Which of the following is an IgE-mediated allergy?
    a. Peanut allergy
    b. Gluten allergy
    c. Contact dermatitis
    d. Lactose intolerance

2. According to the new guidelines, at what age should patients with mild to moderate eczema be introduced to peanut proteins through food?
    a. 2 months
    b. 6 months
    c. 1 year
    d. 4 years

3. Which 2 cytokines are found in the signaling pathway for both AD and IgE-mediated food allergies and are simultaneously blocked by dupilumab?
    a. IL 1 and IL6
    b. IL 2 and IL 15
    c. IL 4 and IL 13
    d. IL 3 and IL 7

4. What condition is Dupixent NOT FDA approved for at this time?
    a. Atopic Dermatitis
    b. Asthma
    c. Eosinophilic esophagitis
    d. IgE-mediated food allergies

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Answers

1. A
2. B
3. C
4. D