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Review

Emerging and Established Therapeutic Strategies for IgE-Mediated Food Allergy

Marco Di Filippo [1,†], Diletta Cordelli [1,†], Marco Virone [1,*], Fabiana Furci [2], Francesco Corbo [1], Steven Paul Nisticò [1], Giovanni Pellacani [1], Annunziata Dattola [1], Ester Del Duca [1] and Camilla Chello [1]

[1] Dermatology Unit, Department of Medical and Cardiovascular Sciences, University of "La Sapienza", 00161 Rome, Italy; marco.difilippo@uniroma1.it (M.D.F.); diletta.cordelli@uniroma1.it (D.C.); francesco.corbo@uniroma1.it (F.C.); steven.nistico@uniroma1.it (S.P.N.); giovanni.pellacani@uniroma1.it (G.P.); annunziata.dattola@uniroma1.it (A.D.); ester.delduca@uniroma1.it (E.D.D.); camilla.chello@uniroma1.it (C.C.)
[2] Provincial Healthcare Unit, Section of Allergology, 89900 Vibo Valentia, Italy; fabianafurci@gmail.com
* Correspondence: marco.virone@uniroma1.it
† These authors contributed equally to this work.

Abstract

Food allergy is an increasingly prevalent global health condition characterized by immune-mediated reactions to dietary antigens and a substantial clinical burden. Growing understanding of IgE-mediated mechanisms has highlighted the central role of type 2 inflammation, effector-cell activation, and impaired immune regulation. These advances have prompted the development of disease-modifying therapies beyond allergen avoidance. This narrative review summarizes recent advances in the therapeutic management of IgE-mediated food allergy. A structured PubMed search was performed to identify clinical trials, randomized studies, and meta-analyses published within the last five years. Both allergen-specific and non-allergen-specific interventions were evaluated. Current evidence supports oral immunotherapy as the most effective strategy for increasing reaction thresholds and inducing desensitization in peanut, milk, and egg allergies. However, safety concerns remain, and sustained unresponsiveness after treatment discontinuation is achieved inconsistently. Sublingual and epicutaneous immunotherapy show improved safety but lower efficacy. Modified allergen approaches, including baked milk and processed peanut products, may improve tolerability and facilitate immune modulation in selected patients. Biologic therapies, particularly anti-IgE agents, demonstrate efficacy both alone and when combined with immunotherapy. Emerging approaches include peptide vaccines, DNA immunization, microbiome-targeted interventions, and early dietary modulation. These strategies may improve durable immune tolerance through personalized, mechanism-based therapeutic approaches. Future progress will depend on optimizing safety, identifying predictive biomarkers, and integrating multimodal approaches to achieve durable immune tolerance.

Keywords: food allergy; oral immunotherapy; sublingual immunotherapy; epicutaneous immunotherapy; biologics; omalizumab; dupilumab; sustained unresponsiveness; microbiome

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1. Introduction

Food allergy (FA) represents a growing global health concern, characterized by an aberrant immune response to otherwise harmless dietary antigens [1–3].

In recent decades, prevalence has increased significantly, particularly in industrialized countries, where up to 8–10% of children are affected, with a substantial proportion experiencing persistent disease into adulthood [4–7].

This rise has been attributed to complex interactions between genetic predisposition and environmental factors, including changes in diet, microbial exposure, and lifestyle, all of which contribute to immune dysregulation and the development of allergic sensitization [8–12].

Food allergy represents a growing global health burden, although its prevalence and allergen distribution vary substantially across geographic regions. Current evidence suggests that food allergies affect approximately 8% of children and up to 10% of adults in industrialized countries, with increasing prevalence also being reported in rapidly developing regions. While cow's milk and hen's egg allergies are among the most common food allergies during early childhood worldwide, marked regional differences exist in the prevalence of specific allergens. In North America, Northern Europe, and Australia, peanut allergy represents one of the most prevalent and extensively studied forms of food allergy, whereas shellfish and fish allergies are particularly common in many Asian countries. Within Europe, additional geographic heterogeneity has been observed, with hazelnut, peanut, and birch pollen-associated food allergies predominating in Central and Northern Europe, while lipid transfer protein-mediated allergies, particularly related to peach and other plant-derived foods, are more frequent in Mediterranean regions [13–15].

Regional dietary habits also influence sensitization patterns, contributing to the prominence of allergens such as shellfish in East and Southeast Asia, chickpea in South Asia, and various fruits associated with pollen–food syndrome in Europe. These geographic differences are likely driven by complex interactions among genetic predisposition, environmental exposures, dietary practices, socioeconomic factors, and urbanization [16]. Importantly, they may also influence research priorities and therapeutic development, as the clinical relevance, target populations, and implementation of emerging treatment strategies may vary according to the local burden of specific food allergens. These variations may influence research priorities and therapeutic development, emphasizing the need for globally representative studies and region-specific management strategies [5,17–19].

The immunopathogenesis of FA is predominantly mediated by IgE-dependent mechanisms, involving type 2 helper T-cell (Th2) responses, production of allergen-specific IgE antibodies, and activation of mast cells and basophils. Upon re-exposure to the allergen, cross-linking of IgE on effector cells leads to the release of inflammatory mediators responsible for clinical manifestations ranging from mild cutaneous symptoms to severe systemic reactions, including anaphylaxis [10,20–22].

Importantly, the severity of reactions is unpredictable and does not always correlate with prior clinical history, contributing to the substantial burden of disease and anxiety experienced by patients and caregivers [23–27].

Among food allergens, peanuts, cow's milk, eggs, and tree nuts are the most common triggers of IgE-mediated reactions [7,28]. Peanut allergy, in particular, is often persistent and associated with severe outcomes, whereas milk and egg allergies are more frequently outgrown, although a subset of patients develops long-lasting disease. Even in cases where natural tolerance eventually occurs, the time course is variable, and patients remain at risk for potentially life-threatening reactions during the active phase of the disease [29–31].

Despite significant advances in understanding the immunopathogenesis of FA, current clinical management remains largely inadequate in addressing the core challenges of the disease. The traditional approach, based on strict allergen avoidance and emergency treatment of accidental exposures, fails to provide a definitive solution and does not modify the underlying immune response.

This limitation is particularly relevant given the increasing prevalence of FA and the substantial burden it imposes on patients and healthcare systems [32].

In this context, the present review aims to provide a comprehensive overview of the most recent advances in the therapeutic management of FA, focusing on efficacy, safety, mechanisms of action, and long-term outcomes of both allergen-specific and non-allergen-specific approaches.

The immunopathogenesis of IgE-mediated FA is summarized in Figure 1, highlighting the key mechanisms involved in allergen sensitization, effector-cell activation, and immune regulation.

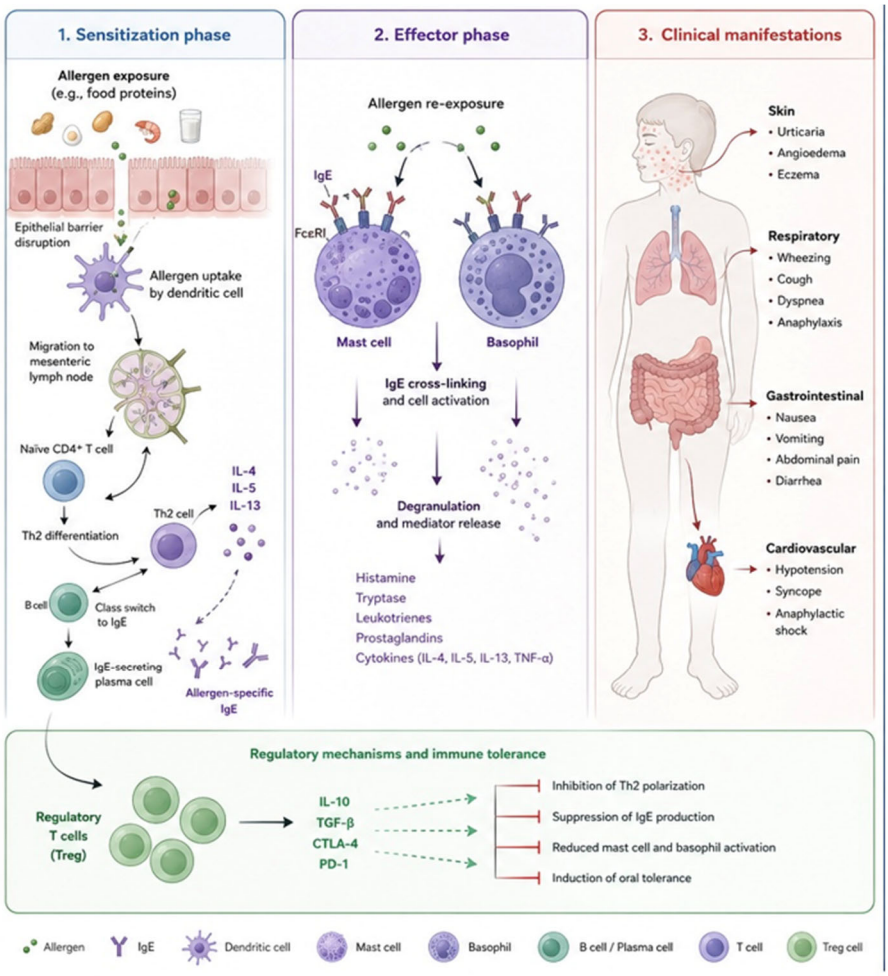


Figure 1. Immunopathogenesis of IgE-mediated food allergy.

During sensitization, food allergens are captured by antigen-presenting cells and promote Th2 polarization, leading to IL-4-, IL-5-, and IL-13-mediated class switching of B cells toward allergen-specific IgE production. Upon re-exposure, allergen-induced IgE cross-linking activates mast cells and basophils, resulting in the release of inflammatory mediators responsible for clinical manifestations ranging from cutaneous symptoms to anaphylaxis. Regulatory pathways involving Treg cells and immunomodulatory cytokines contribute to the maintenance of immune tolerance.

2. Materials and Methods

The review was designed to synthesize evidence from clinical trials and meta-analyses, with an emphasis on studies published in the last five years.

A literature search was performed using the PubMed database to identify relevant studies. The following search string was applied:

("Food Hypersensitivity" [MeSH] OR "food allergy") AND ("therapy" OR "treatment" OR "immunotherapy" OR "biologic*") AND (y_5 [Filter]) AND (clinicaltrial [Filter] OR

clinicaltrialprotocol [Filter] OR clinicaltrialphasei [Filter] OR clinicaltrialphaseii [Filter] OR clinicaltrialphaseiii [Filter] OR clinicaltrialphaseiv [Filter] OR meta-analysis [Filter] OR randomizedcontrolledtrial [Filter]) AND (humans [Filter]) AND (English [Filter]).

The search was restricted to studies published within the last five years and written in English. The literature search was conducted on 1 April 2026 and identified 179 records. Eligible study designs included randomized controlled trials, clinical trials (phases I–IV), clinical trial protocols, and meta-analyses. The literature search primarily focused on human studies; however, selected preclinical studies were also included when they provided important mechanistic insights into emerging therapeutic strategies that are not yet supported by extensive clinical evidence.

PubMed was selected as the primary source because it represents the most comprehensive and widely used biomedical database, providing extensive coverage of clinical trials, randomized studies, and meta-analyses relevant to FA. Given the narrative nature of the review, the aim was not to perform an exhaustive systematic search across all available databases, but rather to identify and synthesize the most clinically relevant and recent evidence.

Titles and abstracts retrieved from the search were screened for relevance. Full texts of potentially eligible studies were then assessed. Studies were included if they investigated therapeutic interventions for IgE-mediated FA, including allergen-specific immunotherapy (oral, sublingual, epicutaneous, or mucosal), biologic therapies, modified allergen approaches, microbiome-based interventions, or emerging treatments. Studies focusing exclusively on prevention, non-IgE-mediated FA, or non-therapeutic management strategies (e.g., avoidance alone) were excluded unless they provided mechanistic insights relevant to treatment. The study selection process was performed independently by two reviewers.

Relevant data were extracted qualitatively from the included studies, including study design, patient population, type of intervention, clinical outcomes (such as desensitization and sustained unresponsiveness (SU)), safety profiles, and mechanistic findings when available. Given the marked heterogeneity in study designs, interventions, and outcome measures, a quantitative meta-analysis was not considered appropriate. Findings were therefore synthesized narratively and organized into thematic sections reflecting the major therapeutic approaches discussed in the literature. Particular attention was paid to treatment efficacy, especially in terms of increased thresholds of reactivity, desensitization rates, and SU, as well as to safety and tolerability profiles, including the frequency and severity of adverse events. Immunological and mechanistic correlates of treatment response were also considered when available, together with the durability of therapeutic effects after treatment discontinuation.

This work was conducted according to the general methodological principles of narrative reviews. Although a structured literature search was performed, formal systematic review registration and risk-of-bias assessment were not undertaken. Given the narrative and exploratory nature of this review, formal registration in PROSPERO was not performed. As this work was conceived as a narrative review, the selection process was not performed according to a predefined systematic review protocol; however, a PRISMA-style flow diagram summarizing the process is provided in Figure 2 [33].

This review has several limitations. First, the heterogeneity of the included studies in terms of design, patient populations, interventions, and outcome definitions limited direct comparability across studies. Second, the absence of a formal risk-of-bias assessment may have introduced methodological inconsistencies in the interpretation of findings. Finally, the rapidly evolving nature of the field may limit the long-term completeness of the evidence discussed.

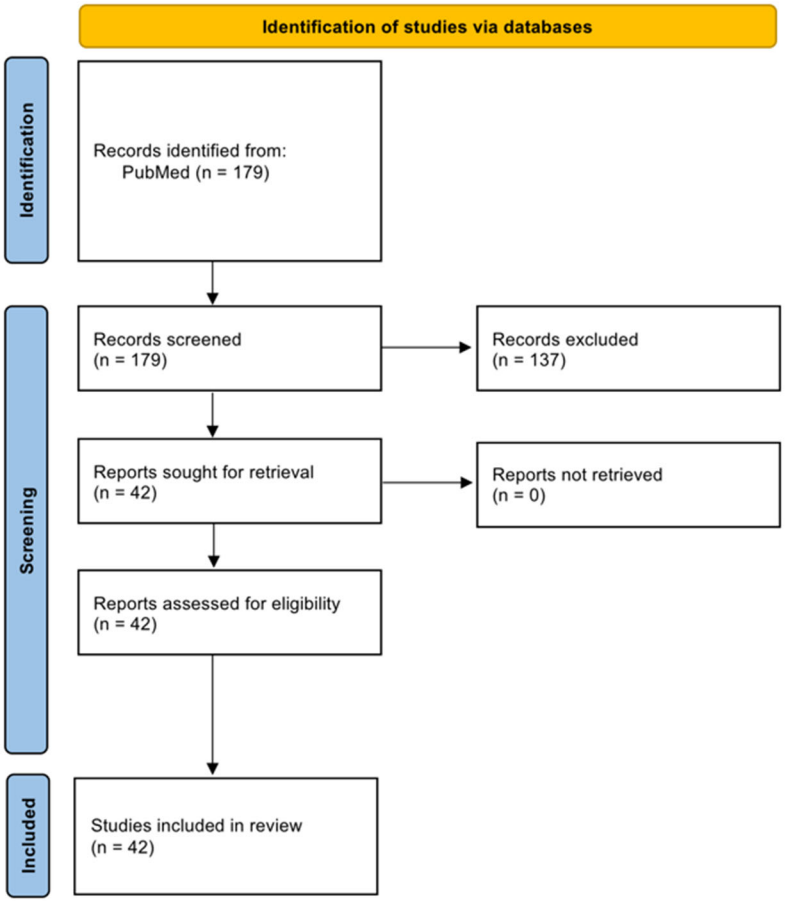


Figure 2. PRISMA flowchart showing identification, screening and inclusion of articles.

3. Results

3.1. Oral Immunotherapy

Oral immunotherapy (OIT) represents the most extensively studied strategy for FA [34–36]. By administering gradually increasing doses of allergen, OIT aims to induce desensitization, defined as an increased threshold of reactivity, and, in some cases, SU after treatment discontinuation [37].

Over the past decade, a large body of clinical trials has demonstrated its efficacy across different allergens, particularly peanut, milk, and egg, establishing OIT as the current backbone of active therapeutic intervention.

Multiple randomized controlled trials have consistently shown that OIT significantly increases the amount of allergen tolerated compared with avoidance strategies. In peanut allergy, OIT enables the majority of treated patients to tolerate clinically meaningful doses, often exceeding thresholds associated with accidental exposure. For instance, controlled trials have demonstrated that patients undergoing OIT achieve markedly higher tolerated doses compared with those maintaining strict avoidance, with substantial between-group differences in desensitization rates [38,39].

Similarly, in milk allergy, baked-milk oral immunotherapy has shown robust efficacy, with a significant proportion of patients achieving high tolerance thresholds after 12 months of treatment, despite baseline severe reactivity [40]. Comparable findings have been reported in multi-food allergy settings, supporting the broad applicability of OIT across allergens.

Importantly, even relatively low maintenance doses can induce meaningful clinical benefits. Studies evaluating low-dose peanut OIT have shown that maintenance doses

as low as 30 mg of peanut protein can significantly increase tolerated doses and induce favorable immunologic changes compared with avoidance [41].

Emerging evidence also suggests that early-life intervention may enhance the effectiveness of OIT. Trials conducted in toddlers have demonstrated higher rates of desensitization and improved safety profiles compared with older children, supporting the existence of a critical "window of opportunity" during immune development [42,43]. These findings are consistent with the concept that immune plasticity is greater in early life, allowing more efficient induction of regulatory pathways and long-term tolerance mechanisms [44,45].

While desensitization during active treatment is well established, the durability of OIT remains a central question. SU, defined as the ability to tolerate allergens after a period of avoidance, has been achieved in a subset of patients, but rates vary widely across studies. Long-term follow-up data indicate that continued exposure may be necessary to maintain protection [46,47].

Despite its efficacy, safety remains the principal limitation of OIT. Treatment-related adverse events are common and range from mild local symptoms to systemic reactions requiring medical intervention. Gastrointestinal symptoms, including abdominal pain and vomiting, are particularly frequent and represent a major cause of treatment discontinuation [48].

Clinical trials have consistently reported high rates of adverse events during both the escalation and maintenance phases of therapy. Even in controlled settings, reactions occur in a significant proportion of administered doses, highlighting the intrinsic risk associated with repeated allergen exposure [49,50]. Efforts to mitigate these risks have yielded variable results. For instance, while premedication with antihistamines can alleviate certain symptoms, it does not appear to lead to a significant reduction in the overall incidence of adverse events [51].

OIT induces complex immunological changes involving both humoral and cellular pathways. These include reductions in allergen-specific IgE, increases in IgG4 levels, and modulation of effector-cell responses. At the cellular level, OIT promotes regulatory T-cell responses and shifts cytokine profiles away from Th2-dominated inflammation [52–54].

Recent transcriptomic analyses have offered a more detailed understanding of these mechanisms [55]. Oral immunotherapy (OIT) appears to downregulate inflammatory gene expression pathways, particularly those linked to neutrophil activation and type 2 cytokine signaling. Importantly, these molecular changes are associated with clinical desensitization and may persist even after treatment discontinuation [55]. Together, these observations point to potential biomarkers that could be useful for monitoring treatment response and identifying patients most likely to benefit.

3.2. Modified Allergen Strategies

A major limitation of conventional food immunotherapy is that native allergens retain full IgE-binding capacity and therefore carry a substantial risk of treatment-related reactions [48,56].

This has driven interest in modified allergen strategies designed to reduce allergenicity while preserving sufficient immunogenicity to promote desensitization or tolerance. Broadly, these approaches include baked or heated milk, boiled or specially processed peanut products, treatment protocols tailored to patients with higher baseline thresholds, and real-food immunotherapy models based on structured consumption of naturally occurring allergen sources. Together, these strategies reflect an effort to make treatment safer, more physiologic, and potentially more adaptable to various clinical phenotypes.

3.2.1. Baked and Heated Milk

Cow's milk allergy has provided one of the clearest clinical models for modified allergen therapy. Extensive heating alters the conformational structure of milk proteins, lowering allergenicity while maintaining antigenic determinants capable of driving immune adaptation [57]. This biological rationale has translated into several clinical approaches.

In a randomized, double-blind, placebo-controlled phase 2 trial, baked-milk oral immunotherapy induced substantial desensitization in children with severe milk allergy who were reactive even to baked milk at baseline [40,58]. After 12 months, 73% of treated participants tolerated 4044 mg of baked-milk protein compared with none in the placebo arm, and most dose-related reactions were mild, despite the severe baseline phenotype. These findings are of particular clinical significance, as they suggest that baked-milk OIT may also be extended, within carefully designed and closely supervised protocols, to patients with more severe phenotypes.

Mechanistic follow-up from the same clinical program suggests that baked-milk OIT is associated with coordinated humoral and cellular remodeling, including increases in milk-specific IgG4 and regulatory signatures alongside decreases in pathogenic Th2-associated populations [58], supporting the view that the reduced-allergenicity matrix does not simply improve tolerability but may also enable meaningful immune reprogramming.

A different standardized approach used a heated and glycated cow's milk protein product (the iAGE product). In this randomized follow-up study, the product appeared safe and feasible for daily use in selected children who initially tolerated it, and no product-related adverse events were reported. However, despite good tolerability and successful introduction of cow's milk in children who later became challenge-negative, the trial did not demonstrate a clear tolerance-inducing advantage over controls [59]. Therefore, it seems that reducing allergenicity alone is unlikely to be sufficient unless it is accompanied by adequate immunologic activity and applied to a well-defined target population [53,60].

3.2.2. Modified Peanut Preparations

Peanuts present a greater challenge than milk, as their major allergens are notably heat-stable, and some processing methods, especially roasting, may even enhance allergenicity [61,62].

For this reason, modified peanut strategies have focused on finding processing methods that reduce IgE reactivity without abolishing T-cell recognition.

One clinically pragmatic model is sequential OIT using boiled peanuts followed by roasted peanuts. In a phase 2 open-label trial, children underwent stepwise exposure beginning with 12 h boiled peanuts, then 2 h boiled peanuts, and finally roasted peanuts. Desensitization was achieved in 80% of participants, withdrawals due to adverse events were infrequent, and rescue epinephrine use was rare; of interest, starting with a less reactive form may allow safer immune engagement before transition to more native peanut [63].

An even more innovative approach was tested with lyophilized peanut protein derived from developing peanuts (LPP-MH), a preparation specifically designed to become less allergenic after extensive heating and baking [64]. In this pilot study of highly allergic children with a single highest tolerated dose below 100 mg, 32 out of 33 participants tolerated more than 300 mg of natural peanut protein after 40 weeks, and no severe allergic reactions requiring epinephrine occurred during challenges or home dosing. At 6 to 12 months of maintenance, the mean cumulative tolerated dose increased further to levels compatible with age-appropriate dietary inclusion. This study is notable as it moves beyond processing existing peanut products and instead focuses on engineering the allergen source itself to create a safer therapeutic substrate. These data suggest that modified peanut preparations may offer a meaningful way to improve safety without

abandoning the desensitization potential of peanut-based therapy. Nevertheless, most evidence still derives from open-label or single-arm studies, and randomized trials are needed for an appropriate comparison to standard peanut OIT.

3.3. High-Threshold Peanut Allergy

Not all peanut-allergic patients have the same clinical vulnerability [27]. Those reacting only at relatively high doses represent an under-discussed subgroup that may benefit from simplified or lower-intensity intervention. A randomized trial in children with high-threshold peanut allergy showed that home-measured peanut OIT using store-bought peanut products produced strikingly high rates of desensitization and durable off-treatment benefit, with no reactions above grade 1 severity and no serious adverse events [65].

3.4. Real-Food Approaches

Modified allergen strategies are also relevant outside classic persistent IgE-mediated FA. In birch pollen-related FA syndrome, where cross-reactive PR-10 proteins such as Mal d 1 drive apple-induced oral symptoms, structured exposure to fresh apples has emerged as a naturalistic immunotherapy model [66]. In a phase II pilot study, daily consumption of selected apple cultivars of progressively increasing allergenicity improved tolerance to apples, reduced skin reactivity, and increased IgG4 responses to both Mal d 1 and Bet v 1, while also improving rhinoconjunctivitis-related outcomes [67]. A later uncontrolled phase II/III trial reinforced these findings, showing durable tolerance to apples, increased tolerance to other Bet v 1 cross-reactive foods, increased Mal d 1-specific IgG4, and evidence of blocking antibody activity [68].

This real-food paradigm may not be generalizable to all FA, particularly those involving heat-stable and systemically dangerous allergens, but it demonstrates that for selected syndromes, structured dietary exposure can function as a practical and biologically meaningful therapeutic tool.

3.5. Alternative Routes of Immunotherapy to OIT

Although oral immunotherapy remains the most established active treatment for FA, its clinical use is limited by frequent treatment-related adverse events, daily ingestion, and variable long-term durability [48]. These limitations have driven the development of alternative routes of allergen delivery designed to engage the immune system while reducing systemic exposure and improving tolerability. Among these, sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and, more recently, oral mucosal immunotherapy (OMIT) all represent the most relevant non-oral-ingestion strategies currently under investigation.

3.5.1. Sublingual Immunotherapy

SLIT delivers very small amounts of allergen to the oral mucosa, where immune processing can occur in a relatively controlled microenvironment [69]. Compared with OIT, SLIT generally uses much lower allergen doses and, therefore, is expected to provide a more favorable safety profile, albeit often associated with more limited degrees of desensitization [70,71].

Long-term open-label data in children treated with peanut SLIT showed that this approach can induce clinically meaningful protection. After 48 months of therapy, the mean successfully consumed dose during the food challenge increased markedly, with 70% of participants achieving clinically significant desensitization and more than one-third tolerating the full challenge dose. Importantly, the median rate of adverse reaction per dose was low, predominantly limited to transient oropharyngeal itching, and no epinephrine was required for treating symptoms. These results support SLIT as a safer, lower-intensity

alternative to OIT, particularly for families prioritizing tolerability and day-to-day feasibility over maximal threshold escalation [70].

Additionally, in a randomized, placebo-controlled trial of peanut SLIT in 1- to 4-year-old children, active treatment produced substantially greater desensitization and remission than placebo. Sixty percent of treated participants passed the month-36 food challenge, and nearly half achieved remission after a 3-month period off therapy, with the best outcomes observed in the youngest children [72]. This finding suggests that SLIT may benefit from the same early-life therapeutic window proposed for OIT, but with a lower treatment burden and a strong safety profile [45].

SLIT may therefore become especially attractive for preschool children, for patients with lower tolerance for OIT-related reactions, or as an intermediate-intensity approach in personalized treatment algorithms.

3.5.2. Epicutaneous Immunotherapy

EPIT is based on the transcutaneous delivery of allergen through intact skin, typically via a patch. This route aims to exploit the immunoregulatory capacity of cutaneous antigen-presenting cells while minimizing systemic allergen exposure. EPIT has consistently shown a favorable safety profile, with most adverse events limited to local skin reactions [73].

The pivotal phase 3 EPITOPE trial demonstrated that 12 months of peanut EPIT in children aged 1 to 3 years was superior to placebo in terms of increasing the eliciting dose of peanut protein [74]. Treatment responses were indeed observed in 67% of children receiving active therapy compared with 33.5% in the placebo group, establishing proof that EPIT can meaningfully raise clinical thresholds in very young children.

After 24 months of treatment, continued enhancement of the treatment effect was observed, and no additional treatment-related anaphylaxis was reported during the extension phase. Moreover, children who switched from placebo to active treatment showed outcomes consistent with the original active arm after 12 months, suggesting reproducibility of effect across cohorts [75]. These data imply that EPIT may provide cumulative benefit over time, even if its initial desensitization effect is more modest than that typically seen with OIT.

Safety data from the REALISE study also support the feasibility of long-term EPIT use in a real-world setting. Over as long as 3 years of active treatment, most treatment-related events were local reactions, which decreased over time, and severe treatment-related adverse events became very uncommon in later treatment years [76,77]. Together, these findings position EPIT as a strong option for patients and families who value safety, compliance, and long-term tolerability, even if the achievable threshold increase may be lower than with aggressive oral regimens [78].

EPIT is also being investigated for cow's milk allergy. In this regard, a randomized trial of Viaskin Milk showed that daily epicutaneous treatment could improve challenge outcomes, particularly in younger children, while maintaining a generally acceptable safety profile dominated by mild to moderate local reactions [79].

Although less evidence has been gathered for non-peanut allergy, these data suggest that epicutaneous delivery could become a broader platform technology rather than a peanut-specific solution.

3.5.3. Oral Mucosal Immunotherapy

OMIT is a newer strategy that differs from classical SLIT by targeting broader immunologically active surfaces of the oral cavity, including gingival and vestibular mucosa, rather than limiting exposure to the sublingual area alone. It has been developed through spe-

cially formulated toothpaste-like delivery systems designed to provide controlled mucosal allergen contact during routine oral hygiene.

A phase 1 placebo-controlled safety study of peanut OMIT in adults showed excellent tolerability: all active participants tolerated escalation to the highest protocol dose, no moderate or severe systemic reactions occurred, adverse effects were mainly local and transient, and adherence was extremely high [80]. Currently, OMIT remains an early-phase platform, and efficacy data are still limited compared with SLIT or EPIT. Nonetheless, its conceptual value is substantial as it may combine some of the safety advantages of mucosal delivery with a simpler and potentially more scalable administration scheme, which could improve compliance in a real-life setting.

3.6. Biologic Therapies

The emergence of biologic therapy has reshaped the therapeutic landscape of FA by introducing a fundamentally different treatment strategy [81]. Whereas classical immunotherapy relies on repeated exposure to the allergen to induce desensitization, biologics target key pathways that underlie allergies and IgE-mediated reactivity [53].

This distinction is clinically important: biologics may increase reaction thresholds without requiring daily allergen ingestion, while also broadening treatment options for patients with multiple food allergies and improving the safety and feasibility of allergen immunotherapy when used as adjunctive agents. FA treatment is thus no longer restricted to allergen-specific desensitization. Instead, it now includes pathway-directed therapies capable of reducing clinical sensitivity across different foods simultaneously [82,83].

The most evident proof of concept for biologic monotherapy in FA comes from the OUtMATCH trial [82]. In this phase 3 study, participants aged 1 to 55 years with peanut allergy plus at least two additional FAs were randomized to omalizumab or placebo for 16 to 20 weeks. Omalizumab was clearly superior to placebo in increasing clinical thresholds: 67% of treated participants met the primary endpoint for peanut compared with 7% of placebo-treated participants, and significant benefits were also observed for cashew, milk, and egg. These findings demonstrate that biologics can raise reaction thresholds across multiple foods without requiring chronic ingestion of each allergen.

This is of great interest, as patients with multi-food allergies are poorly served by single-allergen immunotherapy models. Omalizumab offers a path toward broader protection that is antigen-independent in its mechanism. Importantly, safety outcomes in OUtMATCH were broadly similar between omalizumab and placebo aside from more injection-site reactions in the active-treatment group, suggesting that the benefits in threshold gain are not offset by major safety concerns [84,85].

Of note, omalizumab has also been investigated as an adjunct to OIT; the rationale for using omalizumab as an adjunct to OIT is based on the ability of this monoclonal antibody to reduce circulating free IgE levels and attenuate effector-cell activation, thereby potentially decreasing the incidence and severity of OIT-related reactions and enabling more rapid dose escalation [86]. This adjunctive role is supported by a growing body of work that shows that anti-IgE therapy can reduce adverse events and shorten escalation time when combined with OIT [87].

Furthermore, in the E-B-FAHF-2 trial, all participants received omalizumab-facilitated multi-allergen OIT, while the investigational herbal product E-B-FAHF-2 was tested as an added adjunct. Multi-allergen oral immunotherapy (multi-OIT) with omalizumab proved safe and effective overall: 63.6% of participants were desensitized to 4444 mg protein for each treated allergen, and 24.2% achieved remission after discontinuing therapy. However, the addition of E-B-FAHF-2 did not further improve outcomes. This trial provides important insights for two main reasons. First, it confirms that omalizumab-facilitated

multi-OIT represents an effective clinical approach. Second, it demonstrates that not all additional immunomodulatory agents provide meaningful improvements to this strategy, highlighting the importance of distinguishing between mechanistically promising adjuncts and those that confer a measurable incremental benefit in clinical trials. Of note, remission to high thresholds was achieved in a subset of participants after treatment discontinuation, suggesting that combination strategies may be able not only to accelerate desensitization but also to create more durable protection in selected patients [88].

Compared with omalizumab, dupilumab has so far produced more modest clinical results. The rationale for its use is biologically well supported, given the central role of IL-4 and IL-13 in type 2 immune activation, IgE class switching, and the persistence of allergic inflammation [89]. Consequently, blockade of this pathway may attenuate allergic sensitization and favorably modulate the immunologic milieu during FA treatment. However, the translation into clinical efficacy has been less impressive than anticipated. In a phase II, open-label, proof-of-concept study evaluating dupilumab monotherapy in children and adolescents with peanut allergy, only 8.3% of participants met the primary endpoint, defined as passing the week-24 food challenge [90]. Although dupilumab produced substantial reductions in total and peanut-specific IgE, it did not meaningfully improve desensitization to peanut exposure. This result suggests that lowering type 2 inflammatory tone may not be sufficient to achieve clinically relevant protection in established peanut allergy over a short treatment period.

Of note, in a prospective pilot study of 20 polysensitized adults with moderate-to-severe atopic dermatitis and a documented personal history of severe FA, 16 weeks of dupilumab therapy resulted in a significant reduction in total serum IgE (median 654 to 446 kU/L; $p = 0.049$). A marked decrease was also observed in specific IgE levels to both food and aeroallergens, as well as in IgE directed against molecular food allergen components. Notably, the reduction was particularly pronounced for lipid transfer proteins (Pru p 3, Ara h 9, Cor a 8), which are recognized predictors of severe systemic reactions, including anaphylaxis, and of oral allergy syndrome [91].

Dupilumab has also been tested as an adjunct to peanut OIT. In a randomized phase II trial, dupilumab plus OIT produced a modest increase in efficacy during the up-dosing phase, with a 20.2% increase in the number of patients passing the challenge compared with OIT alone after up-dosing [92]. However, this benefit was not maintained in later phases, and dupilumab did not prevent OIT-related anaphylaxis. The more modest effect observed during up-dosing, with a reduction in peanut allergy-related symptoms, was related in particular to gastrointestinal symptoms, which may still be relevant for adherence and tolerability [93].

Biologic therapy is also helping to clarify which immune pathways are associated with successful desensitization. In mechanistic work derived from omalizumab-assisted multi-OIT, successful outcomes were associated with increased frequencies of allergen-responsive HLA-DR+ regulatory T cells and enhanced IL-10 production by peripheral blood mononuclear cells. By contrast, although omalizumab reduced Th2 cytokine production overall, these cytokines did not clearly discriminate between success and failure of desensitization [94].

Beyond omalizumab and dupilumab, additional biologic targets are emerging as potentially relevant for the future management of IgE-mediated food allergy. Ligelizumab, a next-generation humanized anti-IgE monoclonal antibody with higher affinity for IgE than omalizumab, has been proposed as a more potent strategy to inhibit IgE/FcεRI-mediated mast-cell and basophil activation [95,96]. In a phase 3 randomized, placebo-controlled trial in patients with confirmed peanut allergy, ligelizumab 240 mg increased the proportion of participants tolerating ≥600 mg of peanut protein at week 12 compared with placebo, al-

though the study was terminated early and the results should be interpreted cautiously [97]. Upstream epithelial alarmins also represent attractive targets, as thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33) are involved in the initiation and amplification of type 2 inflammation [98]. Preclinical models suggest that TSLP contributes to food allergy development by promoting Th2-skewed immune responses, intestinal mast-cell accumulation, and allergic symptoms after oral or epicutaneous sensitization [99,100]. Tezepelumab, an anti-TSLP monoclonal antibody, has demonstrated broad activity across allergic and eosinophilic asthma phenotypes by acting upstream of multiple type 2 inflammatory pathways [101]. Moreover, in a randomized trial of cat allergy, tezepelumab enhanced the effects of subcutaneous allergen immunotherapy and induced persistent downregulation of type 2 and mast-cell-related gene signatures, supporting its potential role as an adjunctive biologic in allergen-specific immunotherapy strategies [102]. Anti-IL-33 approaches are also biologically plausible, as IL-33 can promote food anaphylaxis by acting on ST2-expressing mast cells and amplifying IgE-mediated effector responses [103]. In a phase 2a placebo-controlled study, a single dose of the anti-IL-33 antibody etokimab increased short-term peanut tolerance and reduced type 2 cytokine responses in peanut-allergic adults, although larger confirmatory studies are needed [104].

3.7. Next-Generation and Mechanism-Based Therapies

In addition to conventional allergen immunotherapy and biologics, a new generation of therapeutic strategies is emerging that aims to target the immunological mechanisms underlying FA with greater precision and, potentially, improved safety. These approaches move away from the paradigm of administering whole allergens and instead focus on specific epitopes, immune pathways, or regulatory networks.

3.7.1. Peptide Immunotherapy

Peptide immunotherapy represents a refined version of allergen-specific treatment in which short synthetic peptides derived from allergenic proteins are used instead of whole allergens. These peptides are designed to retain T-cell reactivity while lacking the conformational structures required for IgE cross-linking, thereby minimizing the risk of immediate hypersensitivity reactions [105].

Early-phase trials (ASP0892) support both the safety and mechanistic potential of this approach; in a phase 1 trial of peptide immunotherapy for peanut allergy, treatment was well tolerated and associated with immunological changes consistent with targeted immune modulation, including alterations in T-cell responses and cytokine signaling pathways [106,107]. Of note, since peptides do not trigger mast-cell or basophil activation in the same way as whole allergens, they may allow both higher doses and a more rapid administration scheme without the safety concerns typical of OIT.

However, clinical efficacy data remain limited, and it is not yet clear whether peptide-based strategies can achieve the same magnitude of desensitization observed with whole-allergen approaches.

3.7.2. DNA-Based Vaccines

DNA vaccines represent an emerging strategy for the immunotherapy of FA, based on the delivery of plasmid DNA encoding allergenic proteins into host cells, leading to in vivo antigen expression and controlled immune activation [108]. In particular, transcutaneous delivery approaches such as Gene Gun administration enable efficient transfection of antigen-presenting cells, thereby enhancing antigen presentation and downstream immune responses [109].

Preclinical evidence demonstrates that this platform can induce robust production of allergen-specific IgG antibodies, which are considered a key immunological correlate of

protection in IgE-mediated allergies [110]. In murine models, Gene Gun-delivered DNA vaccines encoding shellfish or tree nut allergens elicited significant increases in antigen-specific IgG across multiple genetic backgrounds, with evidence of cross-reactive responses against homologous allergens. Importantly, IgG responses were induced after a limited number of administrations and were associated with minimal induction of allergen-specific IgE compared to sensitized controls [111].

3.7.3. Immunological and Transcriptomic Biomarkers of Response

A key component of next-generation therapies is the identification of biomarkers capable of predicting treatment response, monitoring efficacy, and guiding personalized interventions [112].

Transcriptomic analyses in patients undergoing peanut OIT have demonstrated that treatment is associated with suppression of inflammatory gene expression pathways, particularly those related to neutrophil activation and IL-4/IL-13 signaling. These transcriptional changes correlate with clinical desensitization and persist even after treatment discontinuation, suggesting that they may represent durable markers of immune reprogramming [55].

Furthermore, machine learning approaches applied to transcriptomic data have identified specific gene signatures capable of distinguishing responders from non-responders with relatively high accuracy.

At the cellular level, successful immunotherapy has been associated with expansion of regulatory T-cell populations, increased production of IL-10, and shifts in antibody profiles, including increased allergen-specific IgG4 [113].

3.7.4. Microbiome, Probiotics, Prebiotics, and Dietary Modulation

Increasing evidence suggests that the gut microbiome plays a central role in the development and regulation of allergic diseases, including FA [114,115].

Alterations in microbial composition, reduced diversity, and early-life dysbiosis have been associated with increased risk of allergic sensitization. These observations have led to the hypothesis that modulation of the microbiome may promote the development of immunological tolerance and represent a complementary or even independent therapeutic strategy to allergen-specific immunotherapy [116,117].

One of the most promising applications of microbiome modulation is the combination of probiotics with oral immunotherapy (PPOIT). The rationale is that specific bacterial strains may promote regulatory immune responses, enhance epithelial barrier function, and shift immune balance away from Th2-dominated inflammation [118].

In a multicenter randomized phase 2b trial (PPOIT-003), the addition of *Lactobacillus rhamnosus* to peanut OIT significantly increased rates of SU compared with placebo [116,119]. Approximately 46% of children receiving PPOIT achieved SU versus only 5% in the placebo group, demonstrating a substantial treatment effect. However, rates of SU are similar between PPOIT and OIT alone, suggesting that the benefit of probiotics over optimized OIT protocols remains uncertain. Long-term follow-up at 2 years post-treatment showed continued benefits [119].

More recent open-label data show that in children with egg and milk allergies, high-dose OIT combined with probiotics resulted in SU in approximately 50–55% of participants, along with clinically meaningful improvements in quality of life. These findings support the broader applicability of PPOIT across different food allergens [117].

Of note, a randomized, double-blind, placebo-controlled study in children with atopic dermatitis and cow's milk allergy showed that supplementation with specific Lactobacillus strains improved clinical outcomes, particularly in allergen-sensitized patients, although the effect was not sustained at long-term follow-up [120]. Similar studies have explored heat-

killed Lactiplantibacillus plantarum in combination with OIT in cow's milk allergy, showing increased serum IgG4 levels, indicating immunological tolerance induction, decreased serum IL-5 and IL-9 levels, and modifications of gut microbiome [121].

Prebiotics, non-digestible dietary components that promote the growth of beneficial gut bacteria, have also been explored as a means of influencing immune development. Although clinical data remain relatively limited compared with probiotics, prebiotics may contribute to the expansion of microbial populations associated with tolerance, such as *Bifidobacterium* and *Bacteroides* species [122].

3.8. Prevention Perspectives and Implications for Immune Tolerance

Although primarily investigated in the context of allergy prevention rather than treatment of established disease, early dietary exposure strategies provide important insights into the mechanisms of immune tolerance and may inform the development of future therapeutic approaches. Dietary modulation itself represents another important dimension of microbiome-related therapy. Early introduction of allergenic foods has emerged as a key strategy for allergy prevention and may also influence immune responses in already sensitized individuals [45,123].

In a randomized controlled trial in South African infants, daily egg consumption during complementary feeding was associated with a reduction in overall sensitization to common food allergens, although effects on clinically confirmed allergy were more modest. These findings are consistent with broader evidence suggesting that early and controlled exposure to dietary allergens may promote immune tolerance rather than sensitization [124].

While these interventions are currently considered preventive rather than therapeutic strategies, their ability to promote antigen-specific immune tolerance highlights biological pathways that may be exploited by future disease-modifying treatments.

The therapeutic approaches currently available and those under investigation for IgE-mediated FA are summarized in Figure 3.

The currently available and emerging therapeutic approaches for IgE-mediated FA differ substantially in terms of efficacy, safety, durability of response, and clinical maturity. A comparative summary of the principal therapeutic strategies is provided in Table 1. A summary of the evidence supporting each therapeutic strategy, including evidence level, efficacy outcomes, safety profile, and overall strength of evidence, is provided in Table 2.

Table 1. Summary of established and emerging therapeutic approaches for IgE-mediated food allergy.

Therapy	Desensitization Efficacy	Sustained Unresponsiveness	Safety Profile	Clinical Status
OIT	High. Most effective approach for increasing reaction thresholds, especially for peanut, milk, and egg allergies.	Variable. Continued allergen exposure is often required to maintain protection.	Frequent adverse events, mainly gastrointestinal and oropharyngeal symptoms; systemic reactions may occur.	Most established active therapeutic approach; available in selected clinical settings and approved for peanut allergy in some countries.
SLIT	Moderate. Increases tolerated dose, but usually less than OIT.	Limited but possible, especially in younger children; long-term durability remains uncertain.	Favorable; mostly mild local oropharyngeal symptoms; systemic reactions uncommon.	Investigational/selected clinical use; not broadly approved as standard therapy for FA.

Table 1. *Cont.*

Therapy	Desensitization Efficacy	Sustained Unresponsiveness	Safety Profile	Clinical Status
EPIT	Moderate. Raises eliciting dose, particularly in young children, but generally less than OIT.	Uncertain. Long-term treatment may increase benefit, but durable off-treatment tolerance remains insufficiently defined.	Very favorable; mainly local application-site reactions; systemic reactions rare.	Advanced clinical development; phase III evidence available, especially for peanut allergy.
OMIT	Not yet established. Early data mainly address feasibility and safety.	Unknown.	Excellent early tolerability; mainly transient local symptoms.	Early-phase investigational approach.
Modified allergen strategies	Moderate. Baked milk, heated milk, boiled peanut, and modified peanut preparations may increase tolerance in selected patients.	Limited and heterogeneous evidence; durability remains unclear.	Potentially improved tolerability compared with native allergen OIT, but protocol- and allergen-dependent.	Investigational or used in selected specialist settings; evidence strongest for baked-milk approaches.
Real-food approaches	Low to moderate. May be useful in selected phenotypes, such as high-threshold peanut allergy or pollen–food allergy syndrome.	Possible in selected patients, but evidence remains limited.	Generally favorable when carefully selected and supervised.	Selected clinical/research use; not generalizable to all FA.
Omalizumab monotherapy	High for threshold increase. Effective across multiple FAs without requiring ingestion of each allergen.	Uncertain after discontinuation; optimal treatment duration remains undefined.	Favorable; mainly injection-site reactions.	Clinically advanced; strongest biologic evidence for FA.
Omalizumab-assisted OIT/multi-OIT	High. Facilitates dose escalation and multi-allergen desensitization.	Achieved in a subset after treatment discontinuation; durability requires further study.	Improves tolerability of OIT and may reduce reaction risk, although adverse events can still occur.	Advanced investigational/selected specialist use.
Dupilumab monotherapy	Low. Reduces total and specific IgE but has shown limited clinical desensitization in peanut allergy.	Not established.	Generally favorable.	Investigational for FA; clinical role remains uncertain.
Dupilumab-assisted OIT	Moderate. May modestly improve outcomes during up-dosing, but benefit appears limited.	Not clearly demonstrated.	May reduce some OIT-related symptoms, particularly gastrointestinal symptoms; does not eliminate anaphylaxis risk.	Investigational.
Peptide immunotherapy	Not yet proven clinically. Early studies suggest immunologic modulation rather than established desensitization.	Unknown.	Potentially favorable because peptides are designed to reduce IgE cross-linking.	Early-phase clinical development.

Table 1. *Cont.*

Therapy	Desensitization Efficacy	Sustained Unresponsiveness	Safety Profile	Clinical Status
DNA-based vaccines	Preclinical evidence only; clinical desensitization not established.	Unknown.	Human safety and efficacy not established.	Preclinical/early translational stage.
Microbiome modulation/PPOIT	Moderate when combined with OIT. May support desensitization and SU in selected protocols.	Possible in a subset, but added benefit over optimized OIT alone remains uncertain.	Generally acceptable, but dependent on protocol and concomitant OIT.	Investigational; not standard monotherapy.
Prebiotics/probiotics without immunotherapy	Low. Immunologic effects possible, but limited evidence for clinically meaningful desensitization.	Not established.	Generally favorable.	Supportive/ investigational; not a disease-modifying monotherapy.

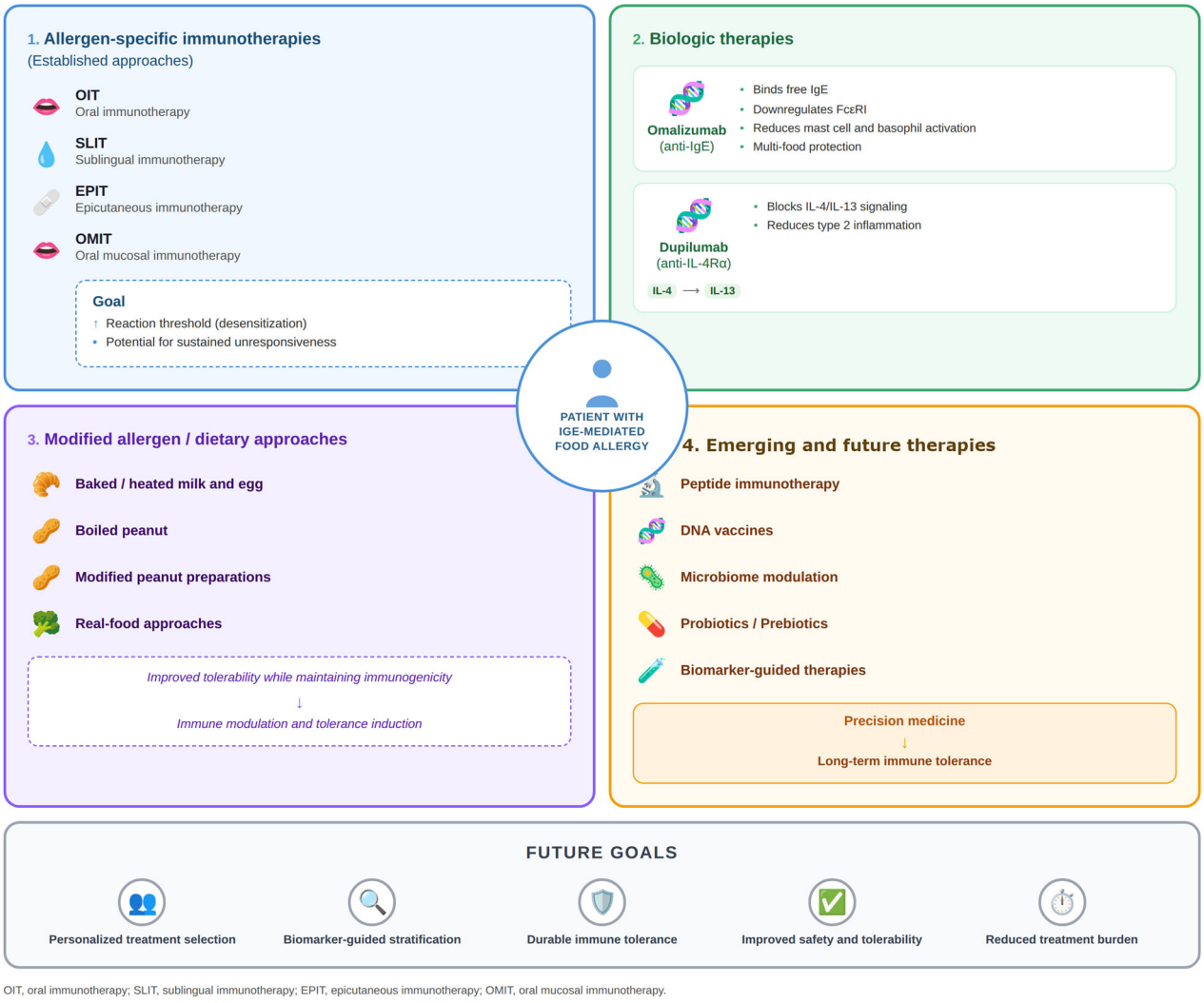


Figure 3. Current and emerging therapeutic strategies for IgE-mediated food allergy.

Table 2. Evidence synthesis of the therapeutic strategies discussed in this review.

Therapeutic Strategy	Key Supporting Evidence Cited in the Review	Highest Level of Evidence Available	Main Therapeutic Effect	Safety/Tolerability Profile
OIT	Peanut, milk and egg OIT trials; low-dose peanut OIT; early-life peanut OIT; long-term follow-up studies [34–55]	Multiple randomized controlled trials, phase III studies, and extension studies	Strong desensitization; increased reaction thresholds; sustained unresponsiveness only in selected patients	Frequent adverse events, especially gastrointestinal and systemic reactions
Baked/heated milk immunotherapy	Baked-milk OIT trial and mechanistic follow-up; heated/glycated milk protein studies [40,53,57–60]	Phase II randomized trial and follow-up studies	Desensitization in selected milk-allergic children; possible immune modulation	Generally improved tolerability compared with native milk OIT
Modified peanut preparations	Boiled peanut OIT; lyophilized/developing peanut protein approach [61–64]	Open-label phase II and pilot studies	Promising desensitization with potentially reduced allergenicity	Encouraging safety, but limited controlled evidence
Real-food immunotherapy for pollen–food allergy syndrome	Apple-based exposure studies in birch pollen-related food allergy syndrome [66–68]	Phase II/phase II–III uncontrolled or pilot studies	Improved tolerance to apple and related PR-10 foods	Generally favorable, but limited generalizability
SLIT	Long-term peanut SLIT; randomized placebo-controlled peanut SLIT in young children [69–72]	Randomized controlled trial and long-term open-label data	Moderate desensitization; possible remission in younger children	Very favorable; mostly local oropharyngeal symptoms
Epicutaneous immunotherapy (EPIT)	EPITOPE trial; extension studies; REALISE safety data; Viaskin Milk trial [73–79]	Phase III randomized trial and long-term extension/safety studies	Moderate increase in eliciting dose, especially in young children	Very favorable; mainly local skin reactions
OMIT	Phase I placebo-controlled peanut OMIT safety study [80]	Phase I safety study	Efficacy not yet established	Excellent early tolerability
Omalizumab monotherapy	OUtMATCH trial and related analyses [82]	Phase III randomized controlled trial	Increased reaction thresholds across multiple foods without allergen ingestion	Generally favorable; mainly injection-site reactions
Omalizumab-assisted OIT/multi-OIT	Adjunctive anti-IgE studies; E-B-FAHF-2 trial with omalizumab-facilitated multi-OIT [86]	Randomized and interventional clinical studies	Facilitates dose escalation and multi-allergen desensitization; remission in a subset	Improved tolerability compared with OIT alone
Dupilumab monotherapy	Phase II proof-of-concept peanut allergy study; polysensitized AD cohort [89]	Phase II study and pilot/prospective clinical data	Reduces total and specific IgE, but limited clinical desensitization	Generally favorable

Table 2. *Cont.*

Therapeutic Strategy	Key Supporting Evidence Cited in the Review	Highest Level of Evidence Available	Main Therapeutic Effect	Safety/Tolerability Profile
Dupilumab-assisted OIT	Randomized phase II trial of dupilumab plus peanut OIT [92,93]	Phase II randomized trial	Modest benefit during up-dosing; no durable, clear advantage	May reduce some OIT-related symptoms, especially gastrointestinal symptoms
Peptide immunotherapy	ASP0892 early-phase peanut allergy studies [106,107]	Phase I studies	Immunologic modulation; clinical efficacy not yet proven	Potentially favorable due to reduced IgE cross-linking
DNA-based vaccines	Gene Gun-delivered DNA vaccine studies [108–111]	Preclinical/translational evidence	Induction of allergen-specific IgG; no established clinical efficacy	Human safety/efficacy not established
Probiotic-assisted immunotherapy	PPOIT-003, PPOIT-003LT, egg/milk probiotic OIT studies [114–122]	Phase II randomized trial and follow-up studies	Sustained unresponsiveness in a subset; benefit over OIT alone remains uncertain	Generally acceptable, but protocol-dependent

Overview of established and emerging treatment approaches for IgE-mediated food allergy. Established allergen-specific immunotherapies include oral (OIT), sublingual (SLIT), epicutaneous (EPIT), and oral mucosal immunotherapy (OMIT), which primarily aim to increase reaction thresholds and induce desensitization. Modified allergen approaches seek to improve tolerability while preserving immunogenicity. Biologic therapies target key immune pathways involved in allergic responses, whereas emerging strategies, including peptide immunotherapy, DNA vaccines, microbiome modulation, and biomarker-guided interventions, aim to achieve more precise and durable immune tolerance through personalized treatment approaches.

4. Discussion

The present review aims to elucidate the progressively evolving therapeutic landscape in the management of FA, shifting from an approach based on allergen avoidance toward active, mechanism-driven therapeutic strategies [125,126]. This evolution reflects both advances in clinical research and an increasingly sophisticated understanding of the immunological basis of allergic disease [127,128].

Importantly, these developments challenge traditional definitions of therapeutic success: rather than requiring complete and permanent tolerance, even partial increases in the threshold of reactivity are now recognized as clinically meaningful outcomes [129].

Despite this progress, significant unmet clinical needs persist: current management strategies still fail to modify the natural history of FA in most patients, particularly in conditions such as peanut allergy and in individuals with severe phenotypes or multiple FAs [130]. In these populations, lifelong avoidance often remains the only viable option [24].

Furthermore, safety concerns continue to limit the broader implementation of disease-modifying therapies [131].

Oral immunotherapy (OIT), albeit highly effective in inducing desensitization, is associated with frequent adverse events, including gastrointestinal and systemic reactions, leading to treatment discontinuation in a subset of patients [38,39,51].

Additionally, the durability of treatment-induced protection remains uncertain, as SU after discontinuation is inconsistently achieved and may require ongoing allergen exposure, raising important questions regarding long-term feasibility and adherence [119].

Within this context, OIT remains the most effective strategy for achieving high levels of desensitization and represents the current backbone of active treatment [41–43,65]. Its immunological effects, characterized by modulation of allergen-specific antibodies, suppression of effector-cell responses, and induction of regulatory T-cell pathways, provide a robust framework for understanding therapeutic benefit [55,94,113]. However, its limitations have catalyzed the development of alternative approaches aimed at improving safety, tolerability, and real-world applicability [2].

Alternative routes of immunotherapy, including SLIT and EPIT, generally achieve lower levels of desensitization compared with OIT but offer substantially improved safety profiles and reduced treatment burden [70,72,74,76,79].

From a clinical perspective, their value should not be interpreted solely in terms of maximal efficacy; rather, for many patients, particularly young children or those unable to tolerate OIT, a moderate increase in reaction threshold achieved with high safety and adherence may represent the optimal therapeutic outcome [24,132].

Modified allergen strategies and real-food-based approaches exemplify the ongoing transition toward interventions that are both safer and more aligned with natural exposure. By decreasing IgE-binding capacity while maintaining sufficient immunogenic potential, these methods aim to optimize the balance between therapeutic efficacy and tolerability [57].

Importantly, these approaches should not be regarded as simplified or less effective versions of conventional OIT, but rather as conceptually distinct strategies that tailor allergen exposure to individual risk profiles: in milk allergy, baked preparations may serve both as a safer entry point and as a bridge toward broader tolerance, while in peanut allergy, boiled or modified preparations may reduce the burden of adverse reactions while maintaining desensitization potential [40,58–60,63,133].

In selected patients with high baseline thresholds, simplified real-food approaches may provide sufficient protection with lower treatment burden, representing a scalable and family-centered model of care [65]. However, heterogeneity in allergen preparation, patient selection, and outcome definitions remains a major limitation, complicating direct comparisons across studies [2,134].

The advent of biologic therapies represents a fundamental paradigm shift, extending treatment beyond allergen-specific desensitization to targeted immune modulation.

Among these, anti-IgE therapy with omalizumab has demonstrated the most consistent and clinically meaningful benefits, including the ability to increase reaction thresholds across multiple allergens without the need for continuous allergen ingestion [82,85].

In addition to its role as monotherapy, omalizumab has proven effective as an adjunct to immunotherapy, facilitating multi-allergen desensitization and improving safety profiles [88].

Beyond omalizumab and dupilumab, emerging biologics targeting upstream mediators of type 2 inflammation may further expand the therapeutic landscape of food allergy. In particular, therapies directed against TSLP and IL-33 are of considerable interest because these epithelial alarmins play a central role in allergic sensitization and amplification of Th2-driven responses [99,100,104]. Similarly, ligelizumab, a next-generation anti-IgE monoclonal antibody with enhanced IgE-binding affinity, has shown promising efficacy in peanut allergy, supporting continued development of more potent IgE-targeted approaches [96,97]. Although clinical evidence remains preliminary, these agents highlight a broader shift from downstream effector-cell inhibition toward upstream immune modulation. Future

studies will clarify whether these strategies can improve long-term outcomes, facilitate sustained unresponsiveness, and serve as effective components of personalized or combination treatment approaches.

In contrast, despite a strong mechanistic rationale targeting IL-4 and IL-13 signaling, dupilumab has shown more limited clinical efficacy, with modest effects on desensitization outcomes [90]. Its role may therefore be more that of an adjunctive therapy in selected settings, particularly where reduction in treatment-related symptoms is desirable, although the clinical relevance of these immunological changes in terms of sustained food tolerance remains to be established [91,92].

Mechanistic insights derived from biologic-assisted immunotherapy further refine our understanding of successful treatment. Emerging evidence indicates that effective desensitization is not solely associated with a simple suppression of Th2 responses but also with the induction of active regulatory pathways, including expansion of allergen-specific regulatory T cells and increased IL-10 production [94].

This shift toward a tolerogenic immune profile may represent the key determinant of durable clinical benefit and provides a foundation for the development of predictive biomarkers and next-generation therapeutic strategies. Indeed, the identification of reliable biomarkers remains one of the most critical unmet needs in the field. Advances in transcriptomic and immunological profiling have identified candidate signatures associated with treatment response, but these have yet to be translated into clinically applicable tools [55,135]. The ability to predict efficacy, safety, and long-term outcomes would represent a major step toward personalized medicine, enabling more precise patient selection and optimization of therapeutic strategies.

Next-generation therapies, including peptide immunotherapy and DNA-based vaccines, seek to address these challenges by targeting specific immune pathways with greater precision and reduced risk of immediate hypersensitivity reactions [106,107]. Although still in early stages of development, these approaches represent a conceptual evolution toward immune reprogramming rather than desensitization alone. Their future integration with biomarker-driven patient stratification may ultimately enable more durable and individualized treatment outcomes.

The role of the microbiome further expands the therapeutic framework, highlighting the complex interplay between immune regulation, barrier function, and microbial ecology. PPOIT has shown promise in enhancing SU [116,117,119,124]. These findings reinforce the concept of FA as a systemic condition influenced by environmental and host-related factors. As such, future therapeutic strategies are likely to incorporate microbiome modulation as one component of a multidimensional therapeutic approach.

The principal clinical implications emerging from the current evidence are summarized in Table 3.

The growing diversity of available interventions reinforces the need to shift toward a stratified framework in which treatment decisions are guided by disease severity, baseline reactivity threshold, number of allergens, age, comorbidities, and patient preferences [2,24].

For instance, patients with severe or multi-food allergy may benefit mostly from biologic therapies or combination approaches.

Early-life intervention is also increasingly recognized as pivotal, with growing evidence indicating the existence of a developmental window during which immune tolerance may be more effectively induced [29,123,124].

Table 3. Summary of the principal clinical implications emerging from the current evidence on IgE-mediated food allergy.

Topic	Key Message
OIT	Currently represents the most effective strategy for achieving desensitization and increasing reaction thresholds in IgE-mediated food allergy. However, treatment-related adverse events remain common, and long-term sustained unresponsiveness is achieved only in a subset of patients.
SLIT and EPIT	Provide a more favorable safety and tolerability profile compared with OIT, although generally at the cost of lower desensitization efficacy. These approaches may be particularly valuable in selected pediatric populations or in patients unable to tolerate OIT.
Biologic Therapies	Omalizumab has emerged as a major advance, particularly for patients with multiple food allergies, by increasing reaction thresholds across different allergens and improving the feasibility of immunotherapy-based approaches.
Modified Allergen Approaches	Strategies based on baked milk, heated milk products, modified peanut preparations, and selected real-food protocols may improve tolerability while preserving immune-modulating potential in appropriately selected patients.
Emerging Therapeutic Platforms	Peptide immunotherapy, DNA-based vaccines, microbiome-targeted interventions, and oral mucosal immunotherapy represent promising next-generation approaches, although further validation is required before routine clinical implementation.
Precision Medicine	Reliable biomarkers capable of predicting treatment response, safety, and sustained unresponsiveness remain one of the most important unmet needs in the field.
Future Directions	Future management is likely to rely on personalized treatment algorithms integrating allergen-specific immunotherapy, biologics, and biomarker-guided patient stratification to maximize efficacy while minimizing treatment burden and risk.

Despite the remarkable progress achieved in recent years, several fundamental challenges continue to limit the development of truly disease-modifying therapies for FA. One of the most relevant unresolved issues is the discrepancy between desensitization and SU; while many immunotherapeutic approaches, particularly OIT, can successfully increase the threshold of reactivity during active treatment, only a subset of patients maintains protection after treatment discontinuation.

This observation suggests that desensitization and SU may rely on partially distinct immunological mechanisms. Desensitization appears largely dependent on continuous allergen exposure and transient suppression of effector-cell activation, whereas SU may require more profound and durable immune reprogramming, including stable induction of allergen-specific regulatory pathways, long-term remodeling of memory immune responses, and persistent changes in allergen-specific antibody profiles.

Although several studies have identified potential correlates of successful treatment, including expansion of regulatory T-cell populations, increased IL-10 production, shifts toward allergen-specific IgG4 responses, and transcriptomic signatures associated with reduced type 2 inflammation, no biomarker has yet demonstrated sufficient reliability for routine clinical use. Consequently, predicting which patients will achieve long-term tolerance remains one of the most important unmet needs in the field [35,136].

Similarly, patients with less complex allergic phenotypes or higher baseline reactivity thresholds may achieve more favorable outcomes [132].

However, robust criteria capable of predicting treatment success or failure are still lacking. The identification of clinical, immunological, and molecular predictors of response

therefore represents a critical research priority, as it could facilitate patient stratification and improve the risk–benefit balance of therapeutic interventions.

The growing number of available treatment options also raises important questions regarding therapeutic selection. Current evidence suggests that efficacy, safety, and treatment burden exist on a continuum rather than representing mutually exclusive outcomes [35].

OIT consistently provides the highest degree of desensitization but is associated with the greatest treatment burden and the highest incidence of treatment-related adverse events. In contrast, SLIT and EPIT generally offer more favorable safety profiles and improved tolerability, although their impact on reaction thresholds is typically less pronounced.

Biologic therapies, particularly omalizumab, introduce a fundamentally different paradigm by increasing reaction thresholds without requiring continuous allergen exposure and by offering simultaneous protection against multiple food allergens.

These characteristics may be particularly advantageous in patients with complex or multi-food allergy phenotypes [35]; rather than identifying a single universally superior strategy, the available evidence increasingly supports the concept that future management will rely on individualized treatment approaches tailored to disease severity, baseline reactivity, patient age, treatment goals, and patient preferences [3].

The optimal positioning of biologic therapies within future treatment algorithms remains another area of active investigation.

Although omalizumab has demonstrated robust efficacy both as monotherapy and as an adjunct to immunotherapy, several questions remain unanswered, including the ideal duration of treatment, the durability of protection after discontinuation, and the patient populations most likely to benefit.

Similarly, emerging approaches such as peptide immunotherapy, DNA-based vaccines, and microbiome-targeted interventions provide compelling mechanistic rationales but currently remain supported primarily by early-phase or proof-of-concept studies.

Finally, translating the promising results observed in clinical trials into routine clinical practice remains a substantial challenge: many interventions require prolonged treatment periods, intensive monitoring, specialized expertise, and a high degree of patient adherence [2,35].

These factors may limit widespread implementation outside dedicated allergy centers and contribute to disparities in access to care. Consequently, future research should focus not only on maximizing efficacy but also on simplifying treatment protocols, improving safety profiles, reducing treatment burden, and identifying patients most likely to benefit from specific interventions.

The successful translation of emerging therapeutic advances into clinical practice is further complicated by marked differences in the availability of diagnostic and treatment resources worldwide. Although an oral food challenge remains the diagnostic gold standard, its availability is often limited by the need for specialized personnel, infrastructure, and emergency preparedness, particularly in low- and middle-income countries [6,17]. Similarly, access to allergen-specific immunotherapy programs, biologic therapies, and multidisciplinary allergy services remains highly variable across healthcare systems. As a result, many patients continue to rely exclusively on allergen avoidance and emergency management strategies. These disparities may contribute to underdiagnosis, delayed treatment, and unequal clinical outcomes across populations [137,138].

In conclusion, FA is transitioning from a condition managed primarily through avoidance to one that can be actively treated and, in some cases, fundamentally modified. While substantial challenges remain, including issues of durability, safety optimization, biomarker validation, and equitable access, the convergence of clinical innovation and mechanistic insight is paving the way toward a more precise and personalized model of care. Further

research will be crucial to translate these advances into standardized, widely accessible, and effective therapeutic strategies that can improve long-term outcomes across heterogeneous patient populations.

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Abbreviations

The following abbreviations are used in this manuscript:

EPIT	Epicutaneous Immunotherapy
FA	Food Allergy
IL	Interleukin
IgG4	Immunoglobulin G4
IgE	Immunoglobulin E
HLA-DR	Human Leukocyte Antigen–DR isotype
LPP-MH	Lyophilized peanut protein-MH
OIT	Oral Immunotherapy
OMIT	Oral Mucosal Immunotherapy
OUtMATCH	Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Children and Adults
PPOIT	Probiotic and Peanut Oral Immunotherapy
SLIT	Sublingual Immunotherapy
SU	Sustained Unresponsiveness
Th2	Type 2 helper T cells
Treg	Regulatory T lymphocytes

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