



# Current insights: a systemic review of therapeutic options for peanut allergy

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## Purpose of review

With increasing prevalence of peanut allergy (PA) globally and the greater risk of potential reactions occurring due to the leading role of nuts in food products, PA has become a significant public health concern over the past decade, affecting up to 5 million of the US adult population. This review details updates and advances in prevalence, diagnosis, and immunotherapies that have occurred over the past year.

## Recent findings

Therapeutic and diagnostic advances remain at the forefront of research and have continued to push the food allergy (FA) field forward to provide a promising role in the detection and treatment of PA. The FA field has researched significant advances in peanut immunotherapy, biomarker diagnosis, and quality of life (QoL) improvement.

## Summary

Given the burden and consequences for individuals with PA, these advances delivered in clinical practice can significantly improve the QoL of individuals with PA and their caregivers. Ongoing studies will continue to investigate long-term outcome measures of desensitisation and effective management plans tailored to the families' needs.

## Keywords

efficacy, oral immunotherapy, peanut allergy, quality of life, safety

## INTRODUCTION

Peanut Allergy (PA) is one of the most common food allergies (FAs) in the United States, with prevalence rates around 4.5 million US adults [1], and is the leading cause of FA-related deaths. The increasing prevalence rates [2] combined with the rise in food products, dishes and flavours containing peanuts or processed in a facility that uses peanuts, it has become a global public health priority to research and develop management and treatment therapies for this condition [3,4]. Here, we discuss recent clinical observations and advances in prevalence, prevention, diagnosis, immunotherapy treatment, and management and quality of life (QoL) over the last year.

## PREVALENCE

PA is generally considered a lifelong condition, with onset usually occurring in childhood and only approximately 20% of children outgrowing it [5–8]. The prevalence of self-reported PA in US adults is

around 1.8–2.9% [1,9], however, there are numerous factors that influence its distribution in the population, including geographical location, diet, age, race and ethnicity [10,11]. PA is more prevalent in females, non-Hispanic whites, individuals with household earnings between \$50,000 and 150,000 and additional health concerns, such as eczema, asthma, and environmental allergies [9]. Females are more likely to develop adult-onset PA compared to males, which is consistent with many previous population-based studies suggesting a female

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## KEY POINTS

- PA are one of the most common and deadly food allergy.
- Early introduction of peanut reduces the development of PA.
- Ara h 2-sIgE is a powerful new tool for PA diagnosis.
- Peanut OIT is safe and effective.
- Continued consumption of peanut is required to maintain the long-term benefits of peanut OIT.

predominance postpuberty with males more prevalent prepuberty [1,12–14]. The gender differences in PA prevalence during puberty suggests hormones may be involved in the development of FA and influence immune response particularly during the menstrual cycle [15–17]. Differences in prevalence of PA is observed within race/ethnicity, whites (non-Hispanic) make up 65.1% of the general US population but only account for 54.7% of the PA cases [18]. In contrast, Asian Americans make up only 3.8% of the general population but account for 6.3% of the PA cases, demonstrating that PA is more likely to occur in some ethnicities than others. There is an increased risk of PA in children of either white or Asian ancestry born in Western countries compared to those born in Asia [19]. One of the reasons for this inconsistency may be due to early exposure to peanut protein (PP) in Asian countries which lowers the risk of developing PA, as well as the different preparation techniques of peanuts; peanuts are mainly boiled in Asian countries compared to Western countries where they are roasted which increases the allergenicity of peanuts [20–22].

## PREVENTION

It is now well accepted that early introduction of peanut containing foods, to high-risk infants reduces the risk of developing PA by 70–80% [20,23–29]. As a result, the National Institute of Allergy and Infectious Diseases (NIAID) published guidelines encouraging parents to introduce peanut products early to their infants to prevent PA [30]. Furthermore, it has been reported that each additional month of delayed PP introduction, increased the odds of PA by 30% in infants with eczema [28], demonstrating the importance of early allergen introduction. Historically family history of FA has been used as a high-risk criteria for the development of FA however, recent findings indicate that without the presence of moderate-severe eczema, infants

with only a family history of PA do not need to be screened before peanut introduction [28]. In addition, the NIAID recommends that healthcare professionals should strongly consider screening high-risk individuals, defined as infants with severe eczema, egg allergy, or both, by measuring sIgE and/or Skin Prick Test (SPT), and Oral Food Challenge (OFC) when necessary, before peanut introduction as early as 4–6 months old [31].

Three years after the release of the NIAID guidelines, a survey of primary health care physicians found that more than half of the participants were unaware of the new guidelines with 40% of them incorrectly believing that the peanuts should not be introduced before 1 year of age [32], demonstrating the need for better education on the introduction of peanuts to infants. Education on infant risk and guiding caregivers on the early introduction of PP is important for implementing the new guidelines and future work should focus on supporting providers knowledge on early introduction of PP as these approaches could help decrease the incidence and prevalence of PA in the paediatric population [33].

## DIAGNOSIS

The gold standard for diagnosis of FA is the double-blind, placebo-controlled OFC [3]. However, in clinical practice the OFC procedure is costly, labour intensive, time and resource consuming, with specialized OFC centres becoming inundated with the increasing number of OFC requests [3,34]. In addition to this, it bears the risk of potential life-threatening anaphylaxis which may discourage patients in pursuing treatments. Therefore, in individuals with suspected PA, SPT and specific immunoglobulin E (IgE) for food allergens are the first-line tests to assess sensitization due to their relatively low cost and rapid results. SPTs and specific IgE have high sensitivity and negative predictive value but have low specificity and low positive predictive value for making an initial diagnosis of FA and therefore may lead to over-diagnosis when used alone [35].

Among PPs, IgE antibodies to Ara h2, are most often associated with severe allergic reactions. Ara h2 is an important predictor of clinical PA and recent studies have reported that Ara h2-IgE is superior to peanut SPT or sIgE for diagnosis of PA with the best profile of high specificity, high sensitivity and lowest risk of a false-positive diagnosis of PA [36–41,42<sup>†</sup>]. Recently it has been suggested that using s-IgE to Ara h2 as a diagnostic method to differentiate peanut tolerance from PA and reduce the need for OFCs [43]. Although peanut sIgE is more diagnostically sensitive, its low specificity

indicates that most patients that test positive in a screening population do not actually have PA [42<sup>■</sup>]. Screening with Ara h 2-sIgE only, instead of peanut s-IgE is more cost-effective, reduces the number of false-positive cases, and reduces the requirement for OFC or referral to an allergic clinic enabling non-specialists to screen, therefore reducing the time taken to diagnose PA [37,42<sup>■</sup>,44].

Novel diagnostic tests such as the Basophil activation test (BAT) using whole blood, and the mast cell activation test (MAT) using serum or plasma, are cellular tests that take all components of sIgE into consideration in comparison to quantifying the levels of IgE [45]. Both BAT and MAT have demonstrated high specificity in diagnosing PA [34,46,47], with BAT showing enhanced sensitivity in comparison to MAT however MAT allowed for deferred testing as it did not require fresh plasma and provided conclusive test results for patients with non-responding basophils [48].

The Peanut Bead Based Epitope Assay (Peanut BBEA) measures and compares IgE antibody binding to the levels of two Ara h 2 peanut epitopes to predict the result of the OFC to peanut [49,50]. Compared to the gold standard OFC, the BBEA test is more effective and efficient [51<sup>■</sup>]. It has an accuracy of 93% for diagnosing PA, greater than the accuracy of SPT and s-IgE, combined with a two to nine-fold reduction in false-positive rate than other diagnostic tests [51<sup>■</sup>]. Ongoing studies suggest that BBEA assay may be capable of indicating what dose of PP may initiate an allergic reaction however further research in this area is needed [52,53]. This low-risk diagnostic test requires small quantities of plasma or serum, is easily adaptable to the standard clinical lab due to its reproducibility and performance and has the potential to reduce the need for OFC [51<sup>■</sup>,54].

## IMMUNOTHERAPY

PA is a potentially life-threatening and lifelong disorder, in which treatment has been limited to complete avoidance of the allergen. Immunotherapy has the potential to improve the management, psychosocial impacts, and socio-economic impacts of this condition, therefore increasing QoL for the individual. Oral immunotherapy (OIT) is based on desensitisation, a treatment where individuals are exposed to increasing doses of an allergen to encourage tolerance and raise the threshold that triggers an allergic reaction [55]. In the PALISADE phase 3 trial, participants were fed daily doses of AR101, a PP-derived biologic OIT drug that delivers a daily maintenance dose of 300 mg of PP, and were screened for doselimiting symptoms at 100 mg PP or less. 67%

tolerated 500 mg of PP, versus 4% with placebo, demonstrating that dosing with AR101 PP allowed for a higher tolerance of PP than placebo [56]. This study demonstrated that consistent OIT treatment with PP could lead to decreased sensitivity to peanut allergen exposure. This led to the US Food and Drug Administration (FDA) approval of the first peanut-derived OIT treatment: Palforzia [57]. With the adoption of the first and only FDA-approved PP in the USA for OIT treatment, Palforzia will next become available for treatment in the UK. An increasing number of clinical trials have reported similar conclusions of ability to tolerate gradual maintenance doses of 300 mg to 4000 mg of PP through OIT [56,58,59], increasing to higher doses of 5000 mg, which is equal to 16–20 whole peanuts [60].

Recent clinical trials indicate that early OIT is well tolerated and safe showing high completion rate [61,62], however the long-term efficacy of sustained unresponsiveness to PP beyond short-term studies had not yet been fully understood. The sustained outcomes in OIT for peanut allergy (POISED) study, demonstrated that a 2-year buildup of peanut OIT could lead to desensitization to 4 grams of peanut, however, without continuous exposure to the protein, sustained unresponsiveness is rarer. The study found that at the 4000 mg PP level, there is an increased likelihood of redeveloping reactivity to peanut when peanut OIT was discontinued or decreased to 300 mg daily, demonstrating that the majority of patients require continued consumption of peanut to maintain tolerance [63]. Assessing beyond the short-term benefits of OIT, the novel POISED study provided better understanding on the durability of desensitization, indicating the need for consistent, high dose exposure to PP over time. At the end of the study, many patients tolerated higher PP thresholds after OIT compared to prior treatment, suggesting that each patient's optimal maintenance dose will ultimately depend on whether a patient's goal is protection against accidental ingestion or a desire to consume PP products. The randomized placebo-controlled trial IMPACT trial assessed the efficacy and safety of peanut OIT in children and the persistence of tolerance after a period of peanut avoidance. After 134 weeks of OFC, the median cumulative tolerated dose was 5005 mg for peanut OIT and 5 mg for placebo. However, after a period 26 weeks of peanut avoidance, this dose dropped to 755 mg for peanut OIT versus 0 mg for placebo, demonstrating that avoidance of peanut after OIT leads to remission in patients [64<sup>■</sup>]. In addition to efficacy, the safety of OIT should be openly discussed with patients as adverse events during treatment are common, such

as mild allergic reactions and in rare cases severe anaphylaxis [65].

Epicutaneous Immunotherapy (EPIT) is an immunotherapy also under investigation for the treatment of PA and delivers allergens through intact skin to induce desensitization using an epicutaneous peanut patch [66,67]. In recent reports from the PEPTITES open-label extension trial (PEOPLE), continued clinical benefit was reported during 2 additional years of peanut EPIT in children aged 4 to 11 years [67]. Results from the phase 3 REALISE clinical trial confirmed that EPIT with Viaskin Peanut 250 µg as an immunotherapeutic agent for management is well tolerated and safe for children with PA [68]. With many immunotherapies for PA in various stages of development, peanut EPIT is not as potent in causing desensitization compared with OIT and sublingual immunotherapy [67], however its high adherence level, long-term sustainability and reduced burden on the patient encourages further investigation in the area [67].

## MANAGEMENT AND QUALITY OF LIFE

The current standard of care and effective management of PA is avoidance of the allergen and use of an Adrenaline Auto-injector (AAI) in the event of an allergic reaction. Ingestion of the allergen can result in mild to severe allergic reactions impacting the skin, respiratory, cardiovascular and gastrointestinal systems and can lead to anaphylaxis, a life-threatening allergic reaction [35]. Living with FA places significant burden on individuals and their families, which can negatively impact the individuals physical and psychological well-being and health-related QoL (HRQoL) [69].

Caregiver anxiety is also associated with the child's severity of PA and reaction history [70]. The 2021 Peanut Allergy Burden Study investigated the real-world impact of caregivers and patients with PA on patient productivity and healthcare resource utilization, finding that 30–44% of PA patients utilized urgent care at least 3 times and 21–29% had at least one overnight hospital stay due to PA over their lifetime [71]. PA was also a burden on housework and schoolwork productivity in adolescents due to their PA. Adults reported losing on average 2.8 h of housework, 8.8 h of employment, and 5.3 h of schoolwork per week due to their PA. PA did not prevent patients from attending school or work, but rather impacted their ability to be fully present and complete the tasks set out. Treatments that can lower or prevent the risk of allergic reaction would subsequently decrease the healthcare resource utilization for patients due to incidental exposure and would decrease productivity lost due to PA for patients.

With OFC and OIT as leading treatment options for PA, researchers sought to understand its effects and possible improvements on HRQoL for PA patients and families. According to a meta-analysis on studies assessing changes in HRQoL after OFC and OIT in participants from 2010 to 2020, OFC and OIT as interventions are both significantly associated with an improvement in HRQoL in patients with FA [72]. OIT reduces the psychosocial burden of FA for patients, families, and caregivers. OFC and OIT are also associated with fewer limitations in dietary choices and social interactions, with patients reported fewer concerns regarding the severity of potential allergic reaction and accidental exposures [71,73]. Therefore, peanut OIT has substantially improved the QoL of PA patients.

Findings from children aged 4–11 years with PA who completed 12 months of EPIT therapy during the phase 3 of the Peanut EPIT Efficacy and Safety Study (PEPTIDES) and the first 12 months of the follow-on open label extension study (PEOPLE) suggest that EPIT treatment had a positive impact on FA QoL on the lives of individuals with PA along with significant reductions in children's and parents' expectation of the possibility of death occurring due to accidental ingestion of a peanut [74]. EPIT desensitization was found to have positive effects for both children and their parents due to less social and dietary restrictions and decreased fear of daily challenges caused by PA. The potential benefits for immunotherapies such as OIT and EPIT to continue to improve the psychosocial burden, management, and QoL of patients and their families suggest positive impacts of the introduction of immunotherapy for these families. As treatments beyond food avoidance continue to be explored, benefits of immunotherapy on the lives of FA patients and caregivers have been demonstrated and continue to be studied [65].

## CONCLUSION AND FUTURE DIRECTIONS

To date, oral and epicutaneous immunotherapies with peanut have consistently demonstrated promise in the safe and effective treatment of PAs, along with a positive impact on the QoL in those affected. Current trials are underway to evaluate novel treatment strategies that build upon the existing fundamentals of EPIT and OIT in an effort to reduce the rate and severity of treatment-associated AEs as well as expedite the desensitization process and improve rates of SU. The majority of such focus on the use of selective biologic agents to temporarily suppress specific immunologic mediators of the allergic response. Current trials include those investigating the use of omalizumab, an anti-IgE antibody, with or without concomitant multi-OIT that includes

peanut (OUTMATCH, NCT03881696); dupilumab, -an anti-IL4Ra antibody, with or without peanut OIT (NCT03793608, NCT03682770); or both biologics in combination with concomitant multi-OIT that includes peanut (COMBINE, NCT03679676). Beyond biologic adjuncts, additional strategies that instead depend on providing peanut exposure in ways that avoid triggering reactive pathways are under evaluation. These agents include an intra-dermal DNA vaccine, ARA-LAMP-vax, that codes for major peanut allergens (NCT02851277, NCT03755713), in addition to nanoparticle encapsulated peanut extract, CNP-201, delivered intravenously (NCT04950504).

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## Conflicts of interest

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