ABOUT THE AUTHORS

Julie Wang, MD

Dr. Julie Wang is Professor of Pediatrics in the Division of Allergy and Immunology at the Icahn School of Medicine at Mount Sinai. Her research focuses on clinical trials investigating novel food allergy therapies, food allergy management, and anaphylaxis in schools. She serves on the Joint Task Force on Practice Parameters, is Chair of the Executive Committee, Section on Allergy and Immunology of the AAP, and serves on the Editorial Board of the Journal of Allergy and Immunology and Journal of Allergy and Immunology: In Practice. She is co-program director for the Mount Sinai Allergy and Immunology Fellowship Training Program.

Shouling Zhang, MD

Shouling Zhang is currently a second year clinical fellow in allergy and immunology at Icahn School of Medicine at Mount Sinai. She graduated from University of Rochester with a dual degree in Biological Sciences: Microbiology and Psychology. She went on to receive her medical degree at Stony Brook University School of Medicine and completed her residency training in pediatrics at Cohen Children's Medical Center in New York. Her interests include clinical research and practice, with a special interest in food allergy and childhood atopy.

COMPONENT DRIVEN ORAL FOOD CHALLENGES IN THE COMMUNITY

The diagnosis of immunoglobulin E (IgE) mediated food allergy is based on the clinical evaluation of a patient's history, physical examination, and specific test results.[1] These tests may include skin prick testing, serum IgE testing, and/or oral food challenge (OFC).[1] Component-resolved diagnosis (CRD) targeting specific allergenic proteins in a food has the potential for improved diagnostic accuracy compared to serum IgE testing to whole allergens.[1-3] An overview of the clinical considerations of how and when to proceed with an OFC will be outlined in this review, with special consideration given to the utility of component testing in making this determination.

Oral food challenges "OFCs" are indicated when the diagnosis of a food allergy is unclear or to assess the resolution to a specific food allergy.[1, 4, 5] Careful consideration of multiple factors is involved when deciding to proceed with an OFC. For instance, the importance of the food in the diet and whether it is likely to be integrated in the diet, are considerations that influence if and/or when a food challenge may occur.[5] Guidance from an individual's history of clinical reactivity, test results, and shared decision making between the patient and provider are needed.[1, 4, 5] A risk-benefit assessment of the possibility of allergic reaction versus the benefit of potentially adding the food into the diet should be discussed between the patient/family and physician.[5] Being familiar with indications for when to offer an OFC is the foundation for allergists to facilitate safe, relevant, and targeted food introduction.[4, 5]

Component testing is a recent and innovative approach that offers additional insights into food allergy diagnosis and management.[1-3] CRD uses recombinant allergens to assess for serum IgE (sIgE) binding to individual proteins within an allergenic food, rather than to a mixture of proteins in an allergen extract, thus distinguishing between sensitization to relevant allergens versus other cross-reactive proteins.[1, 2] CRD testing for plant-derived and animal-derived food allergies are available and can help further guide OFC selections.[6, 7]

For plant-derived food allergies, pollen cross-reactivity should be considered when deciding if an OFC should be offered. In individuals with pollen sensitization, ingestion of plant-derived foods may result in localized symptoms of the oropharyngeal area (i.e., oral allergy syndrome/pollen-food allergy syndrome). This occurs when individuals are sensitized to pollen allergens that cross-react with food allergens including profilins or pathogenesis-related class 10 (PR-10) proteins which are homologous to white birch pollen antigen (*Betula verrucosa* 1 or Bet v 1).[8, 9] These proteins are heat-labile so fruits or vegetables in the raw form trigger symptoms.[10] Without pollen sensitization, allergies to plant-derived foods are due to primary sensitization to more stable proteins, including nonspecific lipid transfer or seed storage proteins, which are more often implicated in systemic allergic reactions and/or anaphylaxis.[11]

In peanut allergy, several studies support the use of CRD.[1, 12] Persistent peanut allergy is associated with detectable IgE levels to specific

seed storage proteins; IgE to Ara h (*Arachis hypogaea*) 2, has been found to be the most predictive component of clinical allergy, outperforming that of whole peanut extract alone.[12-17] Ara h 2 IgE has the greatest specificity in confirming the diagnosis of peanut allergy, and is considered cost-effective.[12] Although an Ara h 2 IgE value of >0.35 kU/L is considered significant, there is no established cutoff level for Ara h 2 IgE, or any peanut component, that seamlessly differentiates between allergy and sensitization at this time.[12] Severe reactions to peanut have been associated with an Ara h 2 IgE level of 2 kU/L or higher, but these cutoffs are limited by low sensitivity (0.78) and specificity (0.45).[12] A recent prospective multicenter study from Germany in which 210 children were challenged orally with peanut estimated a 90% probability for a positive peanut challenge with an Ara h 2 IgE value at 14.4 kU/L, and a 95% probability of reactivity at 42.2 kU/L.[18] Hemmings et al. found that IgE to Ara h 2 and Ara h 6 in isolation were most predictive of peanut allergy, but that a IgE to a combination of allergen components (Ara h 1, 2, 3, and 6) was superior to individual peanut components.[19] Thus, the overall mosaic of specific component proteins may be useful in determining which individuals may have increased risk of allergic reaction, especially when considering IgE binding to Ara h 2.[13, 19] In contrast, sensitization to Ara h 8, which is homologous to Bet v 1, is associated with low risk of clinical reactivity to peanut, and may be considered an indicator for favorable OFC outcome in select individuals without significant sensitization to Ara h 2.[20] Component testing can be helpful for individuals with minimal or no prior reaction history, birch sensitization, older age, and for those with low peanut IgE levels (0.35-15 kU/L).[21] Component testing is less informative with a clear history of recent reaction, lack of birch sensitization, younger children, and/or a remote history of reaction with peanut IgE level ≥15 or levels >25 and <0.35 kU/L.21 While CRD for peanut, especially Ara h 2, has improved the diagnostic accuracy beyond the use of peanut extract alone, it should not replace clinical history and OFC, as there are no universal cutoffs for clinical reactivity.[1, 12, 22]

Component testing is also available for many tree nuts, including cashew, hazelnut, walnut, and Brazil nut. IgE to Ana o 3 (2S albumin protein) is predictive of cashew allergy, and better than cashew-IgE alone.[23, 24] Previous studies have identified the optimum cutoff for the 2S albumin protein, Ana o 3, between 0.16-0.70 kU/L when considering OFC.[25, 26] For hazelnut, sensitization to Cor a 9, an 11S globulin, and Cor a 14, a 2S albumin, are specific for severe food challenge reactions.[27, 28] IgE cutoffs in children for severe hazelnut allergy have been suggested as ≥1 kU/L for Cor a 9 and ≥5 kU/L for Cor a 14.[28] In a German cohort, a 90% probability for a positive hazelnut challenge was estimated for Cor a 14 IgE at 47.8 kU/L.[18] However, Cor a 1 is a heat-labile protein similar to birch pollen that is usually associated with localized oropharyngeal symptoms or hazelnut tolerance, and thus sensitization may indicate a favorable OFC when elevated in isolation.[29] Major walnut (*Juglans regia*, Jug r) allergens include Jug r 1, 2, 3, 4, and 6 and Jug r 5 and 7 are pollen-related. IgE to Jug r 1 and/or Jug r 4 are most predictive of clinical allergy.[30, 31] A prospective cohort study of adults with suspected walnut allergy in the Netherlands found that Jug r 1 had the best discriminative ability to separate between walnut-tolerant and walnut-allergic individuals, compared to Jug r 2 or 3, among a series of double-blind placebo-controlled food challenges to walnut.[32] In this cohort, a cutoff of 1.49 kUA/L (ImmunoCAP Jug r 1) or 2.85 kUA/L (ImmunoCAP ISAC Jug r 1) had a 100% positive predictive value and specificity.[32] A cutoff of 0.1 kU/L (ImmunoCAP Jug r 1) had 91% positive predictive value and specificity (**Table 1**).[32] For Brazil nut, Ber e 1 has been identified as the major allergen, with an optimum cut off as 0.25 kU/L in one UK study of 36 patients with suspected nut allergy.[33] While the role of CRD in tree nuts allergy diagnosis is still being investigated, these studies, many from Europe, illustrate the predictive values of IgE to Ana o 3 (cashew), Cor a 9 and 14 (hazelnut), Jug r 1-4 and 6 (walnut), and Ber e 1 (Brazil nut) in assessing clinical allergy.

Additional plant-derived food allergies with identified component proteins include wheat and soy, however sensitization to these allergens is not consistently associated with clinical allergy or reaction severity.[30, 34] An exception is wheat-dependent exercise-induced anaphylaxis, where IgE to omega-5-gliadin (Tri a 19) has been implicated in clinical reactivity.[35, 36] An optimal cutoff of 0.53 kU/L for omega-5-gliadin IgE has been suggested with an 88% positive predictive value for reactivity, but only 65% specificity.[37] Soy allergens include Gly m 4, Gly m 5, Gly m 6, and Gly m 8.[38] Among these, an optimal IgE cutoff for clinical reactivity has been suggested for Gly m 8 at 3.55 kU/L, however this component has equal sensitivity as soy skin prick test (SPT) or soy IgE.[38] In addition, cross-reactivity of legumes is rare, so legumes (peanut, soybean, green bean,

FOOD	CUTOFF sIgE LEVEL (kU/L) FOR CONSIDERING OFC	STUDY
Milk	BAKED MILK: **Casein IgE:** 4.95 kU/L Milk IgE: 9.97 kU/L	Caubet et al. 2013 [43]
Egg	BAKED EGG: **Ovomucoid IgE:** 1.16-50 kU/L	Bird et al. 2020 [5] Ando et al. 2008 [50] Lemon-Mulé et al. 2008 [51] Caubet et al. 2012 [52] Bartnikas et al. 2013 [53] Saifi et al. 2016 [54]
Wheat	**Omega-5-gliadin (Tri a 19):** 0.53 kU/L	Shibata et al. 2011 [37]
Soy	**Gly m 8:** 3.55 kU/L	Kattan et al. 2015 [38]
Peanut	**Ara h 2:** 2 kU/L – associated with severe reaction 14.4 kU/L – 90% probability of positive OFC 42.2 kU/L – 95% probability of positive OFC	Greenhawt et al. 2020 [12] Beyer et al. 2015 [18]
Cashew	**Ana o 3:** 0.16-0.70 kU/L	Savvatianos et al. 2015 [25] Sato et al. 2019 [26]
Hazelnut	**Cor a 9:** ≥1 kU/L **Cor a 14:** ≥5-47.8 kU/L	Masthoff et al. 2013 [28] Beyer et al. 2015 [18]
Walnut	**Jug r 1** (ImmunoCAP): 1.49 kU/L – 100% positive predictive value and specificity **Jug r 1** (ImmunoCAP ISAC): 2.85 kU/L – 100% positive predictive value and specificity **Jug r 1** (ImmunoCAP): 0.1 kU/L– 91% positive predictive value and specificity	Blankestijn et al. 2017 [32]
Brazil nut	**Ber e 1:** 0.25 kU/L	Rayes et al. 2016 [33]

Table 1: Food Allergen Components and Proposed Cutoff Levels for Clinical Reactivity from Selected Studies

pea, and lima bean) should be considered individually.[39]

CRD has also been used for animal-derived food allergies including milk, egg, shrimp, and red meat. For milk, casein (*Bos domesticus* or Bos d 8) is the major cow milk allergen accounting for up to 80 percent of protein and more severe reactions.[40, 41] Beta-lactoglobulin and alpha-lactalbumin are less clinically relevant. Most milk-allergic children are able to tolerate baked or extensively heated milk.[42] OFC to baked milk should be considered in individuals with favorable history and testing, especially those with favorable casein IgE levels, ideally below 4.95 kU/L when considering both sensitivity and specificity (74% sensitivity, 77% specificity), and with favorable milk IgE levels below 9.97 kU/L (62% sensitivity, 85% specificity).[43] In a small retrospective study, SPT to milk commercial extract was more helpful than a casein SPT and milk IgE levels in determining OFC outcomes.[44] Another retrospective study showed that IgE to milk (p=.011) outperformed a SPT to milk extract (p=.031) and a SPT to fresh milk (p=.473) as the best predictor of baked milk tolerance, suggesting that CRD may not be helpful.[45] Overall, additional data is needed to assess the role of CRD in milk allergy. Other studies that explored the use of boiled milk-specific IgE, cow milk IgE, casein IgE, SPT, and the ratio of specific IgE to total IgE for milk in predicting baked milk OFC outcome have not confirmed their superiority to CRD in diagnostic accuracy.[46-48]

For egg, IgE to ovomucoid (*Gallus domesticus* or Gal d 1) is the best predictor of egg allergy and baked egg tolerance.[49, 50] Similar to milk, most egg-allergic individuals tolerate baked egg.[51] Cutoffs for ovomucoid sIgE that are predictive

of baked egg reactivity range from 1.16-50 kU/L.[5, 50-54] Ovomucoid IgE levels appear to have the greatest predictive value in assessing clinical reactivity to baked egg, and undetectable levels are associated with less than a 10% chance of reactivity to extensively heated (baked) egg.[51]

For shrimp, tropomyosin (*Penaeus monodon* or Pen m 1 and *Penaeus aztecus* or Pen a 1) is the major allergen, and cross-reactivity exists between shrimp and environmental allergens such as cockroach and dust mite.[55] Currently, there is not enough data to suggest that IgE to tropomyosin is predictive of shrimp OFC outcome.[56]

Alpha-gal allergy is a delayed, IgE-mediated, allergy in response to a carbohydrate moiety found in most mammals. Commercial tests for IgE to alpha-gal or galactose-alpha-1,3-galactose are available but have poor sensitivity and specificity, thus favoring fresh meat testing and/or food challenge instead.[57]

In summary, many advances in predicting clinical reactivity have emerged with CRD for both plant and animal-derived food allergies, especially with peanut allergy. **Table 1** summarizes proposed cutoff levels for offering OFC based on existing studies of food allergen components. Consideration of pollen sensitization, cross-reactivity of allergens, and overall trends of skin prick tests and/or serum IgE levels to whole allergen extracts with relevant component proteins are important factors in guiding OFC in practice. CRD is meant to supplement, not replace, a detailed clinical history. It is important to continue to focus on risk of reaction, patient/family preferences, and the nutritional value of a specific food when considering OFC. Staffing and adequate medical supplies in case of allergic reaction should be available for OFC. Ultimately, it is a multifactorial decision to offer and undergo an OFC that involves shared decision making between patient and provider.

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