

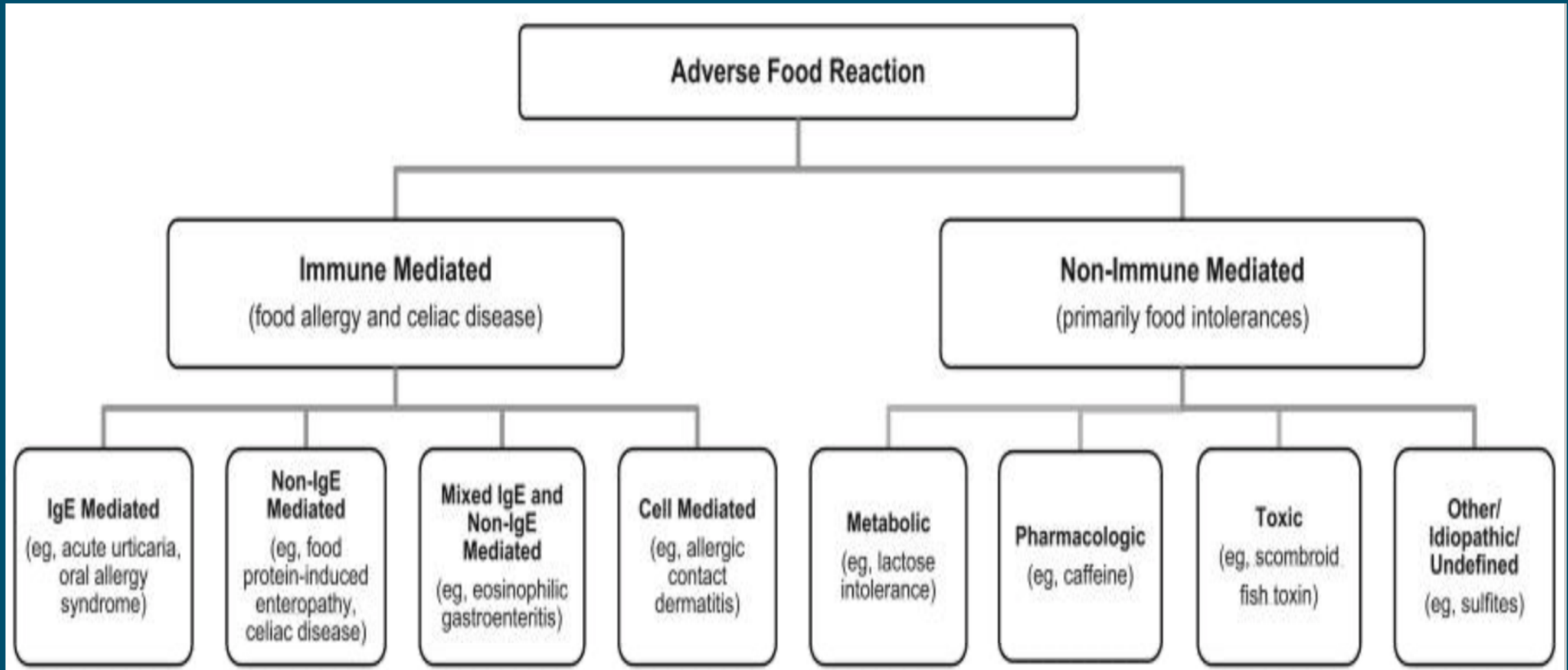
CLASP Co-Management: *Food Allergy-Diagnosis and Treatment*

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Objectives of CLASP Tool for Food Allergies

- To emphasize how common food allergies have become in children
- To identify the most common foods responsible for allergic reactions (sesame newly added to list)
- To distinguish between clinical IgE-mediated food allergies and sensitization to foods (based upon skin/blood tests alone) and need for food challenges
- To recognize that “food sensitivities” is not a meaningful term and does not have clinical significance
- To recognize that food anaphylaxis can occur in infants and that the anaphylaxis symptoms may differ considerably from that of older children and adults
- To know how to evaluate a food allergic child, avoiding general blood tests/food panels, and when is appropriate to refer to an allergy specialist
- To understand that diagnosis on the basis of specific blood testing is enhanced by measuring and understanding component testing
- To be aware that there are treatment modalities now available (OIT) for food allergic children aside from strict avoidance management strategy

Types of Adverse Food Reactions



NIAID-Sponsored Expert Panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58.

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Food Allergy Prevalence Trends

- Food allergy is common and affects up to 10% of children
- Food allergy prevalence appears to be increasing over the past 2-3 decades
- Data from the National Health Interview Survey showed an increase in food allergy prevalence from 1997-2011
- A 2013 review of the literature found an increase in self-reported food allergy of approximately 1.2% per decade with the greatest increase in non-Hispanic black children

JACI 2018;141:41-58; JACI 2011;127:668-76 *J Pediatr* 2017;190:93-9; NCHS Data Brief 2013;1-8;
Ann Allergy Asthma Immunol 112 (2014) 222e229

Food Allergy Prevalence of Specific Foods

| Food Allergy Prevalence of Specific Allergens* | | |
|--|--|--|
| | United States (%) | Worldwide (%) |
| Egg | 0.6-0.8% children (SR)(1% age 0-2) 0.5% adults (SR) | 1.2% (1-2yo; 0.1-2.2%) (CC) Australia 9% (CC) |
| Milk | 2% children (SR) 2.6% adults (SR) | Europe 2% (SR), 0.6% (0.3-1%) (CC) China 1.9% (SR) |
| Peanut | 1.2-2% children (SR) 0.6-0.8% adults (SR) | Europe 0.2%(CC), 1.6% (CC+RH) Low prev in Israel, Asia |
| Tree nuts | 1% (SR) | 0- 1.4% (CC); 0-4.9%(SR) |
| Fish | 0.2-0.4% children (SR) | Israel 0% (SR); Asia 0.2-4.3 (SR) Finland 9% (SR); ; Europe 0.2 % (CC) |
| Shellfish | 0.5-2% children (SR) 2% adults (SR) | Europe: Crustacean 0.1-5.5 (SR); mollusk 0.5-1.5 (SR) Asia: Crustacean 0.5-4 (SR) |

SR=self report; CC=challenge confirmed; RH=reaction history

*Dunlop JH, Keet CA. Immunol Allergy Clin N Am. 2018; 38; p13-25., Sicherer S, Sampson H. J Allergy Clin Immunol. 2018;141:41-48, Gupta RS, et. Al. Pediatrics. 2011; 128(1)e 9-17
 Sicherer SH, et. Al. J Allergy Clin Immunol 2010; 125 (6):1322-6. McGowan EC, Keet CA, et.al. J Allergy Clin Immunol 2013; 132(5): 1216-9.e5, Nwaru B, Hickstein L, et. Al. Allergy 2014; 69(8):992-1007,.
 McWilliam V, Koplin J, et. Al. Curr Allergy Asthma Rep 2015; 15(9):54, Xepapadaki, Fiocchi et al. Allergy 2016; 71(3):350-7, Osborne N, Koplin J, et. Al. J Allergy Clin Immunol 2011; 127(3):668-76.e 1-2,
 Shoemaker A, Sprickelman, et al. Allergy 2015; 70:963-72, Sicherer S, Munoz-Furlong, et. al. J Allergy Clin Immunol 2004; 114(1):159-65, Wu T, Tsai T, et. Al. Intern Med J 2012;42(12):1310-5,
 Moonesinghe H, MackenzieH, et. Al. Ann Allergy Asthma Immunol 2016;117(3):264-72.e4.

Diagnosis of Food Allergy: History

- History is key
 - Timing (minutes to a few hours)
 - Symptoms
 - Quantity and preparation of food (e.g. raw vs. cooked vs. baked)
 - Reproducibility
 - Treatment, resolution/outcome
 - Co-factors (exercise, alcohol, medications (e.g. NSAIDs))
- Testing serves to confirm suspected allergens based on history

Diagnosis of Food Allergy: Testing

- Skin prick testing and food-specific IgE testing
 - **Avoid** panel testing (poor positive predictive value → overdiagnosis, unnecessary avoidance)
 - Sensitization (+ test) alone is **not diagnostic without** history of clinical reaction
 - Larger wheals on skin prick test, higher values of food-specific IgE correlate with higher likelihood of reactivity (not severity of reaction)
 - Negative results- allergy unlikely
- Oral food challenge (See Bird JA et al, J Allergy Clin Immunol 2020; 8(1):75-90.e17)
 - If results indeterminate
 - If negative results but convincing history

Diagnosis of Food Allergy: Testing

TABLE I. Diagnostic cutoffs for specific IgE and skin prick testing with 95% positive predictive

| Foods | Specific IgE ^{1,5-8} | | Skin prick test ^{1,6,9} |
|-------------|--|---|---------------------------------------|
| | 95% PPV | 50% NPV | 95% PPV |
| Cow's milk* | 15 kU/L (32 also reported) Infants ≤2 y: 5 kU/L | 2 kU/L | ≥8 mm Infants ≤2 y: 6 mm |
| Egg* | 7 kU/L Infants ≤2 y: 2 kU/L | 2 kU/L | ≥7 mm Infants ≤2 y: 4-5 mm |
| Peanut | 15-34 kU/L | 2 kU/L if history of reaction 5 kU/L is no history of reaction | ≥8 mm Infants ≤2 y: 4 mm |
| Fish | 20 kU/L | — | |
| Tree nuts | 20 kU/L | | ≥8 mm for walnut ≥12 mm for cashew |
| Sesame | 50 kU/L (86% PPV) | | ≥8 mm |

NPV, Negative predictive value; PPV, positive predictive value.

*These numbers were derived from uncooked milk and direct egg and do not apply to baked milk or baked egg.

Negative results on skin prick testing (<3mm wheal diameter) and sIgE testing (<0.35 kU/L) has high NPV and sensitivity but poor specificity and PPV, *which can contribute to overdiagnosis and unnecessary avoidance*. Several studies have aimed to improve the diagnostic accuracy of these modalities by establishing 95% PPV cutoff points and 50% NPV cutoff points. These cutoff points vary by allergen and by age, with lower cutoffs in infants and young children 2 years of age or less. These values are not definitive, and individuals may tolerate foods despite results above the cutoffs. It's also important to stress that degree of elevation of test results does not correlate with reaction threshold or severity of reaction upon ingestion. A large proportion of results may fall between the PPV and NPV cutoffs, and OFC should be considered in such cases to clarify allergic status.

Diagnosis of Food Allergy: Component Testing

TABLE II. Proposed diagnostic cutoff levels and positive predictive value (PPV) for specific IgE to individual allergen components

| IgE to individual allergen components | IgE (kU _A /L) | PPV |
|--|--------------------------|----------------------|
| Milk casein to diagnose baked milk allergy ¹⁹ | 20.2 | 69% |
| Egg ovomucoid | | |
| to diagnose baked egg allergy ²⁰ | 50 | 95% |
| to diagnose cooked egg allergy ²¹ | 26.6 | 95% |
| to diagnose raw egg allergy ²² | 5.21 | 95% |
| Peanut Ara h 2 ^{10,18,23} | 0.35-42.2 | 90%-95% |
| Hazelnut Cor a 9 ²³⁻²⁵ | 1-2 | 79%-100% specificity |
| Hazelnut Cor a 14 ^{23,26} | 0.72-47.8 | 87%-90% specificity |
| Cashew Ana o 3 ^{27,28} | 0.16 | 98% specificity |
| | 2 | 95% |
| Soya Gly m 8 ²⁹ | 1 | 89% |
| | 3.55 | 74% |
| Wheat Tri a 19 ^{30,31} | 0.04 | 100% |
| | 0.41 | 81% |

Specific IgE to specific proteins within an allergenic food can be measured as well. This is known as component testing or component-resolved diagnostics (CRD). Sensitization to storage seed proteins (such as Ara h 2 for peanut, Cor a 9 for hazelnut or Ana o 3 for cashew) is much more likely to be associated with systemic reactions such as anaphylaxis, while Profilins and PR-10 proteins are homologous to pollen allergens and are typically associated with pollen-food allergy syndrome or sometimes no symptoms at all upon ingestion. Proposed cutoffs from studies have varied widely among different studies. CRD has also been used to try to predict likelihood of reacting to baked milk and baked egg products, as the component proteins casein and ovomucoid are thought to be more heat stable.

Natural History of Food Allergies

- Most children eventually tolerate milk, egg, wheat and soy
- Higher specific IgE at baseline predicts persistence
- Tolerance to baked milk and baked egg precedes tolerance to non-baked forms and may accelerate development of tolerance
- 20% of peanut allergic children will outgrow allergy with lower likelihood if blood test high or skin tests large
- Most children do not outgrow allergies to tree nuts (<10%), sesame, fish and shellfish

General Principles of Management after Diagnosis of Food Allergy

- Avoidance of the food allergen (some exceptions)
- Ensure nutritional needs are met
 - Consider referral to dietician for children with poor growth, eating disorders and infants with multiple food allergies
- Education
- Risk assessment for severe/fatal outcome (asthma, delayed epinephrine use, prior life-threatening reaction, adolescent/young adult)
- Written personalized healthcare plan and emergency action plan
- Emergency preparedness, including prescription and access to emergency medications including self-injectable epinephrine

Avoidance

- ***Complete avoidance***
 - Exceptions: Oral allergy syndrome (OK to eat trigger fruits/vegetables if desired) and patients who tolerate baked products containing egg or milk
- **FALCPA¹** (labeling act) requires the 9 major food allergens to be clearly labeled on food products manufactured in the US
 - Sesame added in 2021
- ***Different advisory warning labels do not denote different risk levels***
 - Examples: may contain; processed in a facility with; made on shared equipment
 - Presence of food allergen is common: for peanut, 7% of products². For milk, 42%³
- ***Cross contamination:*** buffets, ice cream parlors, shared equipment

¹Food Allergen Labeling and Consumer Protection Act of 2004 (P.L. 108-282), updated 4/23/2021

² Allen KJ WAO Journal 2014;7:10

³Crotty MP JACI 2010;125(4):935

Nutrition and Food Allergy

- Traditional cow milk (CM) formula alternatives¹
- Soy formula is not advised in infants with non-IgE mediated CMA or infants <6 months¹
- In FPIES, delayed introduction of complementary foods is not advised², seek Allergy referral for food introduction recommendations

| | Partially Hydrolyzed Formula | Extensively Hydrolyzed Formula | Amino Acid Formula |
|----------------------|---|--|--|
| Examples: | Peptamin Jr Gentlease Good Start Pro-Total Comfort | Alimentum Nutramigen Pregestimil | Neocate Elecare Nutramigen AA PurAmino Alfamino |
| Allergy indications: | -Not recommended for CMA -Contain large CM peptides | -Tolerated by 90% of CMA children -First line in FPIAP -Not advised for anaphylaxis, EoE or severe CMA | -100% efficacy in CMA -First choice for severe CMA, anaphylaxis, multiple food allergies and EoE in infants -Required in 10-20% of CM FPIES ² |

Abbreviations:

CMA: Cow milk allergy

FPIES: Food protein-induced enterocolitis syndrome

FPIAP: Food protein-induced allergic proctocolitis

EoE: Eosinophilic esophagitis

¹D'Auria E et al. Nutrients. 2021; 13(8): 2762.

²Nowak-Wegrzyn et al. J Allergy Clin Immunol. 2017; 139(4) 1111-1126.

Therapies- Oral Immunotherapy (OIT)

- Eating increasing amounts of allergen daily over a specified time to a specified dose
- Peanut (PALFORZIA®) is the first FDA approved therapy for OIT (peanut)
- Goals: To decrease risk of reaction and increase threshold eliciting reactions
- Limitations: ***Does not allow ad lib food allergen ingestion; May not be curative***
- Safety/Adverse Reactions:
 - Gastrointestinal (GI) symptoms are common (oral itching, abdominal pain, nausea) and are the most common reason for stopping OIT¹
 - OIT induced EoE has been reported
 - Anaphylaxis can occur. For example, 14% on active OIT used epinephrine in the PALISADE study (peanut OIT with PALFORZIA®) vs 6.5% on placebo²
- Efficacy: High; 67% on active OIT in PALISADE tolerated 600 mg of peanut at study end²

¹ Nowak-Wegrzyn, A et al. Curr Opin Allergy Clin Immunol 2019;19(6):606-613.

² The PALISADE Group of Clinical Investigators. N Engl J Med 2018; 379:1991-2001.