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REVIEW ARTICLE

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Management of IgE-mediated food allergy in the 21st century

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Abstract

The 21st century has seen the propulsion of research in the field of food allergy, which has driven real changes in the clinical approach. Allergen immunotherapy has been recommended for the active management of food allergy. Data have shown promising additional methods of treatment, including biologics. Efforts have been devoted to the risk stratification of food allergy and the standardization of the assessment of food-allergic severity. Alternative routes of administration of epinephrine are under investigation to minimize any mechanical issue and the fear of injections. Evidence-based guidelines have been published by the main international societies in the field of anaphylaxis and food allergy management and new updates are in preparation. In the coming years, treatment options that are currently in pre-clinical or early clinical evaluation will hopefully lead to safe and effective disease-modifying therapies for food allergy in clinical practice. The identification of reliable biomarkers and the standardization of definitions and measurement approaches, alongside a shared decision-making with patients and families, will be key for the development of personalized care and to help minimize the substantial burden of food allergy.

1 | INTRODUCTION

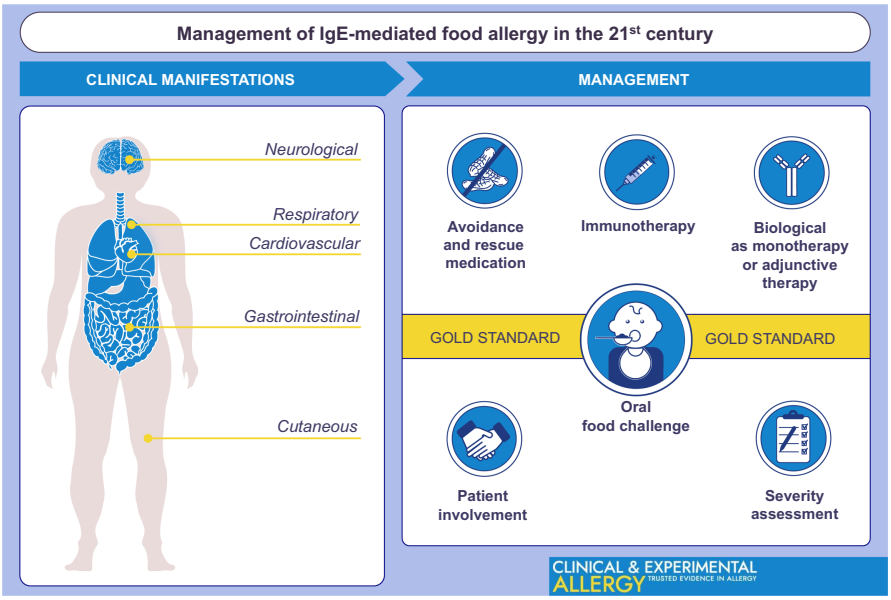
Food allergy is defined as an immune-mediated adverse reaction to food[1] consisting in a loss of tolerance to harmless environmental substances.

An increase in food allergy epidemiological burden has been reported in the last few decades.[2] In parallel, hospital admissions for food-induced anaphylaxis appear to be increased.[3,4]

A systematic review estimated the pooled lifetime and point prevalence of self-reported food allergy in Europe as 17.3% (95% CI: 17.0–17.6) and 5.9% (95% CI: 5.7–6.1), respectively. However, positive oral food challenge (OFC) rate was estimated as 0.9% (95% CI: 0.8–1.1).[5,6]

Food allergy has been associated with various negative impacts on patients and their families,[7] including on health-related quality of life (HRQoL),[8] nutrition,[9] and costs at individuals and societal level.[10] Therefore, the ultimate goal of food allergy care should be the empowerment of patients and their caregivers to manage the risk of food allergy reactions, reduce food-related anxiety and achieve a sense of control over their condition, recognizing that this will be achieved in different ways for different patients.[11]

In this narrative review, we will focus on current novel and future potential approaches and concepts regarding the management of IgE-mediated food allergy (FA), that is immediate, within minutes to a few hours from the culprit food's ingestion to the occurrence



GRAPHICAL ABSTRACT

The 21st century has seen the propulsion of research in the field of food allergy, which has driven real changes in the clinical approach: (a) Oral immunotherapy is the first treatment recommended for the active management of food allergy; (b) Increasing data support biologics as promising therapeutic options as monotherapy or combined with immunotherapy; (c) Proper risk-stratification and severity assessment are pivotal for a targeted and cost-effective approach.

of the allergic manifestations, which is the best studied form of food allergy. This review will provide a state of the art summary of current knowledge and future perspectives on FA ranging from the management of avoidance diets and rescue medication to the active management of FA (such as specific immunotherapy) and current evidence on promising additional methods of treatment (e.g. biologics) as well as the key role of a shared decision-making with patients and families, proper risk stratification and standardizing assessment of FA severity for the development of personalized care to minimize the substantial burden of FA.

Key Messages

- Oral immunotherapy is the first treatment recommended for the active management of food allergy.
- Increasing data support biologics as promising therapeutic options as monotherapy or combined with immunotherapy.
- Proper risk-stratification and severity assessment are pivotal for a targeted and cost-effective approach.

2 | SYMPTOMS AND DIAGNOSIS

FA may result in a large spectrum of clinical manifestations, which may present as cutaneous, gastrointestinal, respiratory, cardiovascular or neurological signs and symptoms, in an isolated or concomitant manner with the same or different timing. Reactions may range from mild local to fatal or near-fatal anaphylaxis. In this century, significant efforts have gone into to attempting to establish a standard definition for reaction severity,[12] with a recently developed scoring system currently undergoing validation.[12,13] A thorough clinical history and evaluation remain fundamental for an accurate diagnosis.[14] These serve as the basis for the interpretation of IgE sensitization observed through in vivo (e.g. skin prick tests) and/or in vitro tests (sIgE), which remain critical for investigating potential triggers.[15] In recent years, a significant overdiagnosis of milk allergy in young children has been estimated in some countries. A recent Delphi consensus[16] has highlighted the importance of reproducibility and specificity for diagnosing milk allergy in children with acute or delayed symptoms temporally related to milk protein ingestion. Consensus was reached that milk allergy diagnosis does not need to be considered for stool changes, aversive feeding or occasional spots of blood in stool, if there is no temporal relationship with milk protein ingestion.

Oral food challenge (OFC) represents the gold standard for diagnosis. While it is safe, it comes with significant barriers, including patient and physician fear of severe reactions, as well as important logistic considerations.[17] There is thus an unmet need for novel diagnostic techniques to inform the diagnosis and management of FA and potentially eventually serve as reliable and safe diagnostic alternatives to OFCs.

Component-resolved diagnosis (CRD) is a diagnostic technique measuring sIgE against specific food allergenic molecules, which has greatly evolved in the last decades.[18] Singleplex or multiplex formats are available on the market, with the spectrum of the available

allergenic molecules rapidly rising.[19] Recently, a peanut bead-based epitope assay has been developed, and it demonstrated an overall accuracy superior to other diagnostic tests.[20]

The potential of basophil activation test[21] and mastocyte activation test[22] has been recently consolidated with, overall, a good diagnostic performance when compared with OFCs. However, additional robust data including cost-effectiveness analyses and consensus on international standards are still required before these are ready for clinical use.

In recent years, other biomarkers have been investigated for FA diagnosis, to monitor food-allergic status over time[23] and help guide the need for OFC, or to support predict natural evolution and prognosis.[24] Potential biomarkers may involve genetic and epigenetic factors, comprising their interaction with environmental risk factors linked to FA.[25] Multi-omics approaches may support the investigation of pathologic mechanisms in FA, potentially leading to insights for novel diagnostic biomarkers.[26]

Furthermore, in the last decades, there is more and more attention to the risk of food allergy overdiagnosis. Reflection on recent advances in the use of diagnostic testing, as well as the application of diagnostic labels, provides an important perspective to understand how far the specialty of allergy and immunology has come in improving the lives of patients and families.[27]

3 | MANAGEMENT OPTIONS

3.1 | Avoidance and rescue medication

The classical approach in managing FA focuses on the strict avoidance of trigger foods and the availability of and training in the use of rescue medication in case of an allergic reaction.[28] The limitations of a management strategy based on strict avoidance include reduced diet diversity, social restrictions impacting on HRQoL,[29] potential risk of nutritional deficiencies, especially in young children, and for some patients, persistent anxiety from the possibility of severe adverse reaction after an accidental random exposure to the culprit food.

In this century, several studies have focussed on assessing the potential effects of OFC and of threshold determination,[30,31] showing they served to reduce uncertainty regarding individual risk, improve anxiety and HRQL and expand diet diversity through a personalization of dietary restrictions. The challenge for the rest of century will be to expand on this work and work hand in hand with industry to define standards and improve food labelling[32] to report specific allergen levels instead of the dichotomic presence or absence of 'may contain', thus creating more options for patients with high thresholds. This would pave the way for a renewed clinical offer with regard to allergen avoidance, which would be tailored to each patient.

Many studies have focussed on the choice of the replacement formula in cow's milk allergy (CMA). Currently, CMA management requires the strict dietary elimination of milk protein from the infant's diet. Guidelines recommend continuing breastfeeding as the ideal nutrition for allergic infants, and some guidelines recommend maternal elimination diet in breastfed infants with persistent signs and symptoms.[33–37] When breastmilk is not available or insufficient an extensively hydrolysed formula (EHF) is the first-choice formula for mild-to-moderate CMA and an aminoacidic formula (AAF) if EHF fails.[33–38] Restrictive criteria for milk allergy diagnosis have been proposed in order to avoid overdiagnosis and excessive use of milk formula substitutes.[16,39,40]

Overall, AAF is recommended for severe CMA and considered the first choice in CMA infants with: anaphylaxis and/or clinical manifestations not fully resolved on EHF.[35,41] AAF is considered 100% effective in treating CMA because no component of an AAF is derived from cow's milk.

Consumption of rice-based infant hydrolysates (HRF) has risen. Already in 2010[35] and confirmed in 2022,[42] the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines suggested that HRF is a safe choice, when EHF formulas are not tolerated. Several studies have showed its safety and efficacy (i.e. normal growth, plasma nutritional parameters and tolerance)[43] supporting the use of hydrolysed rice-based formulas as a possible first-choice for infants with CMA.[38] However, the availability of HRF is limited although growing up across the globe.[38] With the current focus on more sustainable and climate-friendly dietary solutions, evaluation of the suitability of plant-based infant formulas gained an increasing interest both for the CMA management and as a general choice for infant nutrition.

There are currently no guideline recommendations for the use of 'biotics' (pro-, pre-, syn- or post-biotics) for the prevention or treatment of FA due to the heterogeneity and paucity of data.[44,45] However, with the progression of microbiota research, an eventual access to a wider spectrum of 'biotics' to select from and methods to improve microbiota resilience, it is not unrealistic to expect that new effective approaches specifically tailored to the individual patient could be developed during this century.

When reactions occur, appropriate management includes the prompt administration of epinephrine which is the drug of choice for treating anaphylaxis.[46–48] Education is essential if patients at risk of anaphylaxis are to successfully recognize and manage future episodes. In 2022, the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on anaphylaxis recommended providing structured, comprehensive training to improve knowledge and use of adrenaline autoinjectors in people at risk of anaphylaxis.[46] Many patient training approaches are available, including the use of training devices and online tutorials.[49] Some studies have also found that having patients practice using an adrenaline autoinjector or even an empty syringe and needle can reduce anxiety or improve HRQoL, especially in adolescents and young adults.[50]

However, to consistently deliver accurate dosing and function reliably may be sometimes an issue, as well as the short shelf-life and the bulky size of epinephrine auto-injectors.[51] The use of adrenaline infusions has been proposed to manage refractory

anaphylaxis.[52] Determinants of the pharmacokinetics of adrenaline/epinephrine autoinjectors have been investigated, but the strength of evidence is not high, due to a lack of head-to-head comparisons, small numbers of study participants and the failure to acknowledge the biphasic nature of intramuscular adrenaline absorption for analysis purposes.[53] To overcome the mechanical problems, as well as fears associated with needles and administration errors causing injuries[54] in the last years are emerging alternatives to the intramuscular route. These include intranasal, sublingual, inhaled, and needle-free intramuscular administration of epinephrine, all of which could potentially transform our management of anaphylaxis.[55]

In general, intranasal (IN) administration induces minimal side-effects and few contraindications. Due to a slower absorption in comparison with the intramuscular and intravenous routes, the intranasal administration seems to require a higher dose to achieve adequate plasma concentration. Multiple human studies have further demonstrated that IN epinephrine effectively raises plasma epinephrine levels similarly to intramuscular epinephrine with faster absorption.[56]

In 2006, the sublingual administration of epinephrine 40 mg by tablet formulation resulted in epinephrine plasma concentrations similar to those obtained after epinephrine 0.3 mg intramuscular injection in the thigh.[57] In 2021, a novel fast-disintegrating sublingual tablet showed the feasibility of using the sublingual route of delivery for epinephrine.[58]

The term 'gastrointestinal anaphylaxis' describe rapid onset of severe abdominal signs and symptoms as the sole allergic reaction or as part of systemic anaphylaxis.[59] There is currently no treatment that specifically addresses abdominal pain or uterine cramping during food-induced anaphylaxis. Epinephrine has limited efficacy for visceral anaphylaxis, due to its alpha-adrenergic action, which counteracts the relaxing effect of beta-adrenergic receptors on visceral smooth muscle. In 2021, inhaled salbutamol was reported as a novel treatment approach used for severe abdominal pain, caused by an IgE-mediated allergic reaction to peanuts.[60] Inhaled salbutamol is rapidly distributed through the body to exert systemic effect.[61] In this case–control study, the use of salbutamol was associated with a significant improvement of abdominal pain, suggesting it could be an effective treatment for severe gastrointestinal complaints during the reaction. This still needs to be shown prospectively in a randomized trial, but it could realistically have implications for the pharmacologic management of allergic reactions in the coming century.

Current practice is for any patient who injected with epinephrine to activate emergency medical services (EMS) and/or go to a hospital emergency department (ED), whose costs are high. However, the necessity to systematically use EMS with any anaphylaxis is increasingly questioned. During COVID-19 pandemic, Casale et al.[62] described how patients might manage an anaphylactic event without activating EMS. In appropriate patients, self-management of anaphylaxis did not always require activation of EMS as confirmed in 2022,[63] in times without a pandemic.

3.2 | Immunotherapy

In the 21st century, the rise of FA dictates the need for proactive treatment. On this line, the attention focussed on allergen immunotherapy (FA-AIT, food allergen immunotherapy).[27,64] It is potentially a disease-modifying therapy which consists of a titrated oral administration of the culprit food at regular intervals to induce tolerance.[65,66] FA-AIT may increase the amount of food that the patient can tolerate while on treatment (the so-called desensitization), preventing allergic clinical manifestations and reducing the risk of potentially life-threatening allergic reactions.

In 2018, the evidence-based[67] EAACI guidelines recommended for the first-time oral immunotherapy (OIT) as a treatment option for persistent cow's milk, hen's egg or peanut allergies for children from around 4 to 5 years of age to increase threshold of reaction while on treatment.[68] Since then, other guidelines followed[11,69] (Table 1). Since 50%–75% of children with CMA can tolerate baked milk products[71] and children with regular exposure to baked milk might progress to tolerance of unheated milk at a significantly accelerated rate,[72] baked milk has been used to attempt desensitization with variable results.[73] For people who react to very small doses of baked milk, OIT with baked milk is not currently suggested.[68,69]

Current evidence suggests that egg-OIT can desensitize more than 80% of children treated for egg allergy.[74] The first double-blind placebo-controlled (DBPC) trial egg-OIT reported that 27.5%[75] and 50%[76] of the egg-OIT group reached sustained unresponsiveness (SU, i.e. the ability to safely consume a normal serving of food containing the trigger allergen despite a period of absence of exposure) by 2 and 4 years. Patients who did not reach sustained tolerance on the final OFC after avoidance could still tolerate a higher amount of egg that at study entry, suggesting a potential long-lasting benefit in all patients, albeit at various extent. Further studies are needed to confirm these data because of design drawbacks as high rate of loss of follow-up[74] and lack of OFC to most of control patients according to protocol design.[75]

Since 2009,[77] a plethora of studies,[28,78] reported on peanut-OIT. A recent metanalysis from the GA2LEN group shows that OIT induces desensitization for peanut ($p < .05$, RR 9.9, 95%CI 4.5.–21.4, high certainty) without increasing adverse reactions ($p = .06$, RR 1.1, 95%CI 1.0–1.2, low certainty) or severe reactions in peanut allergy ($p < .05$, RR 1.6, 95%CI 0.7–3.5, low certainty).[28]

Moreover the GA2LEN group indicates that OIT induces desensitization for cow's milk ($p < .05$, RR 5.7, 95%CI 1.9–16.7, moderate certainty) and hen's egg allergy ($p < .05$, RR 8.9, 95%CI 4.4–18, moderate certainty).[28] There is low level of evidence that oral immunotherapy may increase the proportion of children able to tolerate peanut ($p < .05$, RR 8.8, 95%CI 1.2–61.6) / egg ($p < .05$, RR 7.1, 95%CI 1.7–29.4) after stopping therapy.[28]

However, safety is one of the main issues of OIT, mainly mild abdominal pain, sometimes more severe as anaphylaxis, rarely eosinophilic esophagitis.[79] The GA2LEN metanalysis reports that OIT may increase (mild) adverse reactions in cow's milk ($p < .05$, RR 3.9, 95%CI

TABLE 1 Key recommendations from the evidence-based guidelines on allergen-specific immunotherapy for food allergy

Paper	Key recommendations
EAACI, 2018[68]	'OIT is recommended as a treatment option to increase threshold of reaction while on treatment in children with persistent cow's milk (Grade A), hen's egg (Grade B), or peanut (Grade A) allergy, from around 4–5 years of age'
DRACMA, 2022[69]	- 'We suggest OIT with unheated cow's milk, rather than no immunotherapy, for those people with IgE-mediated CMA who place a higher value on being able to consume milk (even if in small amounts) with less need to follow a strict avoidance diet, and a lower value on allergic reactions during OIT' - 'We suggest that clinicians do not use OIT with cow's milk in those people with IgE- mediated CMA who place a higher value on avoiding allergic reactions during OIT, and a lower value on being able to consume cow's milk (even if in small amounts) with less need to follow a strict avoidance diet' - 'We suggest that clinicians use omalizumab, compared with not using it, during the initial stages of OIT with unheated cow's milk in people with IgE-mediated CMA' - 'In people with IgE-mediated CMA who do not tolerate unheated and baked milk, we suggest that clinicians do not use OIT with baked cow's milk. (This recommendation concerns persons who react to very small doses of baked milk. Persons with IgE-mediated CMA who do tolerate certain amounts of baked cow's milk can continue consuming it and advance with the amounts tolerated under physician supervision)'
GA2LEN, 2022[70]	The GA2 LEN Task Force: 'recommends offering peanut OIT under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy'. [Certainty of evidence: High] 'suggests offering peanut epicutaneous immunotherapy under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4–11 years with clinically diagnosed, severe, IgEmediated, peanut allergy to increase the amount of peanut tolerated while on therapy'. [Certainty of evidence: Moderate] - 'suggests offering oral immunotherapy under specialist supervision with standardized evidence-based protocols using food products to selected children (aged 4þ years) with clinically diagnosed persistent severe IgEmediated hen's egg or cow's milk allergy to increase the amount of allergen tolerated while on therapy'. [Certainty of evidence: Moderate]
CSACI, 2020[11]	- OIT is indicated for toddlers and preschoolers. While the likelihood of spontaneously outgrowing milk or egg allergy may be greater than for other foods, their impact on patients and families, if not outgrown, is high. Caregivers should be included in shared decision-making about, whether to initiate OIT early for milk and egg and based on individual prognosis (i.e. spontaneously outgrowing), considering that OIT is well tolerated and has high efficacy in this age group OIT is indicated for school-age children and adolescents

Abbreviations: CSACI, Canadian Society of Allergy and Clinical Immunology; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy; EAACI, European Academy of Allergy and Clinical Immunology; FA-AIT, food allergen immunotherapy; OIT, oral immunotherapy.

2.1–7.5, low certainty) and hen's egg allergy ($p < .05$, RR 7.0, 95%CI 2.4–19.8, moderate certainty).[28]

In January 2020, Palforzia® (AR101), a pharmacy-grade standardized peanut OIT formulation, was approved by the US Food and Drug Administration (FDA) and in December of the same year also by the European Medicines Agency (EMA) for OIT in FA (peanut) treatment.[80] Two main studies investigated the safety and efficacy of AR101 in children (4–17 years), with peanut allergy in North America and Europe.[81,82] At the exit DBPCFC, a significant rate of patients in the active group (58%–67%) tolerated doses of 600 mg or 1000 mg peanut protein but not in the placebo group. In a large meta-analysis, there was no evidence that the use of proprietary pharmacy-grade products was associated with greater efficacy or safety compared with studies using grocery-bought peanut product. The meta-analysis showed that risk ($p < .05$, RR 3.12, 95%CI 1.76–5.55) and frequency ($p < .05$, RR 2.72, 95%CI 1.57–4.72) of

anaphylaxis during peanut OIT was irrespective of the formulation was a proprietary product or not.[78]

Clinical practice guidelines, including those upcoming from the GA2LEN Task Force, recommend that the choice of product for OIT should thus be guided by affordability, quality of an alternative, risk–benefit, patient preference and local context should also be taken into consideration.[83]

To improve the safety profile of FA-AIT, alternative routes (such as epicutaneous and sublingual) have been investigated.[28] These use minute amounts of allergen that carry a very low risk of systemic reactions. However, they do not raise the reactivity threshold in the short term or as high as OIT would while taking the daily maintenance dose. Notwithstanding, they appear to induce comparable changes in the allergen immune response over time, which suggest they could potentially offer the same long-term benefits once off therapy. This will need to be formally assessed in head-to-head trials specifically designed to assess sustained tolerance. The GA2LEN group indicates that epicutaneous immunotherapy (EPIT) probably increases the proportion able to tolerate peanut during therapy ($p < .05$, RR 2.6, 95%CI 1.8–3.8, moderate certainty) and sublingual immunotherapy (SLIT) may result in a large increase in the proportion able to tolerate peanut during therapy ($p < .05$, RR 4.7, 95%CI 1.6–13.8, low certainty). It is unclear whether subcutaneous immunotherapy has any impact because the certainty of evidence was very low.[28] The GA2LEN Task Force suggests offering peanut epicutaneous immunotherapy under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4–11 years with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy. However, this task force makes no recommendation for or against offering: epicutaneous immunotherapy to adolescents or adults with IgE-mediated peanut allergy or to people of any age with IgE-mediated cow's milk or hen's egg allergy; subcutaneous immunotherapy or sublingual immunotherapy to people of any age with IgE-mediated peanut, cow's milk or hen's egg allergy.

In order to reduce the limits of FA-AIT, many studies focussed on the association with biologicals with promising results (as described below). Probiotics have been also investigated but more studies are needed.[70]

3.3 | Biological as monotherapy or as adjunctive therapy of OIT

In 2003, Leung et al. reported the first evidence on the potential clinical benefit of a biologic drug in FA patients.[84] TNX-901, an anti-IgE monoclonal antibody, was shown in a double-blind, randomized, dose-ranging trial to increase the reactivity threshold significantly and substantially on OFC in 84 peanut-allergic patients. TNX-901 development in FA was halted due to legal dispute, and subsequent studies have focussed on omalizumab.[85–87] Omalizumab (Xolair®) is an immunoglobulin G1 (IgG1) anti-IgE humanized monoclonal antibody developed by recombinant DNA techniques (anti-IgE mAb) omalizumab binds to the IgE constant Cε3 region of free circulating IgE and prevents the latter from binding to the high-affinity FcεRI receptors on effector cells (primarily basophils and mast cells), interfering with degranulation and release of pro-inflammatory mediators.[88]

More recently, it has been shown that, in addition to binding free IgE, omalizumab can actively displace IgE from its high-affinity receptor and that this effect is dependent on the absolute concentration of omalizumab.[89] Finally, a third mechanism of action, which is particularly relevant in the context of FA, is the creation of IgE-omalizumab complexes themselves. Because the Fab portion of the IgE molecule is still functional, it is able to bind the allergen circulating in the bloodstream and thus compete for the same epitopes as cell-bound IgE, preventing their cross-linking.[90] This mechanism is particularly relevant to prevent systemic reactions in the context of FA.

In 2011, Sampson et al., developed a 4-week, double-blind, placebo-controlled, multicentric study in peanut allergic adolescents and adults testing omalizumab as monotherapy (Table 2). Nine of nine omalizumab-treated participants improved 80.9-fold their tolerated dose of peanut proteins at the week 24 peanut OFC compared with the baseline peanut OFC, whereas only a 4.1-fold improvement was observed in the 5 patients in the placebo group.[85] In 2012, Savage et al., demonstrated with an open label study the efficacy of omalizumab as monotherapy in 14 peanut allergic patients (median age of 23 years): after 6 months of treatment, the median cumulative eliciting dose of peanut protein significantly increased from 80 mg (range, 30–380 mg) to 6500 mg (range, 1830–10,000 mg).[86] In 2019, Fiocchi et al. with a single-centre, real-life, retrospective observational study provided additional real-world insight into omalizumab's potential to shift eliciting allergen thresholds and induce clinically meaningful levels of desensitization to multiple culprit foods when used by itself.[87]

In 2021, Azzano et al. investigated the determinants of the dose-related effect of omalizumab on the reactivity threshold prior to OIT in a large cohort of 181 patients. They report that the effect of omalizumab was dependent on its dosage per weight but independent of the classical dosage per weight and IgE used in asthma. More precisely, the reactivity threshold was shown to increase with lower concentration of free specific IgE, higher concentration of free omalizumab and higher concentrations of specific IgE-omalizumab complexes.[92] Omalizumab has shown to accelerate OIT to several foods with increased safety by reducing the number of adverse events and their severity.

In a phase 1 study, Begin et al. demonstrated that rush OIT to multiple foods with 16 weeks of treatment with omalizumab could allow for a fast desensitization in subjects with multiple food allergies. Nineteen of 25 participants tolerated up to 1250 mg of combined food proteins, requiring minimal or no rescue therapy.[93]

To date, there are three completed clinical trials on the use of omalizumab as adjuvant to OIT. Wood et al. ($n = 57$; 1:1) studied omalizumab during a slow milk OIT schedule and found rates of sustained unresponsiveness (48% vs. 36%) and desensitization (89% vs. 71%) to be comparable with placebo at 2 years. However, they

TABLE 2 Summary of findings from the most relevant studies evaluating the use of omalizumab in food allergy

Treatment	Study (first author, year of publication)	Design and population	Main findings
Omalizumab as monotherapy	Sampson et al., 2011[80]	4-week, double-blind, placebo-controlled, multicentre study in peanut allergic adolescents and adults testing omalizumab as monotherapy	The study intended to randomize 150 subjects, but enrolment was interrupted early because of the severity of two anaphylactic reactions that occurred during the screening OFCs before the administration of omalizumab. 14 participants (9 omalizumab and 5 placebo) completed the trial. Omalizumab-treated participants experienced an 80.9-fold improvement in the tolerated dose of peanut proteins at the week 24 peanut OFC compared with the baseline peanut OFC, whereas only a 4.1-fold improvement was observed in the placebo group
	Savage et al., 2012[81]	Open label study in 14 peanut allergic patients (median age, 23 years) undergoing omalizumab as monotherapy for 6 months	After 6 months of treatment, the median cumulative eliciting dose of peanut protein significantly increased from 80 mg (range, 30–380 mg) to 6500 mg (range, 1830–10,000 mg)
	Fiocchi et al., 2019[4]	Single-centre, retrospective observational study in 15 paediatric patients (median, range; 144, 96–276 months) undergoing Omalizumab as monotherapy for 4 months	After 4 months of omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested. Overall, the median (interquartile range) eliciting threshold in mg of protein was 460.8 (31–1740) at baseline, which improved to 8192 (5568–10,400) after treatment, representing a statistically significant improvement for egg, milk, baked milk, and wheat. 9/15 were able to tolerate without clinical manifestations a full serving size amount of all the foods tested, two others were able to do so to at least one of the foods tested, and four partially improved. In the 11 patients who consumed the full challenge amount without clinical manifestations, the previously allergenic food was added to the diet. Furthermore, patients improved their HRQoL (PedsQL instrument), and reduced symptomatic accidental food allergen exposures
Omalizumab + OIT	The PRROTECT study (Peanut Reactivity Reduced by Oral Tolerance in an Anti-IgE Clinical Trial)[87]	Double-blind, placebo-controlled clinical trial with omalizumab at 4 centres to safely and rapidly desensitize patients with severe peanut allergy	40 high-risk subjects with peanut allergy between 7 and 18 years of age. Those treated with omalizumab were able to undergo a rapid OIT and to tolerate doses of peanut 10 times higher than those treated with placebo
	Wood et al., 2016[88]	Randomized, double-blind, placebo-controlled study, 57 milk allergic subjects randomized to omalizumab or placebo	Open-label milk OIT was initiated after 4 months of omalizumab/placebo. At month 28, omalizumab was discontinued, and subjects passing an OFC continued OIT for 8 weeks, after which OIT was discontinued with rechallenge at month 32 to assess sustained unresponsiveness. They found rates of sustained unresponsiveness (48% vs. 36%) and desensitization (89% vs. 71%) to be comparable to placebo at 2 years. However, they found that omalizumab suppressed systemic reactions to OIT
	MacGinnitie et al., 2017[91]	Randomized, double-blind, placebo-controlled study, 37 peanut allergic subjects were randomized to omalizumab or placebo	At 14 weeks, 79% could tolerate 2 g of peanut proteins, compared to 12% in the placebo group (RR = 6.6), with 7% and 75% protocol failures (RR = 0.09), respectively

(Continues)

TABLE 2 (Continued)

Treatment	Study (first author, year of publication)	Design and population	Main findings
	Azzano et al., 2020[85]	Multi-centre, retrospective observational study in 181 food-allergic patients receiving omalizumab as pre-treatment for OIT	The dose-related effect of omalizumab monotherapy on food reactivity threshold was shown to be independent of its dosage per weight and IgE, as per the asthma monograph, but to rather depend on its dosage weight only

found that omalizumab suppressed systemic reactions to OIT.[94] MacGinnitie et al. (n = 37; 3.5:1) tested omalizumab as an adjunct to an accelerated peanut OIT schedule. At 14 weeks, 79% could tolerate 2 g of peanut proteins, compared with 12% in the placebo group ($p < .01$, RR = 6.6).[91] Andorf et al. also tested omalizumab to placebo as adjunct to an accelerated schedule of multi-food OIT. At 28 weeks, 83% vs. 33% could tolerate 2 g proteins of at least two foods (RR = 2.5). At 8 weeks, there were 8% vs. 67% treatment failures in each group, respectively (RR = 0.12).[95] In August 2018, the FDA granted Breakthrough Therapy Designation for omalizumab for the prevention of severe allergic reactions following accidental exposure to one or more foods in people with allergies.[96]

There are currently three randomized clinical trials assessing the efficacy of omalizumab in FA. The OutMATCHT trial (Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy in Food-Allergic Children and Adults), sponsored by the National Institutes of Allergy and Infectious Disease through the Consortium of Food Allergy Research[97]; the BOOM trial (an 18 months, double-blind, randomized controlled trial comparing an accelerated OIT protocol enabled by 17 weeks of Omalizumab to standard schedule OIT in subjects aged 6 to 25 years with Multiple food allergies), in Canada[98]; and the TOFAC trial (Treatment with Omalizumab in Food-Allergic Children) in Denmark.[99]

Ligelizumab, a new, more potent anti-IgE monoclonal antibody, is currently being developed for this indication. In previous phase 2 trials for asthma, ligelizumab was shown to suppress skin tests, while omalizumab did not, thus suggesting an even greater potential at preventing anaphylaxis. The development of ligelizumab for asthma was halted following a negative trial, in severe asthma.[100] The failure of omalizumab to beat placebo in the same trial may suggests a potential flaw in design or patient selection. Regardless, ligelizumab went on to be studied in chronic urticaria,[101] where it was shown superior to omalizumab. As currently being investigated in FA as a monotherapy, if found even more effective than omalizumab, this molecule could potentially transform the management of patients with severe and multiple FA in the coming century.

Dupilumab is another biologic currently investigated for the treatment of FA, with/without concomitant OIT. Dupilumab is an anti-IL4/13 mAb approved for the treatment of type 2 asthma,[102] nasal polyposis[103] and atopic dermatitis.[104] An ongoing trial is assessing the tolerability of peanut protein in paediatric patients (6–17 years old) treated with dupilumab as monotherapy.[105] A phase 2, multicentre, randomized, double-blind, parallel group, 2 arm study in approximately 40 subjects, aged 4 to 50 years, allergic to cow's milk is evaluating dupilumab as an adjunct to milk oral immunotherapy compared to placebo.[106]

However, by affecting type 2 cellular immunity, it is hoped that it may stop the atopic march and prevent FA in high-risk infants. It is also of great interest in non-IgE-mediated food allergies. Phase 2 and phase 3 trials have found it effective for the treatment of eosinophilic oesophagitis, and there are case reports of successful use in eosinophilic gastroenteritis secondary to type 4 food allergies.[92,93]

On the contrary, mepolizumab, an anti-IL5 mAb, was found ineffective at improving eosinophilic esophagitis signs and symptoms despite reducing the number of eosinophils on biopsies.[107] This suggests that eosinophils may only be an epiphenomenon of type 2 inflammation without a key role in the disease.

Tezepelumab is another candidate for preventing sensitization and treating type 2 inflammation. It is currently studied for asthma with good results, but it is too early to tell if it will be of use for FA.

Unfortunately, the long-term treatment, the very high cost of biologics, as well as the lack of indication for FA create new challenges in terms of access and sustainability.[108]

In summary, new generation of treatments is emerging for IgE-mediated food allergy, using different approaches. Clinical trials of these promising new treatments are underway or planned by pharmaceutical, medical or academic entities, but currently are doing so without achieving consensus on how best to measure clinical effectiveness. There is no agreed set of 'core outcomes' for evaluating these new treatments. Core outcome sets would ensure that trial outcomes are relevant to different stakeholders; and allow to combine evidence in meta-analysis.[109]

3.4 | Patient's involvement

In the 21st century, the role of the individual and his/her well-being have been recognized as central in the management of chronic diseases, including FA.[110] Suffering from FA can impact adversely on several aspects of the individual and social life. Psychological distress is largely driven by the persistent fear of an adverse reaction.[111] Moreover, FA was linked to post-traumatic stress symptoms,[112] and bullying.[113] These factors may indirectly provoke social exclusion, for example from events, restaurants, or specific social activities.[114]

The use of patient-reported outcomes measures (PROMS) such as HRQoL is key to a patient-centred and integrated perspective, together with improved care and outcomes. In this century, the Food Allergy Quality of Life Questionnaires (FAQLQ) have been

developed, validated and recommended as gold standard tools by the EAACI to assess FA-HRQoL.[115] Individuals diagnosed with FA must have the emotional resources to cope with the many challenges that arise from self-management tasks and the social limitations that FA presents. To evaluate the heightened emotions due to FA, in 2021 Coelho et al.[116] adapted the Positive and Negative Affect Schedule (PANAS), one of the most used questionnaires available to measure mood or emotion world-wide, for a population of individuals with FA. Identifying which emotions are related to suffering from FA will help to provide an environment that focuses or promotes these emotions to enhance individual well-being.

In 2022, the same group[117] individuated coping as one predictor of FAQL and adapted the widely used Coping Orientation to Problems Experienced (COPE) Inventory to FA (named FA-COPE Inventory) to facilitate the identification of the most commonly used strategies to deal with FA.

Beyond the use of patient-reported outcome, the concept of patient-centred care implies the inclusion of individual patient preferences in medical decisions. With the new therapeutic options, the number of potential decisions is expected to increase exponentially, the implications of which may be difficult to understand for patients. New shared decision-making tools have started to be designed and are likely to become an important part of food allergy practice in the near future.[118]

Several health systems world-wide consider integrated care as a potential solution to the growing request for improved patient experience and health outcomes (Figure 1). An integrated care requires a multi-disciplinary approach and aims to patient engagement and active involvement of patients in their treatment and care.[115] Furthermore, EAACI guidelines for the management of patients with allergies[119] remark that the interaction between the healthcare professionals and the patients themselves can ensure maximum support for people with allergies.

In addition, a proper education, including information on dietary avoidance strategies, a detailed action plan and epinephrine training, and shared decision-making for individuals with FA and their families is crucial to support a correct management of FA at individual and societal level.[28,46]

Patients suffering from allergic diseases may benefit from mobile health (mHealth) innovations the EAACI created a task force to assess the state of the art as well as the future potential of the information and communication technology (ICT) in the field of allergy.[120] MHealth could have a significant impact on the diagnosis and management of food allergy and anaphylaxis. It could support patients for the documentation of symptoms. Furthermore, apps support allergy patients in the selection of appropriate products, based on their specific allergen profile (eg, FoodMaestro App®, ShopWell®, ipiit®, and others). Automatic alerts signalling to the patient the expiration of his/her adrenalin autoinjector have already been successfully used.[121] However, clinical validation of high-quality tools is necessary before their distribution in order to avoid overdiagnosis and the occurrence of avoidable reactions due to inaccurate information. Close collaboration between the different stakeholders and further research are urgently needed.

3.5 | Severity assessment

A proper management of FA requires a preliminary accurate assessment of the severity of both FA as a whole disease and of any future allergic reactions to ensure decisions are personalized and cost-effective.

The lack of a univocal consensus on the definition of anaphylaxis can lead to an inappropriate treatment.[122]

Recently, the prevalence of severe or protracted anaphylaxis to foods has been investigated. In 2021 a systematic review of 86 studies published between 1946 and 2020 which reported at least 10 or more anaphylaxis events due to food or venom. Of the more than 36,000 events captured, 7.7% were treated with multiple does of epinephrine, suggesting that this outcome was relatively rare.[123]

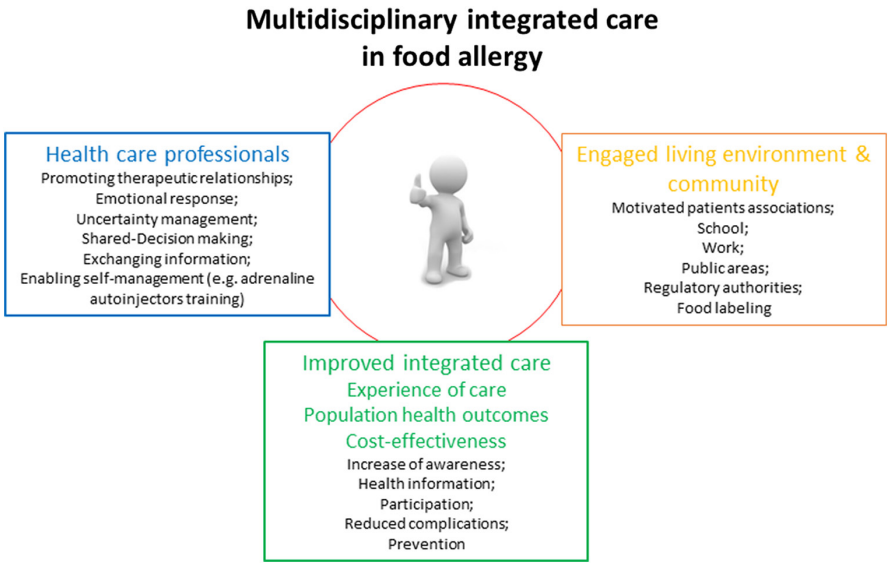


FIGURE 1 Multidisciplinary integrated care in food allergy—adapted from EAACI guidelines for the management of patients with allergies.[119]

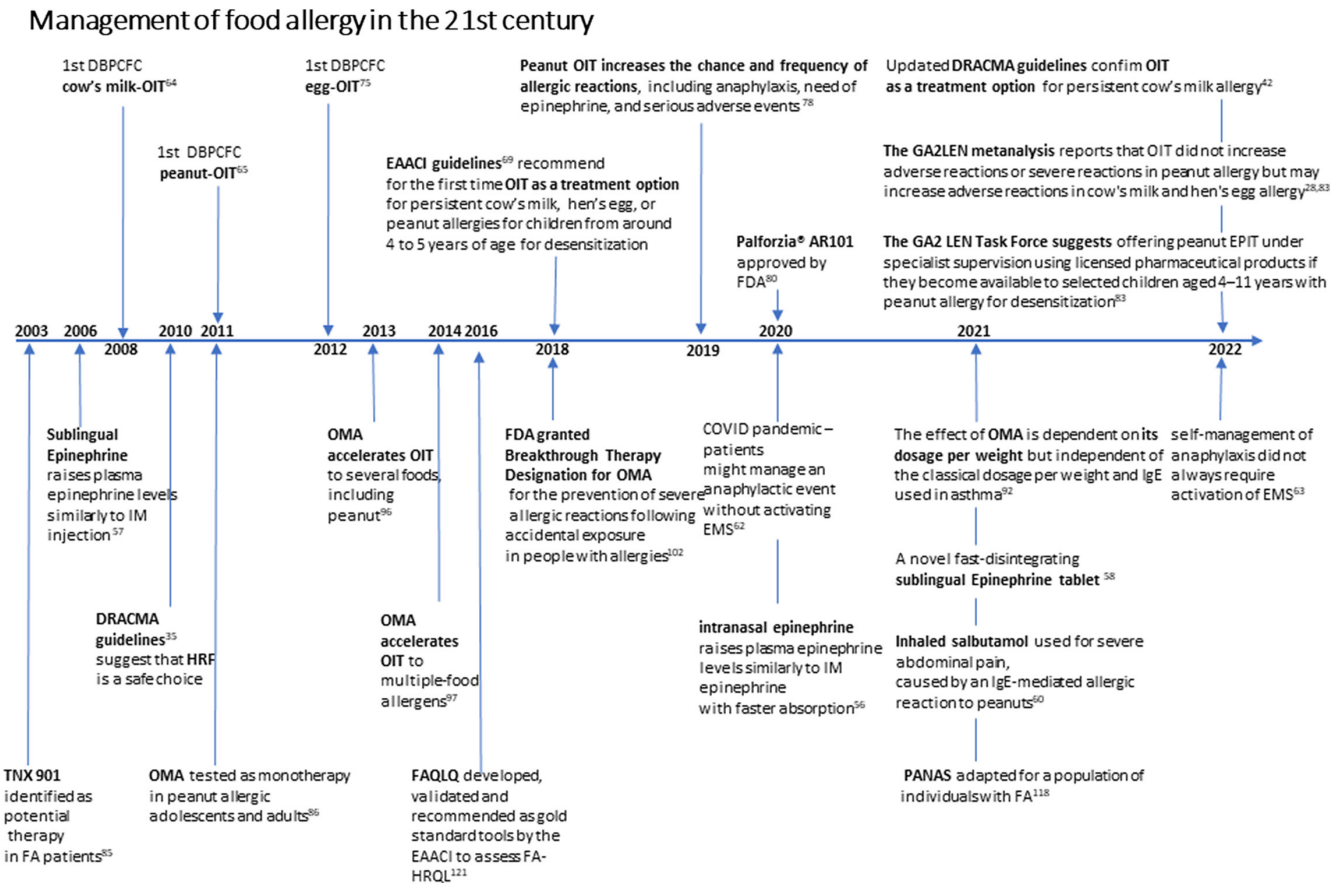


FIGURE 2 Milestones in the management of food allergy in the 21st century. DBPCFC, double-blind placebo-controlled food challenge; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy; EMS, Emergency Medical Services; EAACI, European Academy of Allergy and Clinical Immunology; FA, food allergy; FAQLQ, Food Allergy Quality of Life Questionnaires; FA-HRQL, Food Allergy Health Related Quality of Life; FDA, Food and Drug Administration; HRQL, Health Related Quality of Life; OFC, oral food challenge; OIT, oral immunotherapy; OMA, omalizumab; PANAS, Positive and Negative Affect Schedule; pts, patients; POIT, peanut oral immunotherapy; SU, sustained unresponsiveness.

In 2022, a metanalysis has assessed the risk factors for severe and/refractory to treatment anaphylactic reactions in FA.[124] Specifically, authors showed that prior anaphylaxis,[125] an asthma diagnosis,[126] IgE sensitization profile or basophil activation tests[127] are not good predictors. However, some IgE components may be suggestive of a higher risk of severe reaction, for example Pru p 3 for peach,[128] and the 2S albumins in tree nut allergy,[129,130] although this may be region-dependent. Risk of severe outcomes is higher in adolescence and young adulthood, although the contribution of risk taking behaviour in conducing to severe outcomes is unclear.[131] For this reason, age-specific approaches are required.[49] Evidence for an impact of cofactors on severity is missing.[132] In the coming years, efforts will be devoted to identifying good predictors of severe reactions.

Based on current evidence[13,133] including a preliminary systematic review,[12] an international multidisciplinary panel of experts is going to submit the DEFASE (DEfinition of Food Allergy Severity) score which is the first consensus for the definition of the severity of FA in children and adults. It will include symptom- and non-symptom- related domains. To consider the HRQoL and the economic aspects, together with the symptom-specific metrics will ensure a more patient-centred perspective, particularly given the limitations of current predictors. We expect the DEFASE score will be useful for orienting the levels of diagnostic, management and therapeutic commitment in FA patients in the various geographical contexts. Soon, research should focus on external validation of scoring systems, tailoring of these models to different food allergenic sources, populations, and settings. In addition, as a gold standard, a standardized, harmonized, consensus-based severity scoring system for food allergy needs to be tested for reliability and validity in a range of settings and populations.

4 | CONCLUSION AND FUTURE PERSPECTIVES

The 21st century has seen relevant advances in the management of FA so far (Figure 2). We foresee that in the coming years the drugs currently in pre-clinical or early clinical evaluation will finally allow the possibility of safe and effective therapies for FA in clinical

practice. Specifically, ongoing studies testing biologics will offer therapeutic options as monotherapy or in addition to immunotherapy. The identification of reliable biomarkers and the development of standardized approaches for phenotyping FA may lead to individualized approaches to management of food allergy. Standardized and validated definitions and measurement approaches, alongside shared decision-making with patients and families, will allow for more targeted support and guidance and help to minimize the substantial burden of FA.

In conjunction with standards of care, it is prudent that a multipronged approach towards provision of composite, culturally tailored, supportive interventions targeting demographic variables at the individual level is needed, but this requires further research and validation.[134]

AUTHOR CONTRIBUTIONS

Stefania Arasi conceptualized the structure of the review. All authors identified relevant literature for inclusion. Stefania Arasi, Philippe Begìn, Arianna Cafarotti, Mattia Giovannini contributed to original draft. All authors contributed to critical review of the manuscript, with relevant edits and expert opinion from specialist perspective. All authors approved the final manuscript as submitted.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

All data on which the manuscript is based on are presented within text and tables appropriately referenced.

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