CLINICAL PRACTICE GUIDELINES

FOOD ALLERGY
DIAGNOSIS AND MANAGEMENT

Supplement 1 – Evidence Matrices

2nd EDITION (2026)

ACADEMY OF MEDICINE SINGAPORE

COLLEGE OF PAEDIATRICS AND CHILD HEALTH, SINGAPORE

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

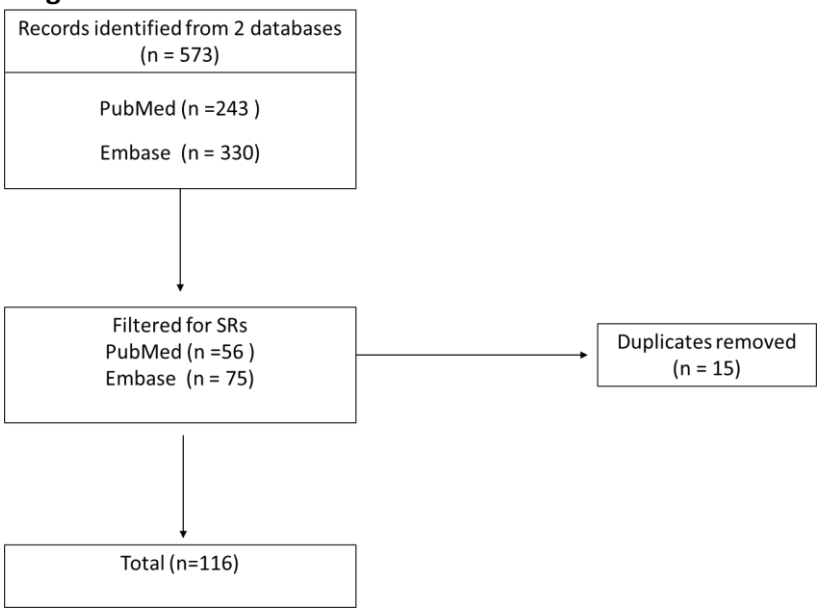
Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Diagnosis of Food Allergy
Subgroup Members:	Elizabeth Tham, Carmen Riggioni
Main Clinical Question(s):	1. What are the validated clinical tests for diagnosis of IgE-mediated food allergies? 2. What is the role of panel testing as a screening tool for IgE-mediated food allergy in the absence of a suggestive clinical history?
Population (age limit, inclusion criteria, excluded groups, special groups):	Q1. Adults and children Q2. Adults and children with suspected food allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Q1. Intervention: Skin prick tests (SPT), sIgEs, component resolved diagnostics Q2. Intervention: panel tests (IgE)
Comparator (if applicable):	Q1. No comparators Q2. Oral food challenges (OFC) as gold standard
Outcomes (specify critical/primary vs secondary):	Q1. Accurate diagnosis of food allergy (oral food challenge proven) Q2. Accurate diagnosis of IgE-mediated food allergy
Publication Dates:	2000 – 2023
Study Designs (specify inclusion/exclusion criteria):	Normal Literature Search, SR not needed Inclusion criteria – Existing CPGs, SRs, MAs, RCTs, Reviews Exclusion criteria – Case reports, non-English papers
Search Strategy:	**Databases Searched:** PubMed, Embase **<u>Diagnosis</u>** PubMed: Search: (("Food Hypersensitivity/diagnosis"[Mesh] OR "Skin Tests"[Mesh]) OR ((Skin test*[Title/Abstract] OR SPT[Title/Abstract] OR Skin prick test*[Title/Abstract] OR specific-IgE test*[Title/Abstract] OR sIgE test*[Title/Abstract] OR specific-IgE test[Title/Abstract] OR Component-resolved diagnostic*[Title/Abstract] OR CRD[Title/Abstract]))) AND (("Immunoglobulin E"[Mesh]) OR ((IgE-mediated[Title/Abstract] OR IgE-specific[Title/Abstract] OR IgE-related[Title/Abstract] OR IgE-dependent[Title/Abstract] OR immunoglobulin E[Title/Abstract]))) Filters: Systematic Review and or Metaanalysis Embase: (('food allergy'/exp OR ((food:ab,ti OR nut*:ab,ti OR peanut*:ab,ti OR treenut*:ab,ti OR milk:ab,ti OR seafood*:ab,ti OR shellfish*:ab,ti OR wheat*:ab,ti OR soy*:ab,ti

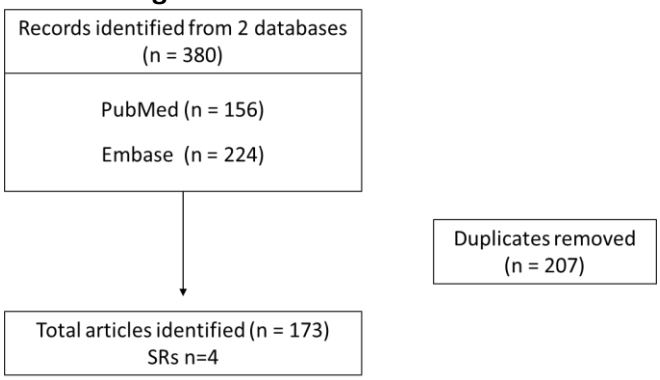
	OR seed*:ab,ti OR legume*:ab,ti OR 'multiple food*':ab,ti OR egg*:ab,ti) AND (allerg*:ab,ti OR hypersensitivit*:ab,ti OR anaphyla*:ab,ti))) AND/OR ('immunoglobulin e'/exp OR 'immunoglobulin e':ab,ti OR 'ige mediated':ab,ti OR 'ige specific':ab,ti OR 'ige related':ab,ti OR 'ige dependent':ab,ti) AND/OR ('skin' test OR 'skin' prick test /exp OR SPT) AND/OR (Component ' resolved diagnosis OR\Componentresolveddiagnosis /exp OR CRD) **Panel testing** PubMed: Search: ((("Food Hypersensitivity/diagnosis"[Mesh] OR "Skin Tests"[Mesh]) OR ((Skin test*[Title/Abstract] OR SPT[Title/Abstract] OR Skin prick test*[Title/Abstract] OR specific-IgE test*[Title/Abstract] OR sIgE test*[Title/Abstract] OR specific-IgE test[Title/Abstract] OR Panel[Title/Abstract] OR panels[Title/Abstract] OR Component-resolved diagnostic*[Title/Abstract] OR CRD[Title/Abstract]))) AND (("Immunoglobulin E"[Mesh]) OR ((IgE-mediated[Title/Abstract] OR IgE-specific[Title/Abstract] OR IgE-related[Title/Abstract] OR IgE-dependent[Title/Abstract] OR immunoglobulin E[Title/Abstract])))) AND (Panel test* Food panel Allergy panel Allergen panel Panels[Title/Abstract]) Sort by: Most Recent Embase: (('food allergy'/exp OR ((food:ab,ti OR nut*:ab,ti OR peanut*:ab,ti OR treenut*:ab,ti OR milk:ab,ti OR seafood*:ab,ti OR shellfish*:ab,ti OR wheat*:ab,ti OR soy*:ab,ti OR seed*:ab,ti OR legume*:ab,ti OR 'multiple food*':ab,ti OR egg*:ab,ti) AND (allerg*:ab,ti OR hypersensitivit*:ab,ti OR anaphyla*:ab,ti))) AND/OR ('immunoglobulin e'/exp OR 'immunoglobulin e':ab,ti OR 'ige mediated':ab,ti OR 'ige specific':ab,ti OR 'ige related':ab,ti OR 'ige dependent':ab,ti) AND/OR ('skin' test OR 'skin' prick test /exp OR SPT) AND/OR (Component ' resolved diagnosis OR\Componentresolveddiagnosis /exp OR CRD) AND (Panel testing' OR Allergy panel OR Allergy test'/exp)

Search outcomes

Diagnostic tests



Panel testing



Subgroup/Chapter Evidence Matrix

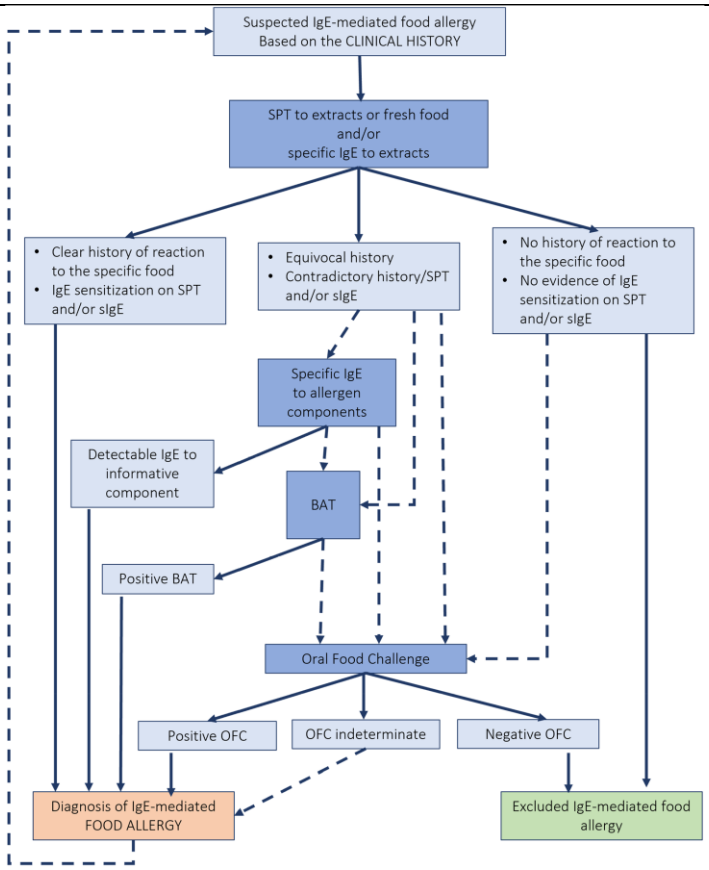
Evidence Matrix No.	*EM1-1*
Clinical/PICO Question:	What are the validated clinical tests for diagnosis of IgE-mediated food allergies?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 1.1: We strongly recommend that in patients with suspected food allergy, a detailed allergy-focused clinical history should be taken as the first step of the diagnostic evaluation** **R 1.2: We strongly recommend that in patients with a history suggestive of IgE-mediated food allergy, skin prick test (SPT) and/or measurement of food specific IgE (sIgE) should be performed as first line tests to support diagnosis.** **R 1.3: We strongly recommend that patients with a history of suspected IgE-mediated food allergy be referred to an allergist where component-resolved diagnostic tests may be performed in selected patients in addition to SPT and/or sIgE to further support diagnosis or in preparation for an oral food challenge.** **R 1.4: We strongly recommend that a medically supervised oral food challenge (OFC) be considered to confirm or exclude food allergy in patients if diagnosis remains unclear after initial evaluation, incorporating shared decision-making with patients.**
Rationale:	**R 1.1: We strongly recommend that in patients with suspected food allergy, a detailed allergy-focused clinical history should be taken as the first step of the diagnostic evaluation** An allergy-focused diet and clinical history is the first step on the food allergy diagnostic pathway. The clinical history allows the provider to identify the mechanism of food allergy (i.e. IgE or non-IgE-mediated), the foods/allergens to be tested, and guides interpretation of the test results. A clear history of the symptoms experienced, temporal relationship to allergen exposure and response to treatment is essential. Symptom history should also always be accompanied by a detailed dietary history. This should include questions on the patient usual diet patterns, particularly whether the implicated allergen and food type had previously been tolerated, any cessation of allergen intake prior to the reaction, any continued consumption of the allergen without incident after the allergic reaction.[1] Other essential components of the clinical history include ascertaining the presence of other allergic co-morbidities, tolerance to co- or cross-reacting foods, possible occupational exposure to allergens, co-factors, and family history of allergic disease. A detailed allergy-focused clinical history will allow to estimate the likelihood (pre-test probability) that a patient has an IgE-mediated food allergy and to guide the selection of IgE sensitization tests and their interpretation to determine the post-test probability of IgE-mediated food allergy, which, in turn, is used for clinical decision-making. A history of regular consumption of age-appropriate portions of the food in the relevant type of processing without developing any allergic symptoms rules out food allergy without the need for testing.

	An allergy-focused dietary history supplemented with assessment of growth patterns (such as serial records of height, weight and BMI over time) will also be able to identify over and under nutrition, potential macro- and micronutrient deficiencies, and identify concerns about development, feeding skills and aversive feeding patterns.[2] **R1.2: We strongly recommend that in patients with a history suggestive of IgE-mediated food allergy, skin prick test (SPT) and/or measurement of food specific IgE (sIgE) should be performed as first line tests to support diagnosis.** **R1.3: We strongly recommend that patients with a history of suspected IgE-mediated food allergy be referred to an allergist where component-resolved diagnostic tests may be performed in selected patients in addition to SPT and/or sIgE to further support diagnosis or in preparation for an oral food challenge.** Following a detailed allergy-focused history, confirmation of the presence of allergen-specific IgE should be sought to support the diagnosis of an IgE-mediated food allergy. This can be achieved through performing SPTs and/or specific IgEs to allergen extracts or individual allergen components (molecular allergology tests). A systematic review of the literature supports the above tests which are currently validated to support the diagnosis of IgE-mediated food allergy.[3] SPTs and specific IgEs are relatively inexpensive and more widely available and are recommended as the first-line tests for evaluation of food allergy. If the clinical history is unclear, or the results of SPT and/or sIgEs are not sufficient to support the diagnosis or are conflicting with the history, specific IgE to allergen components [component-resolved diagnostic (CRD) tests] may be performed to aid in confirmation of the diagnosis. The sensitivity, specificity and predictive value of these tests vary between allergens and different populations, and interpretation is specific to the food allergen, geographical location and the individual being tested.[4] These tests should be therefore performed by a trained allergy specialist to allow accurate interpretation of the test results in the context of a supporting clinical history, established cut-offs and confirmation via an oral food challenge (OFC) if required. **R1.4: We strongly recommend that a medically supervised oral food challenge (OFC) be considered to confirm or exclude food allergy in patients if diagnosis remains unclear after initial evaluation, incorporating shared decision-making with patients.** A good clinical history and validated allergy diagnostic tests (SPTs, sIgEs and CRDs) may be sufficient in most cases in clinical practice to achieve a robust diagnosis of food allergy. However, an OFC may be required in some cases where diagnosis may still be uncertain. These may include instances such as a) The patient reports clinical symptoms, but no IgE sensitization has been demonstrated b) It is necessary to confirm that the allergy has been outgrown, in patients who have been strictly avoiding the food c) IgE sensitization has been demonstrated but the food has never been consumed or tolerated, and avoidance is ongoing d) Clinical history and allergy diagnostic test results are conflicting

	OFCs are high-risk procedures and should thus be performed only under the supervision of a trained allergy specialist, by medical personnel trained in the recognition and management of anaphylaxis, and in a facility equipped to provide resuscitation and advanced life support.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):	**Skin prick tests and sIgEs** **Santos AF et al, Allergy 2023.[4]; Riggioni C et al, Allergy 2023.[3]** **Component resolved diagnostics** **Santos AF et al, Allergy 2023.[4]; Riggioni C et al, Allergy 2023.[3]** Algorithm for Food Allergy Diagnosis

Diagnostic Test		Cow's milk	Egg	Peanut	Hazelnut	Cashew	Sesame	Wheat	Shrimp
Skin prick test	Cut-offs (mm)	4 (3-8)	5 (3-8)	4 (3-8)	5 (3-7)	5 (4-6)	8 (4-10)	3 (3-5)	3 (3-5)
	Sensitivity	0.52 (0.24; 0.79)	0.68 (0.37; 0.88)	0.84 (0.69; 0.92)	0.82 (0.68; 0.91)	0.93 (0.89; 0.96)	0.70 (0.55; 0.82)	0.53 (0.23; 0.81)	0.62 (0.44; 0.77)
	Specificity	0.80 (0.65; 0.90)	0.77 (0.64; 0.86)	0.86 (0.79; 0.91)	0.78 (0.44; 0.94)	0.92 (0.82; 0.96)	0.89 (0.76; 0.95)	0.72 (0.57; 0.84)	0.90 (0.31; 0.99)
Specific IgE to allergen extracts	Cut-offs (KU/L)	3.5 (0.9 - 10.5)	3.5 (1.7 - 5.5)	4.3 (0.35 – 10)	2.34 (0.6-6.3)	1.1 (0.6 - 3.1)	7.5 (0.9 – 50)	0.6 (0.35 – 5.6)	1.2 (0.5 – 3.1)
	Sensitivity	0.82 (0.59; 0.94)	0.85 (0.77; 0.90)	0.81 (0.71; 0.88)	0.79 (0.71; 0.85)	0.94 (0.89; 0.97)	0.70 (0.23; 0.95)	0.72 (0.54; 0.84)	0.96 (0.42; 1.00)
	Specificity	0.92 (0.80; 0.97)	0.73 (0.63; 0.80)	0.83 (0.71; 0.90)	0.62 (0.38; 0.81)	0.64 (0.54; 0.74)	0.83 (0.26; 0.99)	0.79 (0.68; 0.86)	0.63 (0.46; 0.78)

Diagnostic Test		Cow's milk	Egg	Peanut	Hazelnut	Cashew	Wheat	Shrimp
Specific IgE to allergen components	Cut-offs (KU/L)	Casein 2.6 (1.0 – 5.3)	Ovomucoid 0.8 (0.35 – 3.7)	Ara h 2 0.44 (0.3 – 1.3)	Cor a 14 0.64 (0.35-3.5)	Ana o 3 0.4 (0.2; 0.6)	Omega-5-gliadin 0.3 (0.1-0.6)	Pen a 1 1.1 (0.6; 4.4)
	Sensitivity	0.67 (0.53; 0.78)	0.74 (0.54; 0.87)	0.82 (0.77; 0.86)	0.73 (0.53; 0.87)	**0.96 (0.91; 0.98)**	0.79 (0.68; 0.88)	0.62 (0.45; 0.76)
	Specificity	**0.93 (0.85; 0.97)**	**0.91 (0.87; 0.93)**	**0.92 (0.87; 0.95)**	**0.95 (0.90; 0.98)**	**0.94 (0.88; 0.97)**	0.78 (0.66; 0.86)	0.89 (0.75; 0.95)

	 **Santos AF et al, Allergy 2023.**[4] - The Basophil Activation Test (BAT) is currently used as part of clinical diagnostics in some locations, but its use in routine clinical care is currently limited worldwide due to resource constraints.
Certainty and Magnitude of Effects:	NA
Risk/Harm vs Benefit Considerations:	• **R1.1:** Taking a detailed allergy-focused clinical history is low-risk and highly beneficial as it guides appropriate next steps in diagnosis and management. • **R1.2:** SPT and sIgE testing are minimally invasive with low risk. The main risk lies in false positives, potentially leading to unnecessary food avoidance. • **R1.3:** Referral to an allergist and use of component-resolved diagnostics improve diagnostic precision, reducing the risk of overdiagnosis or misdiagnosis. • **R1.4:** Medically supervised oral food challenges carry some risk of allergic reactions but offer the highest diagnostic certainty. The benefits of definitive diagnosis generally outweigh the risks, especially under clinical supervision.
Patient/ caregiver values	• Most patients and caregivers value a clear diagnosis, reduced uncertainty, and avoidance of unnecessary dietary restrictions. • Many prefer less invasive initial testing (history, SPT/sIgE) and are generally willing to undergo OFC if adequately informed and reassured about safety. • Shared decision-making, particularly around OFCs, aligns well with patient-centred care preferences.

	Stakeholder feedback (if available):
Resource, Cost Considerations:	• **Clinical history:** No direct cost; low resource burden. • **SPT/sIgE:** Moderate cost and widely available; but cost-effective as first-line tools. • **Referral and component-resolved diagnostics:** Higher cost and requires specialized resources; may not be available in all settings. In Singapore, adequate resources exist and access to allergy specialist care is easy. • **OFC:** High resource intensity due to need for medical supervision, and costs are moderately high. Comes with risks of allergic reactions but cost-benefit may be considered in light of being able to expand one's diet and improve quality of life.
Equity **Acceptability** **Feasibility**	**Equity** • Disparities may exist in access to allergists, component-resolved testing, and supervised OFCs, particularly in the less educated or lower socioeconomic classes. • Subsidized care, and funding subsidies are, however, available in the public healthcare institutions. Ensuring adequate education is essential to facilitate access across the population. **Acceptability** • High acceptability for history-taking and SPTs; moderate acceptability for sIgEs due to need for blood taking. • Referral to specialists and advanced diagnostics are acceptable but may be limited by access or wait times. • OFCs are acceptable when properly explained and conducted in safe environments, though anxiety about reactions can affect willingness. **Feasibility** • History-taking and basic allergy testing are feasible in most primary or secondary care settings. • Referral to allergists and access to advanced testing/OFCs may be less feasible in low-resource or rural areas due to staffing and infrastructure limitations. • Implementation is feasible but may require system-level coordination, training, and resource allocation. **Stakeholder feedback (if available):**

Workgroup Consensus Survey (RAND/UCLA):

R 1.1: We strongly recommend that in patients with suspected food allergy, a detailed allergy-focused clinical history should be taken as the first step of the diagnostic evaluation

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	4%	9	0.0	8.4	No Disagreement

R 1.2: We strongly recommend that in patients with a history suggestive of IgE-mediated food allergy, skin prick test (SPT) and/or measurement of food specific IgE (sIgE) should be performed as first line tests to support diagnosis.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	5%	9	0.6	7.9	No Disagreement

R 1.3: We strongly recommend that patients with a history of suspected IgE-mediated food allergy be referred to an allergist where component-resolved diagnostic tests may be performed in selected patients in addition to SPT and/or sIgE to further support diagnosis or in preparation for an oral food challenge.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
2	9	29%	9	1.0	7.6	No Disagreement

R 1.4: We strongly recommend that a medically supervised oral food challenge (OFC) be considered to confirm or exclude food allergy in patients if diagnosis remains unclear after initial evaluation, incorporating shared decision-making with patients.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
6	9	9%	9	0.0	8.4	No Disagreement

External Review Feedback:	NA
Public Consultation:	NA

References:

1. Skypala, I. J., Venter, C., Meyer, R., deJong, N. W., Fox, A. T., Groetch, M., Oude Elberink, J. N., Sprikkelman, A., Diamandi, L., & Vlieg-Boerstra, B. J. (2015). The development of a standardised diet history tool to support the diagnosis of food allergy. *Clin Transl Allergy*, *5*, 7.
2. Lyons, S. A., Knulst, A. C., Burney, P. G. J., Fernandez-Rivas, M., Ballmer-Weber, B. K., Barreales, L., Bieli, C., Clausen, M., Dubakiene, R., Fernandez-Perez, C., Jedrzejczak-Czechowicz, M., Kowalski, M. L., Kummeling, I., Kralimarkova, T., Mustakov, T. B., van Os-Medendorp, H., Papadopoulos, N. G., Popov, T. A., Potts, J., . . . Le, T.-M. (2021). Predicting food allergy: The value of patient history reinforced. *Allergy*, *76*(5), 1454-1462.
3. Riggioni, C., Ricci, C., Moya, B., Wong, D., van Goor, E., Bartha, I., Buyuktiryaki, B., Giovannini, M., Jayasinghe, S., Jaumdally, H., Marques-Mejias, A., Piletta-Zanin, A., Berbenyuk, A., Andreeva, M., Levina, D., Iakovleva, E., Roberts, G., Chu, D., Peters, R., . . . Santos, A. F. (2024). Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy. Ibid., *79*(2), 324-352.
4. Santos, A. F., Riggioni, C., Agache, I., Akdis, C. A., Akdis, M., Alvarez-Perea, A., Alvaro-Lozano, M., Ballmer-Weber, B., Barni, S., Beyer, K., Bindslev-Jensen, C., Brough, H. A., Buyuktiryaki, B., Chu, D., Del Giacco, S., Dunn-Galvin, A., Eberlein, B., Ebisawa, M., Eigenmann, P., . . . Skypala, I. (2023). EAACI guidelines on the diagnosis of IgE-mediated food allergy. Ibid., *78*(12), 3057-3076.

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Non-IgE Mediated Food Allergies
Subgroup Members:	Loh Wenyin
Main Clinical Question(s):	1. Is fluid resuscitation effective in the management of acute FPIES reactions? 2. Are antiemetics effective in the management of acute FPIES reactions? 3. Is intramuscular adrenaline effective in the management of acute FPIES reactions?
Population (age limit, inclusion criteria, excluded groups, special groups):	Included: Human children and adults diagnosed with FPIES
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Acute management of FPIES
Comparator (if applicable):	Placebo or avoidance
Outcomes (specify critical/primary vs secondary):	Safety and feasibility
Publication Dates:	2000 – 2023
Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria – Existing clinical guidelines; Systematic reviews (SRs); Randomised controlled trials (RCT) will be favoured over non-randomised clinical trials (in the systematic reviews, and to supplement SRs' if newer information changes existing impression of evidence), Case reports
Search Strategy:	**Databases Searched:** Medline, Embase, PubMed, Cochrane Library, CINAHL **Grey Literature Sources?** No **Search Terms:** ("Food Protein-Induced Enterocolitis" or "Food Protein Induced Enterocolitis" or FPIES) ("Fluid Resuscitation" or Hypotension) (Antiemetics or Anti-emetics or Aprepitant or Chlorpromazine or Cyclizine or Dexamethasone or Diazepam or Dimenhydrinate or Diphenhydramine or Domperidone or Doxylamine or Droperidol or Granisetron or Haloperidol or Lorazepam or Meclizine or Methylprednisolone or Metoclopramide or Olanzapine or Ondansetron or Palonosetron or Prochlorperazine or Promazine or Scopolamine or Thiethylperazine or Trifluoperazine or Triflupromazine or Tropisetron) (Epinephrine or Adrenaline or Epifrin or Epitrate or Lyophrin or Medihaler-Epi) Filters applied as per inclusion criteria above.

Search Outcomes:	**Number of studies:**

	Medline (Ovid)	Embase (Ovid)	PubMed	Cochrane Library	CINAHL	Total	After Deduplication
Set 1 Fluid Resuscitation	19	57	20	0	5	101	59
Set 2 Anti-ematics or Ondansetron	22	115	24	5	0	166	118
Set 3 Adrenaline	8	53	9	1	0	71	53

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM2-1*
Clinical/PICO Question:	Is fluid resuscitation effective in the management of acute FPIES reactions?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**GPP2.1: We recommend that severe acute Food Protein-Induced Enterocolitis Syndrome (FPIES) be treated as a medical emergency and the priority should be haemodynamic support with aggressive fluid resuscitation.** **GPP2.2: For patients presenting with mild symptoms, a trial of oral rehydration may be attempted.**
Rationale:	The severity of acute FPIES reactions range from mild-moderate to severe[1]. Symptoms can lead to dehydration and in more severe cases, hypotension. Treatment is supportive with appropriate fluid rehydration. For patients presenting with mild symptoms, a trial of oral rehydration with milk or clear fluids may be attempted. As hypovolemic shock can occur in up to 15% of patients[2], severe acute FPIES must be managed as a medical emergency with aggressive fluid resuscitation and vasopressors for hypotension not responsive to fluid resuscitation.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines:** Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111. **SRs/MAs:** - **Other more recent literature or local data:** **-**
Certainty and Magnitude of Effects:	Not graded (GPP)
Risk/Harm vs Benefit Considerations:	Risks of appropriate fluid resuscitation is minimal while death is certain if appropriate fluid resuscitation is not given for hypovolemic shock.
Patient/ caregiver values	Patients and their families value timely and appropriate emergency treatment of allergic reactions, including acute FPIES. **Stakeholder feedback (if available): NIL**
Resource, Cost Considerations:	Patients presenting with an acute FPIES reaction should be managed at a medical facility equipped to manage emergencies including hypovolemic shock.
Equity **Acceptability**	Access to the emergency department should be available to all individuals. **Stakeholder feedback (if available): NIL**

<table>
<tr><td>Feasibility</td><td></td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP2.1: We recommend that severe acute Food Protein-Induced Enterocolitis Syndrome (FPIES) be treated as a medical emergency and the priority should be haemodynamic support with aggressive fluid resuscitation.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>5</td><td>9</td><td>13%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table>
GPP2.2: For patients presenting with mild symptoms, a trial of oral rehydration may be attempted.
Number voted = 19; Number abstained = 0
<table>
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<tr><td>5</td><td>9</td><td>16%</td><td>8</td><td>1.6</td><td>7.2</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td>NA</td></tr>
<tr><td>Public Consultation:</td><td>NA</td></tr>
<tr><td colspan="2">References:
1. Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111.
2. Caubet et al. Clinical features and resolution of FPIES: 10-year experience. JACI 2014; 134:382.</td></tr>
</table>

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM2-2*
Clinical/PICO Question:	Are antiemetics effective in the management of acute FPIES reactions?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 2.3: We conditionally recommend ondansetron to be considered as an adjunctive therapy in patients ≥6 months of age with acute FPIES reactions.**
Rationale:	Ondansetron appears to reduce frequency of vomiting and hospitalization in acute FPIES with minimal adverse effects based on retrospective cohort studies.[1,2] Ondansetron must be avoided in infants <6 months of age (due to lack of safety data) and in patients with heart defects/arrhythmias (due to the risk of prolonged QT).
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	Other guidelines: Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111.[3] SRs/MAs: - Other more recent literature or local data: -
Certainty and Magnitude of Effects:	**Certainty of evidence:** Low **Magnitude of effect:** Persistent vomiting noted in 19% of patients who received parenteral ondansetron vs 93% who only received IV fluids and steroids in largest retrospective case-control study.[1]
Risk/Harm vs Benefit Considerations:	Adverse effects appear minimal based on retrospective cohort studies.
Patient/ caregiver values	Patients and their families value timely and appropriate emergency treatment of allergic reactions, including acute FPIES. **Stakeholder feedback (if available): NIL**
Resource, Cost Considerations:	Ondansetron may not be available in all medical facilities.
Equity **Acceptability** **Feasibility**	Ondansetron may not be available in all medical facilities. Furthermore, some patients may have concerns regarding intramuscular and intravascular administration. Given that ondansetron is indicated as an adjunctive therapy in patients ≥6 months of age, priority would still be ensuring adequate hydration and maintaining haemodynamic stability.

<table>
<tr><td></td><td>Stakeholder feedback (if available): NIL</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 2.3: We conditionally recommend ondansetron to be considered as an adjunctive therapy in patients ≥6 months of age with acute FPIES reactions.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>7</td><td>9</td><td>8%</td><td>9</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
<tr><td colspan="2">References:
1. Miceli et al. Ondansetron in acute FPIES a retrospective case-control study. Allergy 2017;72:545
2. Le S et al. Efficacy of oral ondansetron in acute FPIES: a case series of 6 patients. Allergy 2020;75:2949
3. Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111.</td></tr>
</table>

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM2-3*
Clinical/PICO Question:	Is intramuscular adrenaline effective in the management of acute FPIES reactions?
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**GPP 2.4: Intramuscular adrenaline is ineffective and should not be used to treat acute FPIES reactions.** However, in patients with atypical FPIES presenting with a reaction consistent with an IgE-mediated reaction, appropriate management should be instituted including administration of intramuscular adrenaline for anaphylaxis.
Rationale:	FPIES is a non-IgE mediated food allergy and adrenaline has no effect on emesis.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	Other guidelines: Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111.[1] SRs/MAs: - Other more recent literature or local data: -
Certainty and Magnitude of Effects:	Not graded (GPP)
Risk/Harm vs Benefit Considerations:	Intramuscular adrenaline is not expected to improve symptoms in acute FPIES and patients are likely to experience side effects from its administration.
Patient/ caregiver values	Patients and their families value timely and appropriate emergency treatment of allergic reactions, including acute FPIES. **Stakeholder feedback (if available): NIL**
Resource, Cost Considerations:	Additional resource/cost considerations are not expected as the recommendation is to not use IM adrenaline in acute FPIES.
Equity **Acceptability** **Feasibility**	Patients with both IgE-mediated food allergy and FPIES may be confused as to when IM adrenaline is indicated. Adequate knowledge will be necessary to understand when IM adrenaline is indicated (for anaphylaxis) and this can be mitigated with adequate counselling and having actions plans to guide management in the event of an allergic reaction. **Stakeholder feedback (if available): NIL**

<table>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 2.4: Intramuscular adrenaline is ineffective and should not be used to treat acute FPIES reactions.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>6</td><td>9</td><td>12%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
<tr><td colspan="2">References:
1. Nowak-Wegrzyn et al. ICON for the diagnosis and management of FPIES. JACI 2017;139:1111.</td></tr>
</table>

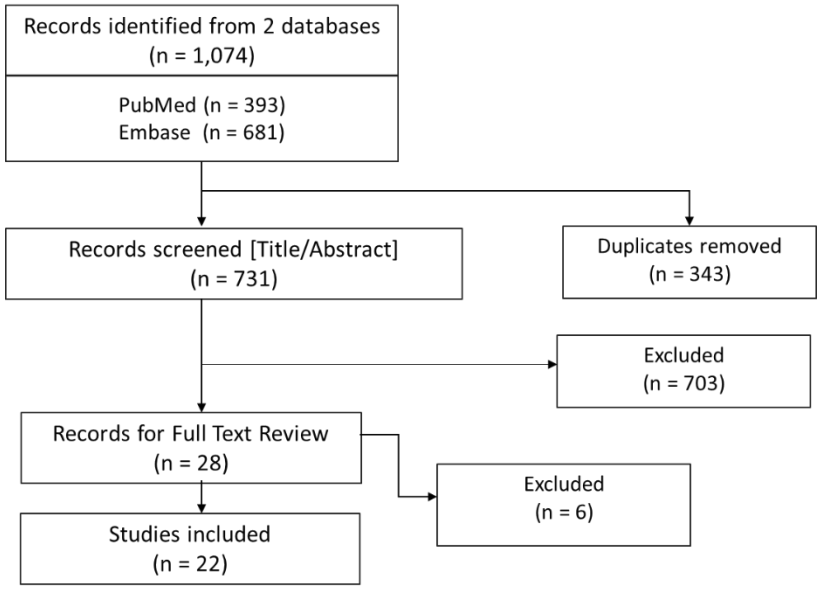
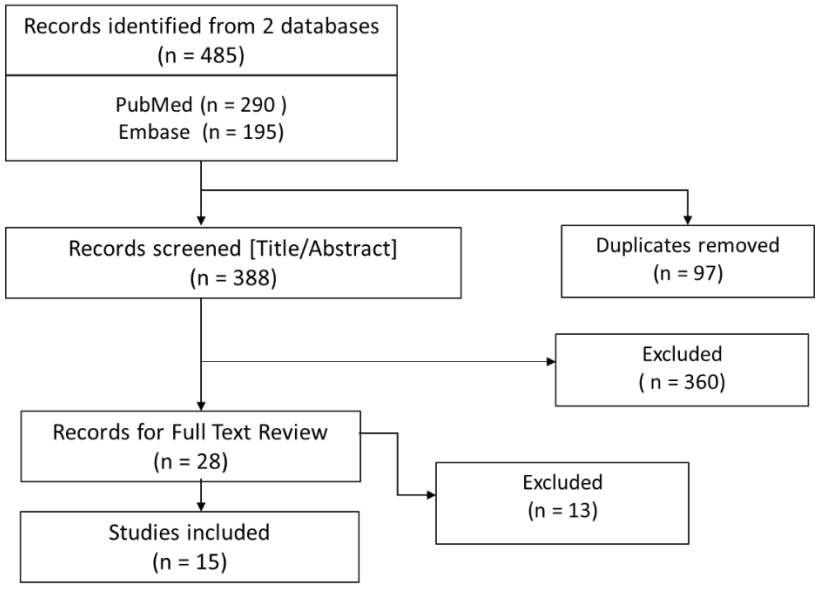
Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

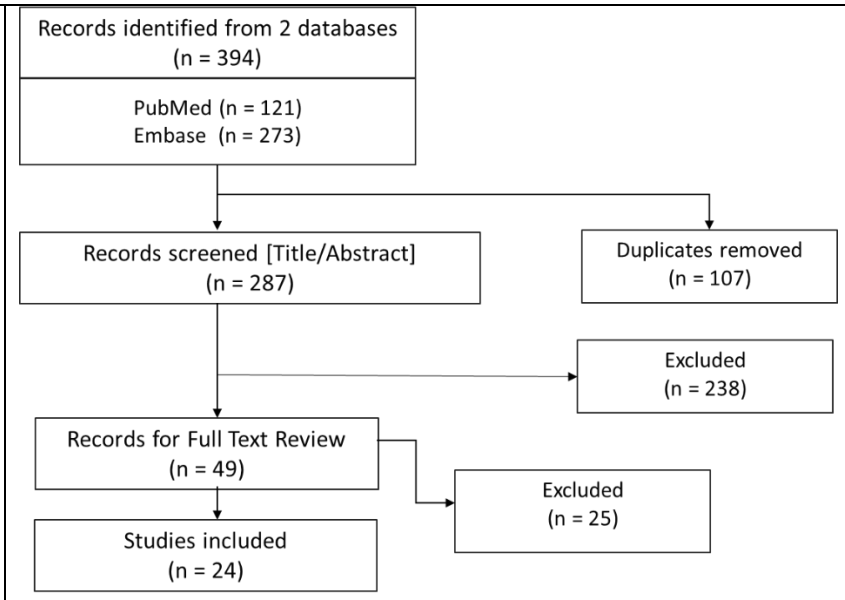
Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Cow's Milk Allergy (CMA)
Subgroup Members:	Samantha Lee May Ping
Main Clinical Question(s):	1. What are the safe milk alternatives for children and adults with cow's milk allergy? 2. Is maternal cow's milk dietary elimination required for breastfed infants with cow's milk allergy? 3. Is baked milk products safe in children with cow's milk allergy?
Population (age limit, inclusion criteria, excluded groups, special groups):	Adults and children with cow's milk allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	1. Milk replacement formula (extensively hydrolysed formula, amino acid formula, soy formula, hydrolysed rice formula, partially hydrolysed formula) 2. Mammalian milks 3. Plant-based beverages 4. Maternal cow's milk dietary elimination in breastfeeding mothers 5. Extensively heated or baked milk
Comparator (if applicable):	Strict avoidance or placebo
Outcomes (specify critical/primary vs secondary):	Safety and feasibility
Publication Dates:	2000 – 2024 (included publications in 2024 to include WAO DRACMA Guideline Update)
Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria – Existing CPGs, SRs, MAs, RCTs Exclusion criteria – Cohort study, case reports, animal research, in-vitro/lab research, non-English papers
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:**

	Clinical Question 1 - What are the safe milk alternatives for children and adults with cow's milk allergy? 1 Milk Hypersensitivity/ (3106) 2 (allerg* or hypersensitivit*).ab,ti. (279744) 3 (consumed or consumption* or cross-react* or react* or co-react* or drink or drank or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-sensiti#ation or cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. (3040883) 4 ("mammalian milk?" or "cow* milk" or "goat* milk" or "camel* milk" or "sheep* milk" or "milk replacement*" or formula).ab,ti. (121556) 5 ("meta-analysis" or "meta analysis" or "guideline" or "guidelines" or "guidance" or "practice guideline" or "practice guidelines" or "position paper" or "review" or "systematic review").ab,ti. (2964280) 6 1 or 2 (280253) 7 3 and 4 and 5 and 6 (415) 8 limit 7 to (english language and yr="2000 - 2024") (376) Clinical Question 2 - Is maternal cow's milk dietary elimination required for breastfed infants with cow's milk allergy? 1 exp Breast Feeding/ or Milk, Human/ 2 (breastfeed* or "breast feed*" or "breast milk" or breastmilk or "human milk").ab,ti. 3 1 or 2 4 exp Infant/ 5 (infant? or newborn? or baby or babies).ab,ti. 6 4 or 5 7 Milk Hypersensitivity/ 8 ((milk adj2 allerg*) or (milk adj2 hypersensitivit*)).ab,ti. 9 7 or 8 10 ("meta-analysis" or "meta analysis" or "guideline" or "guidelines" or "guidance" or "practice guideline" or "practice guidelines" or "position paper" or "review" or "systematic review").ab,ti. 11 3 and 6 and 9 and 10 12 limit 11 to (english language and yr="2000 - 2024") Clinical Question 3 – Is baked milk products safe in children with cow's milk allergy? 1 Milk Hypersensitivity/ (3107) 2 ((milk adj2 hypersensitivit*) or (milk adj2 allerg*)).ab,ti. (3272) 3 1 or 2 (4538) 4 exp Child/ (2222709) 5 (child or children or toddler? or preschooler?).ab,ti. (1496824) 6 4 or 5 (2690310) 7 (heated or baked or cooked).ab,ti. (42866)

	8 3 and 6 and 7 (117) 9 limit 8 to (english language and yr="2000 - 2024") (111)
Search Outcomes:	**Number of studies:** Clinical Question 1 - What are the safe milk alternatives for children and adults with cow's milk allergy?  Clinical Question 2 - Is maternal cow's milk dietary elimination required for breastfed infants with cow's milk allergy?  Clinical Question 3 – Is baked milk products safe in children with cow's milk allergy?


Records identified from 2 databases
(n = 394)
PubMed (n = 121)
Embase (n = 273)
Records screened [Title/Abstract]
(n = 287)
Duplicates removed
(n = 107)
Excluded
(n = 238)
Records for Full Text Review
(n = 49)
Excluded
(n = 25)
Studies included
(n = 24)

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-1*
Clinical/PICO Question:	What are the safe milk alternatives for children and adults with cow's milk allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.1: We strongly recommend using extensively hydrolysed cow's milk formula (eHF-CM) or soy formula (SF)* as first choice, and an amino acid-based formula (AAF) as second choice in infants with cow's milk allergy who need a breastmilk alternative. [EM3-1]** ***When initiating SF, clinicians should discuss with caregivers the low but possible risk of concomitant soy allergy, particularly in infants with no prior soy exposure.** **R 3.2: We conditionally recommend that hydrolysed rice formula (HRF) can be considered as an alternative first choice (if available) in infants with cow's milk allergy.** **R 3.3: We strongly recommend against using partially hydrolysed cow's milk formula and mammalian milks (goat/sheep) in children with cow's milk allergy (both IgE and non-IgE-mediated) due to high risk of allergic reactions.** **GPP 3.4: In children (≥ 2 years old) and adults diagnosed with cow's milk allergy who need a milk substitute, fortified plant-based beverages can be used. They should not be used as a main source of nutrients in infants < 1 year old.** Remarks: Soy formula (SF) can be offered as first option for infants with cow's milk allergy (CMA) based on limited evidence that clinical reactions to soy is rare in Singaporean children with CMA. It is also more palatable and less expensive than eHF or AAF. Some caregivers may still be concerned about the adverse effects of phytoestrogens (isoflavones; which may possess weak oestrogenic activity) especially in male infants, despite research evidence that it is not a concern. AAF is more expensive than other formulas, with limited accessibility (requires prescription). Thus, we do not suggest this as the first option. However, it can be used for selected group of infants with: • Persistent symptoms or allergic reactions while on eHF • Faltering growth/ failure to thrive • Multiple food allergies requiring multiple food elimination • Severe cow's milk allergy/FPIES • Eosinophilic oesophagitis/eosinophilic gastrointestinal disease • Presence of allergic symptoms while exclusively breastfed In infants with cow's milk FPIES whose tolerance to rice is unknown, it is advisable to avoid using hydrolysed rice formula until further evaluation. eHF or AAF is recommended if poor growth and/or multiple non-IgE-mediated food allergies.
Rationale:	The recommendations for milk alternatives in patients with CMA are based on evidence on safety, efficacy, nutritional adequacy and cost-effectiveness.

Extensively hydrolysed formula is recommended as the first choice due to its proven safety and efficacy (moderate certainty of evidence) while supporting nutrition and growth.[1-6]

SF is recommended as the alternative first choice, especially in infants > 6 months, due to its cost-effectiveness, palatability, and accessibility[5]. Only <15% of infants with CMA have concomitant soya allergy[7,8]. In a retrospective review of Singaporean children with IgE-mediated CMA[9], the rate of concomitant soy allergy is even lower, <5%. Based on a 2014 systematic review/meta-analysis, it was shown that despite the high concentrations of phytoestrogens, phytates and aluminium in SF, it is safe and does not impair reproductive and endocrine functions or cause aluminium toxicity in humans.[10]
In FPIES (non-IgE-mediated CMA), the rate of cross-sensitization to soy is low in Asian population.[11]Hence, if soy formula is to be used, soy introduction under medical supervision is recommended if soy tolerance is not yet established.

AAF is recommended as the second choice and reserved for selected cases of severe or complex CMA, due to its higher cost, poor palatability and limited availability.[1-5] It is critical for patients with persistent symptoms while on eHF, multiple food allergies requiring multiple food eliminations, or poor growth.[4,11]

HRF can be considered as an alternative first choice[1,12] (if available) due to its safety, acceptability and palatability especially in a rice-consuming population like Singapore. However, its high cost and limited accessibility remain a barrier locally. It is not recommended in non-IgE-mediated CMA due to limited data on safety and efficacy in these patients.

Partially hydrolysed formula and mammalian milks are not recommended due to high risks of allergic reactions including anaphylaxis[14-17], and lack of efficacy in CMA management. Some mammalian milk products may have nutritional and hygiene inadequacy concerns.[3,4,5,13]

Fortified plant-based beverages may be used as an alternative milk for older children (≥ 2-year-old) and adults. They are widely available and culturally acceptable across many communities. When used as directed and with appropriate nutritional consideration, the benefits of fortified plant-based beverages in providing an accessible and tolerable alternative are expected to outweigh any potential harms. Nutritional adequacy and allergy to specific ingredients must be considered prior to consumption. These beverages are inappropriate for infants under 1 year as they are nutritionally inadequate to support normal growth and development and should not be used as the main drink.[4,13,18]

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this*

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Bognanni et al 2024[1]	R1-4	Clinical Practice Guideline	Global		Children	GRADE approach	Suggest for EHF or hydrolysed rice formula as first option. AAF as 2nd option. Soy formula as 3rd option.

section can be a narrative summary.)								
	Muraro et al 2022[3]	R1-5	Clinical Practice Guideline	Global		Children & adults	AGREE II, GRADE approach	Suggest use of EHF or AAF, if better tolerated or more appropriate. Suggest against partially hydrolysed formula and mammalian milks (goat/sheep). Suggest against soy-based formula for infants < 6 months due to unknown effect of phytate, aluminium and phytoestrogen content.
	Luyt et al 2014[4]	R1-5, GPP1	Clinical Practice Guideline	UK		Children & adults	GRADE (A-E)	Suggest for EHF or AAF as the alternative formula of choice. Recommend against partially hydrolysed formula and mammalian milks. AAF suitable first line option but reserved for those infants with (due to higher cost): • multiple food allergies • severe CMA • allergic symptoms or severe atopic eczema when

								exclusively breastfed • severe forms of non-IgE-mediated cow's milk allergy (e.g. FPIES, eosinophilic oesophagitis, enteropathies) • faltering growth • reacting to or refusing to take eHF & at nutritional risk. Soy formula should not be the 1st line choice of milk substitute for infants < 6 months unless family wishes for infant to be on vegan diet. Plant-based milk/beverages are not suitable as a main drink for infants < 1 year. A nutritionally complete formula should always be chosen, preferably up to 2 years. Their use should be under the supervision of a dietitian to ensure adequate calcium intake.

	Kemp et al 2008[5]	R1-5	Consensus panel opinion	Australia		Children	Expert consensus	Recommend eHF as first choice for infants < 6 months for immediate CMA (non-anaphylactic), FPIES, FPIAP, atopic eczema. Recommend soy formula as first choice for infants > 6 months with immediate CMA, atopic eczema and gastrointestinal symptoms, in the absence of failure to thrive. Recommend AAF in severe CMA with anaphylaxis and eosinophilic oesophagitis. Recommend against partially hydrolysed formula and other mammalian milks (goat's milk).
	Venter et al 2024[13]	R5, GPP1	Clinical Practice Guideline	Global		Children & adults	Narrative review	Use of other mammalian milks is not recommended for the management of CMA due to high level of cross-reactivity and nutritional concerns.

								Plant-based beverages (e.g. soy, coconut, almond, rice, oat, hazelnut, cashew, walnut, pea, quinoa, hemp, tigernut) can be considered for toddlers (≥ 1 year) who are eating well and in children and adults. Plant-based beverages should not be used as a main drink in infants < 1 year old and should not be recommended to those with food allergies to any of the ingredients.
	Strozyk et al 2020[6]	R1-2	Systematic Review	Europe & UK	1285	Children	Systematic review (Cochrane, MEDLINE, EMBASE; up to Feb 2020) Inclusion criteria: RCTs including cross-over trials Patient: Children with CMA (IgE-mediated, non-IgE-mediated, mixed) Intervention: EHF	15 trials included. eHF is well tolerated by most children with CMA. Compared with eHF group, vomiting was more frequent in the AAF group (1/32 vs 8/30; p<0.01). No significant difference in growth, height and weight gain between eHF, AAF

							(whey +/- casein) Comparator: AAF, soy formula, EHF/LGG Outcome: Allergic reactions, tolerance acquisition, growth and quality of life. Exclusion criteria: trials using other plant-based or other animal milk-based formulas, partially hydrolysed formulas	and soy formula groups.
	Meyer et al 2017[11]	R1	Clinical Guideline	UK & US		Children	Literature search via PubMed (1980 to Aug 2017). Inclusion criteria: Systematic reviews, RCTs, prospective non-randomised studies, observational studies Exclusion criteria: Case reports, studies testing the hypoallergenicity of formulas, not conforming to	eHF will lead to symptom resolution for most children with CMA but there is a cohort that will require AAF. A blanket approach for using AAF is not advised due to cost implication for caregivers and health care systems. AAF can be used in selected group of patients: - symptoms not fully resolved on EHF

							current guidelines.	- Faltering growth/failure to thrive - multiple food eliminations - severe complex gastrointestinal food allergies - Eosinophilic oesophagitis - FPIES - anaphylaxis (limited evidence) - symptoms while breastfeeding
	Huggett et al 1997[19]	R1	Observational study	Switzerland	4	Children (2.0 – 5.5 months)	Plasma concentrations of isoflavones were measured at 2-weeks of feeding with soy-based formula (free isoflavones, total isoflavones after hydrolysis with glucuronidase and sulphatase). Results: Plasma concentrations of total isoflavones varied greatly (1.01 – 3.44 μmol/L). However, none of the plasma samples contained detectable free	Phytoestrogens (isoflavones) present in the plasma of soy formula-fed infants are in conjugated form, thus, unable to exert the hormonal effects observed in animal studies.

							isoflavones even after 4 weeks of continuous feeding.	
	Zeiger et al 1999[8]	R1	Prospective, cohort	US	93	Children (<3.5 years)	Patient: Children <3.5 years with documented IgE-associated CMA Exposure: Evaluation for soy allergy by double-blind, placebo-controlled food challenge, open challenge, or convincing previous history of an anaphylactic reaction to soy. Children tolerant to soy at entry received soy formula and were followed up for 1 year. Outcome: Soy allergy, growth parameters (anthropometric Z-score).	Only 14% (95% CI, 7.7-22.7) of IgE-mediated CMA children has concomitant soy allergy. Improved growth ($p < 0.05$) observed in soy-tolerant cohort ingesting soy formula during the 1 year follow up.
	Klemola et al 2002[7]	R1	Prospective, randomised, multicentre	Finland	170	Children (2-11 months)	Patient: Infants with documented CMA Intervention: Randomly	Soy formula was well tolerated by most infants with CMA. Cumulative incidence of adverse reactions

							assigned to receive either soy formula (n=80) or EHF (n=90). Computer generated randomisation, in blocks of 4, stratified according to 3 centres and age (0-2, 3-5, 6-8 and 9-11 months) They were followed up till 2 years old Outcome measures: Primary: Incidence of adverse reactions (OFC-confirmed) to soy formula & EHF. - SPT (cow's milk formula, EHF, soy formula) at time of diagnosis, ages 1 and 2 years. - IgE milk & soy were measured at time of diagnosis and at ages 1 and 2 years.	confirmed by DBPCFC was low (10% in soy, 95% CI 4.4-18.8%; vs 2.2% EHF, 95% CI, 0.3-7.8%, respectively). Adverse reactions to soy were similar in IgE-mediated and non-IgE mediated CMA (11% vs 9%, respectively). However, the infants in this study did not have severe enterocolitis or enteropathy). Adverse reactions to soy formula confirmed by OFC were more common in younger (<6 months) than in older (6 to 12 months) infants (5 of 20 VS 3 of 60; respectively, P = 0.01).
	Chong et al 2022[9]	R1	Retrospective review	Singapore	313	Children	Retrospective review of medical	27 (8.6%) CMA children were

							records between 2011 – 2016.	sensitized to soy milk, of which 18 (5.7%) had documented allergic reactions to soy.
	Vandenplas et al 2014[10]	R1	Systematic review, meta-analysis	Global		Children	Systematic review (PubMed, Embase, LILACS, ARTEMISA, Cochrane, Bandolier & DARE). Meta-analysis carried out whenever possible. Inclusion criteria: cross-sectional, case-control, cohort studies, clinical trials Outcome: Anthropometric growth, bone health, immunity, cognition, reproductive and endocrine functions.	Anthropometric growth patterns of children fed with soy formula (SF) were similar to those of children fed Cow's milk formula (CMF) or human milk (HM). Despite the high levels of phytates and aluminium in soy formula, Hb, serum protein, Zn and Ca concentrations and bone mineral content were found to be similar to those of children fed CMF or HM. The levels of isoflavones (genistein and daidzein) are higher in SF-fed children, but no strong evidence of a negative effect on reproductive and endocrine functions. Two studies with very low quality of evidence (one cross-

								sectional, and one case–control study) showed that SF is a risk factor for the presence of breast tissue during the second year of life (OR 2·44, 95% CI 1·11, 5·39, P 0·01). However, there is a prospective cohort study with larger sample size showed moderate quality of evidence that soy does not have an effect on the larche (SMD -0.02, 95% CI; -0.33, 0.29) Immune measurements and neurocognitive parameters were similar in all the feeding groups. In conclusion, SF is a safe feeding option for children.
	Fiocchi et al 2022[12]	R2	Expert consensus	Global		Children	2 Virtual round table series with international experts in paediatric food allergy (May 2021,	HRF can be recommended as a first-line alternative to cow's milk-based eHF or AAF, where available, in the dietary management of CMA.

							October 2021). Involved repeated voting followed by statement amendment to reach 100% agreement.	
	Meyer et al 2018	R2	Observational	UK, Europe		Children	The arsenic content in various brands of HRF (dry formula powder) sourced from Italy, France and Belgium were analysed using Ion Chromatography-Inductively Coupled Plasma Mass Spectrometry.	Inorganic arsenic levels in the HRF samples tested were very low (0.16 – 0.23 µg/kg body weight). This is well below the stipulated safe range by WHO and European Food Safety Authority.
	Caffareli et al 2002[14]	R3	Observational	Italy	24	Children (11 months – 9 years)	Patient: Children with CMA Intervention: SPT cow's milk, Specific IgE milk, OFC to PHF-whey, EHF-casein/whey, AAF (n=20) Control: Placebo (soy formula) (n=4) Outcome: Clinical reactions, positive OFC	29% (5/17) children with CMA reacted to PHF. Two (12%) children who received PHF experienced anaphylaxis. eHF-casein was tolerated by at least 90% of CMA children.
	Jarvinen et al	R3	Narrative review	Global		Children	Literature review to	Most patients

	2009[15]						examine recent studies on CMA and allergenicity of milk from other mammalian species.	with CMA cannot tolerate goat's or sheep's milk. Previous studies have shown that mare's or donkey's milk is better tolerated.
	Cox et al 2020[16]	R3	Narrative review	Global		Children	Literature review	Mammals share significant sequence homology and immunological cross reactivity between mammalian milks. Risk of clinical reactivity to goat's or sheep's milk is high >90%, and to camel's or mare's milk is very low, <5%.
	Bellioni et al 1999[17]	R3	Observational study	Sweden	26	Children	Patient: children with a positive DBPCFC to cow's milk Intervention: DBPCFC to goat's milk Control: Placebo (soy formula) Outcome: Positive DBPCCFC	24 children with CMA (92%) also reacted to goat milk. All had positive SPT and serum specific IgE to both cow's and goat's milk.
	Verduci et al 2019[18]	GPP1	Narrative review	Italy		Children	Literature review on different composition (micro- and macronutrients) of milk from different mammalian species and	Plant-based beverages should not be used as a substitute for cow's milk in children <24 months. Additionally, they may contain added

							plant-based beverages.	sugars and sweeteners.

Certainty and Magnitude of Effects:

Intervention	Certainty of Evidence
Extensively hydrolysed cow's milk formula	Moderate
Amino acid formula	Moderate
Soy formula	Moderate
Hydrolysed rice formula	Moderate
Partially hydrolysed formula	Moderate
Mammalian milks	Moderate
Plant-based beverages	Very low

Risk/Harm vs Benefit Considerations:

Intervention	Benefits versus Risks/Harms
Extensively hydrolysed formula (eHF)	• Benefits outweigh possible harms. eHFs are well tolerated and do not negatively affect nutrition or growth.
Amino acid formula (AAF)	• Benefits outweigh possible harms for selected group of children. AAF supports normal growth and may support longitudinal catch-up growth.
Soy formula (SF)	In appropriately selected individuals (children > 2 years old and adults), the benefits of soy formula clearly outweigh the potential harms. Soy formula is well tolerated and does not negatively affect nutrition or growth in this age group. It is readily available over the counter, more palatable, and less expensive than extensively hydrolysed formula (EHF) or amino acid formula (AAF), making it a practical and accessible option. Soy is also a staple ingredient in the local diet, supporting its cultural acceptability and familiarity among patients and caregivers. Taken together, these practical advantages, combined with its established tolerability profile in appropriately selected individuals, support a clear net benefit for its use in this population. • Only <15% of infants with CMA have concomitant soya allergy [Klemola, Zeiger]. In a retrospective review of Singaporean children with IgE-mediated CMA (Kok Wee), majority can tolerate SF; only ¬5% has concomitant soy allergy. • In a single prospective randomised study (Klemola, n=170), concomitant soy allergy occurred more

		commonly in infants under 6 months than in those 6 - 12 months old (25% vs 5%, respectively, p=0.01). • SF contains high concentrations of phytate, aluminium and phytoestrogens (isoflavones). Animal studies have shown that high dose phytoestrogens can adversely affect the development of reproductive organs and fertility [King, BSACI]. However, there is no evidence of similar effects in humans. Studies have shown that most of the phytoestrogens present in the plasma of SF-fed infants are in conjugated form, thus, unable to exert the hormonal effects observed in animal studies (Huggett). Based on a 2014 systematic review/meta-analysis (Vandenplas), despite the high levels of phytates and aluminium in SF, it does not impair the absorption of minerals and trace elements or cause aluminium toxicity (except in preterm infants or infants with renal failure). There is no evidence of negative effect of phytoestrogens on reproductive and endocrine functions.
	Hydrolysed rice formula (HRF)	• Benefits outweigh possible harms. HRFs are well tolerated and do not negatively affect nutrition or growth. It is more palatable than eHF or AAF. Rice is also a staple diet in our local population. However, currently, access to HRF is limited and is not readily available in Singapore. • There are concerns about inorganic arsenic content in rice milk. A recent study found that inorganic arsenic levels in HRF are within the safety range as stipulated in European Food Safety and World Health Organization regulations (Meyer, Fiocchi). • Limited data for use in infants with non-IgE-mediated CMA.
	Partially hydrolysed formula (PHF)	• Possible harms, including risk of anaphylaxis, outweigh the benefits. • Several studies reported increased allergic reactions to PHFs.
	Mammalian milks	• Possible harms, including risk of anaphylaxis, outweigh benefits. There is high degree of cross reactivity with cow's milk proteins, especially for goats'/sheep's milk (>90%). • > 80% can tolerate donkeys', mares' or camels' milk but they are not recommended due to nutritional & hygiene concerns.
	Plant-based milks	• There is insufficient evidence to weigh up the potential harms versus benefits. • Plant-based beverages include soy, coconut, rice, oat, almond, cashew, hazelnut, walnut, pea, quinoa

		and sesame. These differ in terms of nutrition composition and characteristics. Hence, it is important to compare their nutritional composition against that of cow's milk and ensure that they are fortified with calcium and vitamin D. • In infants < 1 year old, plant-based beverages are nutritionally inadequate to support normal growth and development in comparison to infant formulas or breastmilk and should not be used as the main drink. • Adverse effects from inappropriate use can lead to poor growth, malnutrition, electrolyte derangement, kidney stones, and severe nutrient deficiencies including iron deficiency anaemia, rickets and scurvy.
Patient/ caregiver values	Breastfeeding is preferred, but when this is not possible, the best alternative should be chosen based on individual patient's factors (e.g. disease severity, galactosemia, persistent lactose intolerance), tolerance or palatability, and patient's/family's values and preferences.	

Intervention	**Patient/caregiver values**
Extensively hydrolysed formula (eHF)	• Some caregivers may prefer plant-based formula that does not contain animal proteins (e.g. vegan). • Some caregivers may be concerned about the palatability ('bad taste').
Amino acid formula (AAF)	• Some caregivers may prefer AAF because it does not contain milk/animal proteins. • Some caregivers may be concerned about 'green stools' or 'bad smell or taste' of the formula.
Soy formula (SF)	• Some caregivers may prefer SF because it does not contain any animal proteins for cultural, religious or lifestyle reasons (e.g. vegan). They may also prefer SF due to better palatability compared to EHF or AAF. • Some caregivers may still be concerned about the adverse effects of phytoestrogens (isoflavones) which may possess weak oestrogenic activity.
Hydrolysed rice formula (HRF)	• Some caregivers may prefer HRF because it does not contain any animal proteins (e.g. vegan). • Some caregivers may prefer HRF than SF due to concern of phytoestrogen content in SF.
Partially hydrolysed formula (PHF)	• Some infants may prefer the taste of PHF compared to eHF. • Some caregivers may prefer PHF due to easy accessibility and better palatability.

		• However, it is not recommended due to its lack of efficacy and safety.
	Mammalian milks	• Some caregivers may prefer goat's milk formula due to easy accessibility (over the counter), better palatability and lower cost. However, it is not recommended due to high degree of cross reactivity with cow's milk proteins and risk of allergic reactions including anaphylaxis.
	Plant-based beverages	• Some caregivers may choose plant-based beverages due to cultural, religious or lifestyle preferences (e.g. vegan) or health-related perceptions (e.g. gut health).

Stakeholder feedback (if available):

Resource, Cost Considerations:

Intervention	Resource/Cost
Extensively hydrolysed formula (eHF)	The price is higher than standard cow's milk formula but lower than AAF.
Amino acid formula (AAF)	AAF is more expensive than other formulas. Thus, we do not suggest this as the first option. We suggest this option only for selected group of infants.
Soy formula (SF)	The price is quite similar to standard cow's milk formula, lower than eHF and AAF.
Hydrolysed rice formula (HRF)	We are unable to provide any information on the cost as it is not yet available in local retail stores.
Partially hydrolysed formula (PHF)	PHF is more expensive than standard cow's milk and soy formula but is cheaper than EHF and AAF.
Mammalian milks	The price of goat's milk formula is quite similar to standard cow's milk formula. Donkeys', mares' or Camels' milk are expensive.
Plant-based beverages	The price is lower than infant formulas but higher than fresh cow's milk.

Equity Acceptability Feasibility

Intervention	Equity	Acceptability	Feasibility
Extensively hydrolysed formula (eHF)	No reimbursements or subsidies. Financial assistance may be available for those eligible after financial assessment.	Some caregivers are concerned about the palatability of the formula. Two studies suggested that palatability of whey-based eHFs containing lactose may be more palatable.	Limited accessibility (prescription required; only available in some hospitals and retail pharmacies).

			If a child does not accept the taste of eHF, caregiver can try to mix and titrate the formula with breastmilk (avoid storing in mixed form to avoid autodigestion).	
	Amino acid formula (AAF)	No reimbursements or subsidies. Financial assistance may be available for those eligible after financial assessment.	Some caregivers/ clinicians prefer AAF because it does not contain milk proteins. Some caregivers may be concerned about 'green stools' or 'bad smell and taste'.	Limited accessibility (prescription required).
	Soy formula (SF)	No reimbursements or subsidies.	Some caregivers prefer SF because it does not contain any animal proteins (e.g. vegan). Some caregivers may still be concerned about the adverse effects of phytoestrogens (isoflavones) which may possess weak oestrogenic activity. Some caregivers/clinicians may prefer SF due to better palatability compared to EHF or AAF.	OTC
	Hydrolysed rice formula (HRF)	No reimbursements or subsidies.	Some caregivers/clinicians may prefer HRF because it does not contain any animal/milk proteins. Some caregivers may prefer HRF than SF due to concern of phytoestrogen content in SF.	Limited accessibility
	Partially hydrolysed formula (PHF)	No reimbursements or subsidies.	Some infants may prefer the taste of PHF compared to EHF. Some caregivers may prefer PHFs due to easy accessibility and better palatability.	OTC

Mammalian milks	No reimbursements or subsidies.	Some caregivers may prefer goat's milk formula due to easy accessibility, better palatability and lower cost.	OTC
Plant-based beverages	No reimbursements or subsidies.	Some caregivers/clinicians may prefer plant-based beverages because it does not contain any animal/milk proteins. Some caregivers may prefer plant-based beverages due to easy accessibility, perceived health benefits and lower cost.	OTC

Abbreviations:
CMA – Cow's milk allergy
OTC – Over the Counter

Stakeholder feedback (if available): NA

Workgroup Consensus Survey (RAND/UCLA):

R 3.1: We strongly recommend using extensively hydrolysed cow's milk formula (eHF-CM) or soy formula (SF)* as first choice, and an amino acid-based formula (AAF) as second choice in infants with cow's milk allergy who need a breastmilk alternative. [EM3-1]

***When initiating SF, clinicians should discuss with caregivers the low but possible risk of concomitant soy allergy, particularly in infants with no prior soy exposure.**

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	9%	9	1	8	No Disagreement

R 3.2: We conditionally recommend that hydrolysed rice formula (HRF) can be considered as an alternative first choice (if available) in infants with cow's milk allergy.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
5	9	14%	8	1	8	No Disagreement

R 3.3: We strongly recommend against using partially hydrolysed cow's milk formula and mammalian milks (goat/sheep) in children with cow's milk allergy (both IgE and non-IgE-mediated) due to high risk of allergic reactions.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	5%	9	0	8	No Disagreement

GPP 3.4: In children (≥ 2 years old) and adults diagnosed with cow's milk allergy who need a milk substitute, fortified plant-based beverages can be used. They should not be used as a main source of nutrients in infants < 1 year old.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
4	9	16%	8	1	8	No Disagreement

External Review Feedback:

Public Consultation:

References:

1. Bognanni A, Fiocchi A, Arasi S, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XII - Recommendations on milk formula supplements with and without probiotics for infants and toddlers with CMA. World Allergy Organ J. 2024;17(4):100888.
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Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-2*
Clinical/PICO Question:	Is maternal cow's milk dietary elimination required for breastfed infants with cow's milk allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no)*	**R 3.5: We strongly recommend against routine maternal cow's milk dietary elimination for breastfed infants with IgE-mediated cow's milk allergy, unless the infant is symptomatic whilst being exclusively breastfed. If a trial of maternal cow's milk elimination is required, this should only occur for an initial period of 2 to 4 weeks, followed by reintroduction into the maternal diet to establish diagnosis.** **GPP 3.6: In breastfed infants with suspected Food Protein-Induced Allergic Proctocolitis (FPIAP) (non-IgE-mediated CMA), a trial of maternal cow's milk elimination should be considered. If a trial of maternal cow's milk elimination is required, this should only occur for an initial period of 2 to 4 weeks, followed by reintroduction into the maternal diet to establish diagnosis.** **GPP 3.7: In breastfed infants with suspected FPIES (non-IgE-mediated CMA), routine maternal cow's milk elimination in breastfeeding mothers is not recommended unless infant is symptomatic while exclusively breastfed.** **GPP 3.8: If maternal cow's milk dietary elimination is required, Vitamin D and calcium supplementation should be advised and referral to dietitian for nutritional counselling can be considered for mother.**
Rationale:	Breastfeeding remains the optimal source of nutrition for infants. Hence, active support for mothers to continue breastfeeding is essential. >99% of infants with IgE-mediated CMA will tolerate breastmilk from a mother who is not on elimination diet.[1] The concentrations of cow's milk protein (ß-lactoglobulin) detected in breastmilk of most lactating mothers are very low (in nanogram/millilitre), and less likely to cause an allergic reaction.[2,3] Hence, most breastfeeding mothers do not necessarily need to avoid cow's milk in their diet, unless the infant is symptomatic whilst being exclusively breastfed.[1,2,4,5] The potential harms associated with maternal cow's milk exclusion during breastfeeding in infants with CMA outweigh the benefits. These include reduction in immune-enhancing factors in breastmilk and negative impact on nutritional, financial and social well-being of the mother and family.[1] In **FPIAP (non-IgE-mediated CMA),** a trial of maternal CM avoidance is only advised if the clinical history is strongly suggestive of CMA. If a trial of maternal cow's milk elimination is required, this should only occur for an initial period of 2 to 4 weeks (assessing for symptom improvement/resolution) followed by reintroduction into the maternal diet (assessing for recurrence of symptoms). [1,5,6] In **FPIES (non-IgE-mediated CMA),** only 5% of CMA infants are symptomatic whilst being exclusively breastfed[5,7]. However, the amount of cow's milk/dairy intake in mother's diet during breastfeeding may have an impact on the reaction threshold in acute FPIES.

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
McWilliam et al 2023[1]	R1, GPP1-3	Clinical Practice Guideline	Global		Children	Narrative Review	DO NOT recommend routine maternal cow's milk elimination in breastfed infants with CMA, unless symptoms are evident while the infant is exclusively breastfeeding. >99% of infants with IgE-mediated CMA will tolerate BM from mother who is not on elimination diet. Active support to continue breastfeeding is essential. Only 1 case report of anaphylaxis in a young, breastfed infant with CMA. Lack of high-quality evidence. If maternal cow's milk dietary elimination is required, referral to dietitian, along with Vitamin D & calcium supplementation should be advised.
Muraro et al 2022[4]	R1	Clinical Practice Guideline	Global		Children	AGREE II, GRADE approach	Suggest that most breastfeeding mothers whose infants have a food allergy do not need to avoid the offending food themselves. They rarely will react to very low levels of allergens in breastmilk.
Gamirova et al 2022[3]	R1	Systematic Review	Europe, UK, Australia		Children	10 interventional and 7 observational studies.	Levels of food proteins in human milk are much lower than ED for 1% of allergic individuals. Probability of an IgE mediated allergic reaction in a food-allergic infant breastfed by mother consuming the relevant food is

								estimated to ≤1:1000.
	Luyt et al 2014[2]	R1	Clinical Practice Guideline	UK		Children	GRADE (A-E) approach	Mothers should be encouraged to continue breastfeeding and usually do not require dietary dairy restrictions unless the infant has symptoms whilst being breastfed.
	Meyer et al 2019[5]	GPP1-3	Position paper (expert consensus)	Global		Children	Systematic literature search using PubMed, Cochrane and EMBASE databases (1990 – May 2018) Study population consisting of breastfed children with non-IgE-mediated food allergies. Levels and quality of evidence assessed using Scottish Intercollegiate Guidelines Network (SIGN) grading system. Delphi method used for reaching consensus on recommendations.	Do not recommend routine allergen avoidance in breastfeeding mothers unless a child presents with symptoms whilst breastfeeding, in which case it may be required. The cornerstone for diagnosis of non-IgE-mediated food allergy remains a maternal elimination diet for 2-4 weeks with symptom improvement/resolution of the presenting symptoms, followed by reintroduction with symptom deterioration, unless convincing history of FPIES or severe associated symptom is present when reintroduction would not occur. During breastfeeding, the amount of allergen intake may have an impact on acute FPIES. In FPIES, maternal avoidance is not required if breastfed infants only react to a food introduced during complementary feeding.
	Vandenplas et al 2024[6]	R1, GPP1-3	Position Paper	Global		Children	Literature search using Medline database. Include systematic	CMA in exclusively breastfed infants is a rare condition. Dietary restrictions in a breastfeeding

							reviews and meta-analyses (till May 2022). Consensus agreement using score 1-9. If 4 or more panel members voted <6, there was <75% consensus, and the statement will be rejected. Open for public consultation between September 30 and October 12, 2022.	mother are usually not necessary. In rare cases when CMA is suspected in an exclusively breastfed infant, a diagnostic maternal CM-free diet for 2–4 weeks whilst continuing to breastfeed may be considered. In order to confirm the diagnosis, CM should then be reintroduced in the maternal diet with monitoring of symptoms. In case of a prolonged maternal elimination diet, supplementation of mothers with calcium and vitamin D is recommended, while supplementation with iodine and vitamin B12 can be considered.
	Allen et al 2022[8]	R1, GPP3	Delphi consensus study	UK		Children	Delphi study (CREDES guidance) involving two rounds of anonymous consensus building and an open meeting between January and July 2021. Literature review using Medline & Embase databases.	Maternal dietary restriction is not usually necessary for a breastfed infant with CMA. Ensure adequate maternal dietary intake of Calcium and Vitamin D if mother requires dietary dairy elimination.
	Mehr et al 2017[7]		Cross-sectional	Australia	230	Children (<2 years)	An Australia-wide survey (2012-2014) was undertaken through the Australian Paediatric Surveillance Unit, with monthly notification of new cases of acute	The incidence of FPIES in Australian infants (<24 months) was 15.4/100,000/year. 5% reacted during exclusive breastfeeding.

							FPIES in infants by 1400 participating paediatricians.	

Certainty and Magnitude of Effects:	The certainty of evidence (GRADE approach). **R3.5:** Low **GPP3.6 – 3.8:** Not graded (GPP)
Risk/Harm vs Benefit Considerations:	Possible harms from maternal cow's milk dietary elimination in breastfeeding mothers, outweigh the benefits. Maternal dietary exclusion of cow's milk may reduce immune-enhancing factors in breastmilk and negatively affects maternal nutrition. Additionally, it can lead to heightened maternal anxiety and reduction in quality of life for both the mother and family.
Patient/ caregiver values	Some caregivers may find it challenging to adhere to an elimination diet, which can sometimes lead to increased anxiety and impaired social functioning for both the mother and family. **Stakeholder feedback (if available):**
Resource, Cost Considerations:	Elimination diets can place a significant burden on caregivers and families due to restrictions in social activities and cultural celebrations. Some mothers may experience guilt or anxiety due to perception that the infant's symptoms are caused by foods consumed in their diet. This emotional and psychological stress can negatively affect a mother's motivation to continue breastfeeding, resulting in the use of milk substitutes or formulas, which is more costly.
Equity **Acceptability** **Feasibility**	Cow' milk and dairy products are ubiquitous in the diet, making complete avoidance particularly difficult. Maintaining a strict elimination diet often requires label reading, meal planning and thorough preparation, which can be time-consuming and overwhelming. Sourcing for suitable substitutes can also be logistically challenging. These feasibility issues may lead to reduced motivation to continue breastfeeding, which may in turn lead to the use of breastmilk substitutes or infant formulas contributing to fiscal and financial burden. Some caregivers may feel guilty or anxious as they are concerned about inadvertently causing the infant's symptoms with the food that they consume. Some caregivers may experience isolation due to social restrictions. As a result, they may resort to using breastmilk substitutes, which they perceive as more socially acceptable or practical in these circumstances. **Stakeholder feedback (if available):**

Workgroup Consensus Survey (RAND/UCLA):

R 3.5: We strongly recommend against routine maternal cow's milk dietary elimination for breastfed infants with IgE-mediated cow's milk allergy, unless the infant is symptomatic whilst being exclusively breastfed. If a trial of maternal cow's milk elimination is required, this should only occur for an initial period of 2 to 4 weeks, followed by reintroduction into the maternal diet to establish diagnosis.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	6%	9	1	8	No Disagreement

GPP 3.6: In breastfed infants with suspected Food Protein-Induced Allergic Proctocolitis (FPIAP) (non-IgE-mediated CMA), a trial of maternal cow's milk elimination should be considered. If a trial of maternal cow's milk elimination is required, this should only occur for an initial period of 2 to 4 weeks, followed by reintroduction into the maternal diet to establish diagnosis.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	9%	9	1	8	No Disagreement

GPP 3.7: In breastfed infants with suspected FPIES (non-IgE-mediated CMA), routine maternal cow's milk elimination in breastfeeding mothers is not recommended unless infant is symptomatic while exclusively breastfed.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	6%	9	1	8	No Disagreement

GPP 3.8: If maternal cow's milk dietary elimination is required, Vitamin D and calcium supplementation should be advised and referral to dietitian for nutritional counselling can be considered for mother.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus

	5	9	16%	9	1	8	No Disagreement
External Review Feedback:							
Public Consultation:							

References:

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Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-3*
Clinical/PICO Question:	Is baked milk products safe in children with cow's milk allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.9: We strongly recommend that patients with cow's milk allergy should be assessed for tolerance to baked milk products. If tolerated, regular consumption of baked milk products should be recommended.**
Rationale:	Majority (70-80%) of patients with cow's milk allergy are able to tolerate baked milk products.[2-5] The process of baking utilizes high heat (e.g. 180°C for 30 minutes) which alters the conformation of heat-labile proteins, resulting in loss of conformational epitopes and reduced allergenicity of cow's milk proteins. The addition of wheat/grain matrix in baked products creates the matrix effect by decreasing the exposure of cow's milk proteins to the gut's immune system and reduced the allergenicity further.[3,6] Since cow's milk is ubiquitous in our diet, strict avoidance of all forms of cow's milk can impose significant dietary restrictions and adversely impact the quality of life of patients and their family.[7] Incorporating baked milk products facilitates liberalization of diet, improves nutritional status and quality of life, and potentially decreases parental anxiety.[5,8] It is safe and well-tolerated with low risk of severe allergic reactions/anaphylaxis (<10%).[3,5] Currently, there is insufficient evidence to draw conclusions that consumption of baked milk products accelerates the resolution of cow's milk allergy (majority are observational studies with high heterogeneity and only 1 RCT).[7,9] However, tolerance to baked milk may be used as a marker to identify transient versus persistent phenotype in patients with CMA.[4]
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Nowak-Wegyrzyn et al 2008[3]	R1	Prospective cohort	US	100	Children (2.1 – 17.3 years)	Intervention: Heated milk-tolerant subjects to incorporate heated milk products (muffin/waffle) daily (at least 1 – 3 servings per day) Comparator: Heated milk-reactive subjects to avoid all forms of milk. Re-evaluation every 3 months.	75% tolerated baked milk. 9% (8/91) had anaphylaxis to heated milk during challenge. Heated milk-reactive subjects had significantly larger skin prick test wheals and IgE milk and casein levels and have a more severe phenotype with higher risk of anaphylaxis (35%).

	Kim et al 2011[4]	R1	Prospective cohort	US	88	Children (2.1 – 17.3 years)	Intervention: BM-tolerant participants to incorporate baked milk daily Comparator: BM-reactive participants completely avoid all forms of cow's milk. OFC to unheated cow's milk at 6-12 months.	74% tolerated baked milk. 60% of BM-tolerant participants became tolerant to unheated cow's milk. Only 9% of BM- reactive became cow's milk tolerant ($p < 0.001$). Tolerance of BM is a marker of transient allergy phenotype and reactivity to BM suggests a more persistent phenotype. Incorporating BM into diet appears to accelerate the development of tolerance compared to strict avoidance.
	Lambert et al 2017[7]	GPP1	Systematic review	UK	3 studies included	Children (0-18 years)	Systematic review (Medline, Embase, CINAHL). Inclusion criteria: RCTs, case-control or cohort studies). Patient: Children with CMA Intervention: baked milk Comparator: strict avoidance, none Outcome: Resolution of CMA confirmed by OFC.	There is very weak or little evidence to support that ingestion of BM products accelerates resolution of CMA (low quality studies, high heterogeneity and risk of bias).
	Esmaeilzadeh et al 2018[9]	GPP1	Randomised controlled	Iran	84	Children (0.5 -3 years)	Randomised controlled trial with allocation ratio of 1:1.	88.1% of BM-tolerant patients in the BM consumption

							Patient: Children with CMA who is BM-tolerant confirmed by OFC. Intervention: Daily consumption of baked milk products (muffin for 6 months followed by pizza for another 6 months) Comparator: Complete avoidance of all forms of milk Outcome: Tolerance to unheated milk (OFC-confirmed) at 1 year	group developed tolerance to unheated milk vs 66.7% of those in the BM avoidance group (p=0.018). Conclusion: BM introduction in patients with CMA can accelerate tolerance to unheated cow's milk.
	Cogurlu et al 2022[5]	R1	Prospective cohort	Turkey	36	Children (< 2 years)	OFC-confirmed cow's milk allergic patients underwent OFC to baked milk. BM-tolerant group to incorporate baked milk into diet daily with 3-monthly intervals of OFC. BM-reactive group completely avoid all forms of cow's milk and offered 3-monthly OFC.	80.5% tolerated baked milk at median age of 12 months (IQR, 8.2-23.2). Baked milk tolerant patients outgrow milk allergy at an earlier age (14 months; IQR 10.0-15.0) than patients who are BM-reactive (23.5 months; IQR 20.0-31.0)(p=0.005). 3 out of 26 (8.3%) experienced anaphylaxis during BM OFC. Regular ingestion of BM improves nutritional content and quality of life, facilitates dietary

								expansion and decrease FA-related anxiety.
	Anagnostou et al 2024[6]	R1	Systematic review and meta-analysis	US, Canada	29 studies included	Children (0-18 years)	Systematic review (Medline, Embase, Cochrane, Web of Science Core Collection, CINAHL till Feb 2023). Inclusion criteria: RCTs, cohort studies, case-control, case-series Patient: Children with IgE-mediated CMA Intervention: Incorporation of baked milk into the diet Comparator: strict avoidance Outcomes: Rate of resolution of CMA, rates of allergic reactions/anaphylaxis, rates of epinephrine use.	Given only 2 BM studies, no outcomes were meta-analysed, with only 3 outcomes reported in these studies. No conclusion can be drawn with regards to if BM ingestion accelerates the development of tolerance (low quality studies, high risk of bias, and high heterogeneity).
	BSACI 2014[2]	R1	Clinical Practice Guideline	UK		Children		Majority (75%) of children with CMA are able to tolerate BM products. Home reintroduction may be attempted in children who have had only mild symptoms (only cutaneous symptoms)

								on noteworthy exposure (e.g. a mouthful of fresh milk), no reaction to milk in the past 6 months, and a significant reduction in sIgE/SPT wheal diameter.
	Venter et al 2024[1]	R1	Clinical Practice Guideline	US		Children		Management of CMA includes establishing tolerance to baked milk. BM diet can result in greater dietary options, improved nutrition and potentially decrease parental anxiety with regards to accidental ingestion. Several small studies reported that regular BM consumption might accelerate tolerance acquisition of milk, while others found no difference.

Abbreviation:
BM – baked milk
CMA – cow's milk allergy

Certainty and Magnitude of Effects:	Safety of baked milk products: moderate certainty of evidence Acceleration of acquisition of tolerance: very low certainty of evidence Improvement in quality of life and reduction in parental anxiety: very low certainty of evidence
Risk/Harm vs Benefit Considerations:	Benefits outweigh possible harms. Studies have shown that it is safe with low risk of severe allergic reactions/anaphylaxis (<10%). Inclusion of baked milk products into the diet can broaden dietary options, enhance nutrition, and improve social functioning and quality of life.
Patient/ caregiver values	Some children may dislike the taste or texture of baked milk goods.

<table>
<tr><td></td><td>Some caregivers may be concerned about high sugar content in baked products. Some may perceive baked goods as an unhealthy option due to the association with processed carbohydrates and fats.
Preparing baked milk products at home to meet nutritional requirement may require additional time, effort, and resources. This can be particularly burdensome for some caregivers who have limited cooking skills or busy schedules.

Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>Baked milk goods, such as muffins and breads, are made with affordable and widely available ingredients, making this approach practical and sustainable for most patients and families.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Incorporation of baked products into diet is socially acceptable and convenient. This allows patients with CMA to enjoy more diverse food and participate in social and cultural events. Commercial baked products is readily available in stores and affordable (ensure that milk is listed as third ingredient or further down in the ingredients list).

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 3.9: We strongly recommend that patients with cow’s milk allergy should be assessed for tolerance to baked milk products. If tolerated, regular consumption of baked milk products should be recommended.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>26%</td><td>9</td><td>1</td><td>8</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

1. Venter C, Meyer R, Groetch M, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines update - XVI - Nutritional management of cow's milk allergy. World Allergy Organ J. 2024;17(8):100931.
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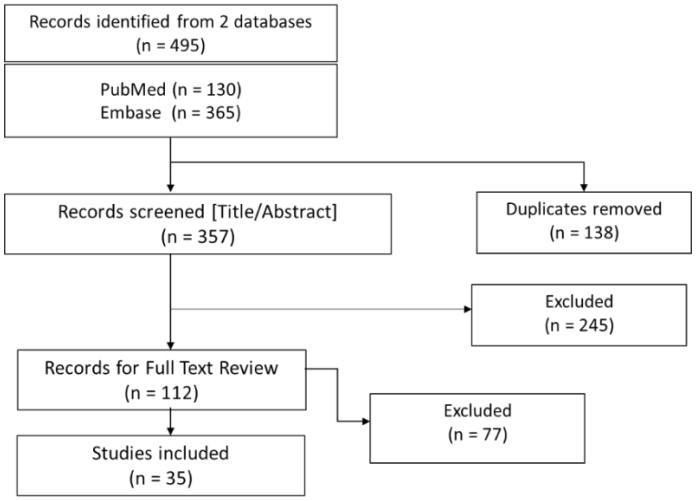
Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Egg Allergy
Subgroup Members:	Samantha Lee May Ping
Main Clinical Question(s):	1. Is MMR, influenza or yellow fever vaccination safe to be administered in the primary care setting in adults or children with egg allergy? 2. Are baked egg products safe in children with egg allergy? 3. Are lysozyme-containing products or mucolytics safe in adults or children with egg allergy?
Population (age limit, inclusion criteria, excluded groups, special groups):	Adults or children with egg allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	1. MMR vaccination in primary care setting 2. Influenza vaccination in primary care setting 3. Yellow fever vaccination in primary setting 4. Extensively heated or baked egg 5. Lysozyme-containing products or mucolytics
Comparator (if applicable):	None (1,2,3), Strict avoidance (4,5)
Outcomes (specify critical/primary vs secondary):	Safety (risk of allergic reactions) and feasibility
Publication Dates:	2000 – 2024 (include publications in 2024 to include latest CDC publication on influenza vaccines in egg-allergic patients)
Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria – Existing CPGs, SRs, MAs, RCTs, cohort studies Exclusion criteria – Case reports, animal research, in-vitro/lab research, non-English papers
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** 1 Egg Hypersensitivity/ (971) 2 ((egg adj2 hypersensitivit*) or (egg adj2 allerg*)).ab,ti. (1385) 3 1 or 2 (1778) 4 exp Child/ (2224255)

	5 (child or children or toddler? or preschooler?).ab,ti. (1498920) 6 4 or 5 (2693030) 7 (heated or baked or cooked).ab,ti. (42915) 8 3 and 6 and 7 (154) 9 limit 8 to (english language and yr="2000 - 2024") (147) 10 Measles-Mumps-Rubella Vaccine/ or Influenza Vaccines/ (31014) 11 ("MMR vaccin*" or "MMRV vaccin*" or "flu vaccin*" or "Measles Mumps Rubella vaccin*" or "Measles, Mumps, Rubella vaccin*" or "Measles-Mumps-Rubella vaccin*" or "Measles Mumps Rubella Varicella vaccin*" or "Measles, Mumps, Rubella, Varicella vaccin*" or "Measles-Mumps-Rubella-Varicella vaccin*" or Pluserix or Priorix or Trimovax or "Triviraten Berna" or Virivac or ProQuad).ab,ti. (4501) 12 10 or 11 (32788) 13 3 and 12 (182) 14 limit 13 to (english language and yr="2000 - 2024") (131)
Search Outcomes:	**Number of studies:** Clinical Question 1 - Is MMR, influenza or yellow fever vaccination safe to be administered in the primary care setting in adults or children with egg allergy?  Clinical Question 2 – Are baked egg products safe in children with egg allergy? **Number of studies:** Number of potential studies identified by database searches: 502 (Embase 344, PubMed 158) Total number of studies screened once duplicates were removed: 368 Number and type of studies included: 29 Clinical Question 3 - Are lysozyme-containing products or mucolytics safe in adults or children with egg allergy? **Number of studies:** Number of potential studies identified by database searches: 8 Number and type of studies included: 5

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-4*
Clinical/PICO Question:	Is MMR, influenza or yellow fever vaccination safe to be administered in the primary care in adults or children with egg allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.10: We strongly recommend that Measles, Mumps and Rubella (MMR) or Measles, Mumps, Rubella and Varicella (MMRV) or influenza vaccine be given in primary care to patients with egg allergy of any severity, with routine precautions.** **R 3.11: We strongly recommend against split dosing, prior allergy testing to vaccines or eggs, prior allergy specialist review or extended observation post administration of MMR, MMRV or influenza vaccines in patients with egg allergy.** **R 3.12: We strongly recommend that patients with egg allergy who require Yellow Fever vaccination should be referred to an allergy specialist for assessment and supervised administration.**
Rationale:	The MMR vaccine is cultured on chicken fibroblast cell cultures and contains no, or at most very little quantities (picogram) of residual egg protein, insufficient to cause an allergic reaction.[1,2] Studies have shown that it has been safely administered to large numbers of egg-allergic individuals in primary care settings. [3-8] Allergic reactions to MMR vaccines are rare and more likely to be attributed to non-egg vaccine components, such as gelatin.[2] Most influenza vaccines are grown in chick embryos and may contain residual egg protein.[3,9] The only reported case of a death following influenza vaccination, published in 1969, provides limited details, and its causal relationship to egg allergy remains unclear.[10] Recent randomized trials and prospective studies involving H1N1 and seasonal influenza vaccines, where the residual egg ovalbumin content is restricted to ≤1 µg/dose, have shown that individuals with egg allergy can safely receive influenza vaccine without any additional precautions.[11-14] A recent review of 28 studies,[14] including 4,315 individuals with egg allergy (656 of whom had a history of egg anaphylaxis), found no severe reactions associated with influenza vaccination. Most of the current influenza vaccines contain very low amounts of ovalbumin (<0.12 mcg/ml) and can be administered safely in primary care by the intramuscular route, even in those with prior history of anaphylaxis to egg.[2,3,4,15-18] The intranasal live attenuated influenza vaccine (LAIV) is also grown in hen's egg, and therefore, contains egg protein. The ovalbumin content of LAIV is very low (<0.12 mcg/ml) and has been shown to be safe to administer to children with egg allergy in any setting, including primary care and schools.[3,4,11-13] Current evidence has shown that split dosing, prior allergy testing, or longer observation periods have shown no differences in the rate of adverse reactions, and therefore, these practices are unnecessary.[1-4,8,16] Presence of egg allergy does not increase the risk of allergic reactions or anaphylaxis to the MMR, MMRV or influenza vaccines.[5,6,12-14] Anaphylaxis to MMR and influenza vaccines are extremely rare, approximately less than one per million doses, and may be attributed to other vaccine components, such as gelatin or neomycin.[2] Thus, patients with suspected allergic reaction or anaphylaxis to the vaccines should not

undergo further vaccination and referral to an allergy specialist for further evaluation is warranted.[2,3,4,8,17,18]

The Yellow Fever Vaccine (YFV) is a live vaccine cultured in hen's eggs and contains generally higher residual egg protein than in influenza vaccines.[19] Anaphylaxis following yellow fever vaccination in individuals with egg allergy has been reported, although these incidents are rare.[1,20] Therefore, several international guidelines have recommended that patients with egg allergy who requires yellow fever vaccination should be referred to an allergy specialist for assessment and supervised administration, ideally at least 2 months prior to travel to endemic regions.[1,3,4,8] Further evaluation with vaccine skin testing (e.g. skin prick test, intradermal test), single/graded dosing or desensitization may be considered in these patients.[2,4,7,21]

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

MMR vaccinations

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Abrams et al 2024[1]	R1-2	Narrative Review	Canada		Children & Adults	Literature review	Vaccines for MMR and MMRV are grown in chick embryo fibroblast cultures; however, the vaccines themselves contain little to no egg protein. The Canadian Immunization Guide (CIG) advises that MMR or MMRV vaccines can be administered in a routine manner in individuals with egg allergies without allergy consultation, skin testing, or prolonged observation. The JTFPP similarly supports the safety of MMR or MMRV vaccination in individuals allergic to eggs without any special precautions or testing. Referral to an allergist prior to vaccination

								is not necessary.
	Australasian Society of Allergy & Clinical Immunology (ASCIA) 2022[3]	R1-2	Clinical Practice Guideline	Australia		Children & adults	Literature review	MMR or MMRV vaccine is cultured on chicken fibroblast cell cultures and contains no residual egg allergen. It has been safely administered to large numbers of egg-allergic individuals. The rare allergic reactions to MMR vaccines that have occurred have been attributed to non-egg ingredients such as gelatin. Egg allergic individuals can be safely vaccinated with the MMR or MMR-V vaccine which contains no egg protein. Special precautions such as split dosing, prior allergy testing with the vaccine or egg, allergy specialist review before vaccination, or prolonged waiting period after administration are not required.
	Leech et al 2021[4] (BSACI)	R1-2	Clinical Practice Guideline	UK		Children & adults	GRADE (A-E)	The MMR vaccine is cultured in chick embryo fibroblast cell culture and not from hen eggs

								themselves. It does not contain hen egg allergens in clinically relevant quantities. All children/adults with egg allergy should receive the MMR immunization in primary care (Grade B recommendation).
	Chua et al 2018[8]	R1-2	Joint consensus statement	Hong Kong		Children & Adults	Expert consensus	All patients with suspected or confirmed egg allergy should receive the MMR/MMRV vaccination as a matter of routine in primary care. Should there be any significant concerns from patients, parents or health care professionals, health care professionals who are capable of recognising signs and symptoms of an allergic reaction can provide 15 to 30 minutes of monitoring following vaccination. Individuals who have developed or are suspected to have developed an allergic reaction to the vaccine or other vaccine components (such

								as gelatine or neomycin) should not undergo further vaccination with these products. Referral to an allergy specialist for further evaluation can be considered.
	Tan et al 2016[5]	R1	Prospective, observational	Malaysia	87	Children	Prospective observational study between Mar – Dec 2014. Patient: Infants admitted to paediatric ward for MMR vaccination due to suspected egg allergy Intervention: Intramuscular injection of MMR vaccine Comparator: none Outcome: Allergic reactions Exclusion criteria: HIV positive, suspected or confirmed primary immunodeficiency.	54 infants with egg allergy VS 33 infants without egg allergy. 2/54 (3.7%) developed rashes within 2 hours post-injection which spontaneously resolved. None had anaphylaxis. No statistically significant association between history of egg allergy and allergic reactions to MMR vaccine (p=0.632).
	Dreskin et al[2] (WAO) 2016	R1	Joint consensus statement (ICON)	Global		Children & Adults	Expert consensus with representatives from WAO, EAACI,	The manufacture of vaccines containing live virus produced in chick embryo fibroblast

							AAAAI and ACAAI.	cultures (measles and mumps) and human diploid cell culture (rubella) has resulted in a vaccine that contains no, or at most picogram quantities of egg protein, insufficient to cause an allergic reaction. Persons with egg allergy can safely receive measles or MMR vaccines. Most anaphylactic reactions to the MMR vaccine have been attributed to gelatine allergy.
	Boyce et al[7] 2010 (NIAID)	R1	Clinical Practice Guideline	US		Children	GRADE approach	Recommends that children with egg allergy, even those with a history of severe reactions, to receive MMR or MMRV vaccines.
	Cerece do et al 2007[6]	R1-2	Prospecti ve, observati onal	Spain	26	Children (15 months)	Prospecti ve, observati onal (Jan 2005 – May 2006) Patient: 15 months old children with egg allergy Interventi on: SPT to undiluted MMR Priorix vaccine	All patients received single dose MMR vaccine as none of them had a positive SPT. No immediate or delayed reaction (neither local nor systemic) was found.

						followed by single (SPT negative) vs split dosing (SPT positive) and 30 min observation period Comparator: None Outcome: Exclusion criteria: Patients who had received Adrenaline	

Influenza vaccinations

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Blanton et al[16] 2024 (CDC)	R1-2	Systematic Review	Global		Children & Adults	GRADE approach Systematic review (Medline, Embase, PsycInfo, CINAHL, NTIS, Scopus, Cochrane Library, and ClinicalTrials.gov; up to Oct 2021) Inclusion criteria: RCTs, observational studies, case reports, case series, safety surveillance system reports Patient: Adults & Children with egg allergy	31 trials include. Most studies were observational studies. No studies included a relevant comparison group. No instances of death, anaphylaxis (meeting Brighton criteria Levels 1-3 or otherwise unspecified), or hospitalization were reported among the studies. There was one report of single patient with Brighton Level 1 anaphylaxis associated with monovalent vaccine. <1.5% of mild reactions

							Intervention: Receipt of egg-based influenza vaccines (full-dose or split-dose) Comparator: Placebo, nonegg-based influenza vaccine, no vaccine, none Outcome: Allergic reactions requiring hospitalization, anaphylaxis, death Exclusion criteria: Animal studies, duplicate reports, clinical trial registry summaries, and review articles	were reported. Conclusion: It is safe for all persons aged >6 months with egg allergy to receive influenza vaccine and no additional safety measures are needed beyond those recommended for recipients of any vaccine.
	Abrams et al 2024[1]	R1-2	Narrative Review	Canada		Children & adults	Literature Review	Most influenza vaccines are grown in chick embryo and may contain residual egg protein. Both the CIG and JTFPP advise that influenza vaccine can be administered in a routine manner in individuals with egg allergies without any special precautions or testing and irrespective of the severity of a patient's previous

								allergic reaction to egg.
	Bryant et al[17] 2023 (American Academy of Paediatrics Committee on Infectious Diseases)	R1-2	Technical Report	US		Children & adults	Literature Review	Strong evidence that individuals with egg allergy can safely receive influenza vaccine without any additional precautions. The presence of egg allergy in an individual is not a contraindication to receive IIV or LAIV. Vaccine recipients with egg allergy are at no greater risk for a systemic allergic reaction than those without egg allergy. Precautions such as choice of a particular vaccine, special observation periods, or restriction of administration to particular medical settings are not warranted and constitute an unnecessary barrier to vaccination. Not necessary to inquire about egg allergy before administering influenza vaccine, including on the screening forms. Children who have had a previous

								allergic reaction to influenza vaccine should be evaluated by an allergist to determine whether future receipt of the vaccine is appropriate.
	Australasian Society of Allergy & Clinical Immunology (ASCIA)[3] 2022	R1-2	Clinical Practice Guideline	Australia		Children	Expert consensus	The amount of egg ovalbumin in the pandemic and seasonal inactivated influenza vaccines is limited to <1 ug of egg protein per vaccine dose. Influenza vaccine can be administered in community vaccination clinics as a single dose followed by the recommended routine 15 (Australia) or 20 (New Zealand) minute waiting period. In individuals who have had suspected anaphylaxis following administration of the influenza vaccine itself, further vaccination should be avoided without specialist allergy assessment. If there is significant parental or health professional anxiety, the vaccine may

								be administered in primary care settings with a longer waiting period of 30 minutes. **<u>Not recommended</u>** -"Split dosing" -Allergy testing with the vaccine or to egg prior to administration -Ingestion of egg as a pre-condition to administering the vaccine -Vaccination in specific hospital-based vaccination clinics -Allergy specialist review before influenza vaccination.
	Leech et al[4] 2021 (BSACI)	R1	Clinical Practice Guideline	UK		Children & adults	GRADE (A-E)	Children with egg allergy can receive the nasal live attenuated influenza vaccine (LAIV) and most children and adults can receive the intramuscular influenza vaccine in primary care, unless they have had anaphylaxis to egg requiring admission to intensive care (Grade B recommendation).
	Chua et al[8] 2018	R1-2	Joint Consensus Statement	Hong Kong		Children & Adults	Expert consensus	Influenza vaccines can be safely administered, and

									are recommended, for disease prevention in egg-allergic individuals. They are recommended to be administered in an outpatient or ambulatory setting. Only those patients who have previously required admission to an intensive care unit for severe anaphylaxis to egg should be referred to an allergist for further evaluation prior to influenza vaccination. Should there be any significant concerns from patients, parents or health care professionals, health care professionals who are capable of recognising signs and symptoms of an allergic reaction can provide 15 to 30 minutes of monitoring following vaccination. Specialist evaluation is recommended prior to yellow fever vaccination in egg-allergic individuals. Individuals who have

								developed or are suspected to have developed an allergic reaction to the vaccine or other vaccine components (such as gelatin or neomycin) should not undergo further vaccination with these products. Referral to an allergy specialist for further evaluation can be considered.
	AAP Committee on Infectious Diseases[17] 2018	R1-2	Policy Statement	US		Children	NA	All children with egg allergy of any severity can receive either an IIV or LAIV without any additional precautions beyond those recommended for any vaccine. It is not necessary to inquire about egg allergy before the administration of any influenza vaccine, including on screening forms. Influenza vaccine recipients with egg allergy are at no greater risk for a systemic allergic reaction than those without egg allergy. Precautions, such as

								choice of a particular vaccine, special observation periods, or restriction of administration to particular medical settings, are not warranted and constitute an unnecessary barrier to immunization. Children who have had a previous allergic reaction to any component of the influenza vaccine, for any reason, should be evaluated by an allergist to determine whether future receipt of the vaccine is appropriate.
	Greenhawt et al [18] 2017	R1-2	Clinical Practice Guidelines	US		Children & Adults	Systematic literature review, in conjunction with consensus expert opinion and workgroup-identified supplementary documents. GRADE (A-D)	Influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy. (Strength of recommendation: strong; Evidence level: A/B) No special precautions beyond those recommended for the administration of any vaccine to any patient are necessary for administration of influenza vaccine to egg

									allergic individuals. [Strength of recommendation: strong; Evidence level: A/B]. Previously recommended precautions, such as choice of a specific vaccine based on ovalbumin content, skin testing with the vaccine, divided or graded dosing, special medical settings and specific waiting periods are unnecessary. Use of non–egg-based influenza vaccines (ccIIV3, RIV3, or RIV4) in egg allergic individuals in the age groups for which they are approved is acceptable but not medically necessary or preferred. [Strength of recommendation: moderate; Evidence level: C/D]. Live attenuated influenza vaccine (LAIV) may be administered to patients with egg allergy of any severity in the age group for which it is approved. [Strength of

								recommendation: strong.; Evidence level: A/B]
	Kassianos et al[9] 2016	R1	Joint consensus statement	UK, Netherlands		Children & Adults	Expert consensus	Many seasonal influenza vaccines are produced using chick embryos and so can contain egg protein. Such vaccines are contraindicated in individuals who have severe anaphylaxis to egg protein. Seasonal influenza vaccines that are egg-free or with a low ovalbumin content (<0.12 µg/mL) are now available, and the latter may be suitable for individuals who have only a mild to moderate egg allergy. In children (except for those with severe egg anaphylaxis which has previously required intensive care), the intranasal vaccine can be used. Those with a clinical risk factor contraindicating the use of the nasal spray should be offered an inactivated influenza vaccine with very low ovalbumin content.

								Children and adults with a history of severe anaphylaxis to egg should be referred to specialists for vaccination in hospital.
	Dreskin et al (WAO) [2] 2016	R1-2	International consensus statement	Global		Children & Adults	Expert consensus with representatives from WAO, EAACI, AAAAI and ACAAI.	Egg allergy does not appear to impart an increased risk of an anaphylactic reaction to immunization with either inactivated or live attenuated influenza vaccines currently available in the United States and Europe (contain <1 mcg of ovalbumin per dose). Egg-allergic individuals may be vaccinated against influenza using full dose trivalent influenza vaccine (TIV) without prior influenza vaccine skin test, irrespective of a past severe reaction to egg and without any particular consideration, including immunization Setting.
	Turner et al [12] 2015	R1	Multicentre prospective, cohort (open label, phase IV intervention study)	UK	779	Children (2-18 years)	Phase IV open label (Sep 2014 – Feb 2015), 30 hospitals in UK.	No systemic allergic reactions occurred (upper 95% CI for population 0.47% and in participants with

				SNIFFLE-2				Patient: Children 2-18 years with egg allergy (including history of anaphylaxis to egg or history of severe but stable asthma). Intervention: Quadrivalent LAIV (intranasal), 30 min observation Comparator: None Outcome: incidence of allergic reaction (within 2 hours of vaccination), incidence of delayed symptoms up to 72 hours post-vaccination, change in asthma control test score in children with asthma or recurrent wheeze. Exclusion criteria: egg anaphylaxis requiring invasive ventilation, poorly controlled severe asthma, contraindication to LAIV	anaphylaxis to egg 1.36%). Nine participants (1.2%, 95% CI 0.5% to 2.2%) experienced mild symptoms, potentially consistent with a local, IgE mediated allergic reaction. Delayed events potentially related to the vaccine were reported in 221 participants. 62 participants (8.1%, 95% CI; 6.3% to 10.3%) experienced lower respiratory tract symptoms within 72 hours, including 29 with parent-reported wheeze. No participants were admitted to hospital. No increase in lower respiratory tract symptoms occurred in the 4 weeks after vaccination.

							(other than egg allergy).	
	Turner at al [13] 2015	R1	Prospective, multicentre, open label, phase IV intervention study	UK	282	Children (2-17 years)	Phase IV open label (Sep 2013 – Jan 2014), 12 hospitals in UK. Patient: Children 2-17 years with egg allergy (including history of anaphylaxis to egg or history of severe but stable asthma). Intervention: Quadrivalent LAIV (intranasal), 1 hour observation Comparator: None Outcome: incidence of allergic reaction (within 2 hours of vaccination), incidence of delayed symptoms up to 72 hours post-vaccination, change in nasal airway patency Exclusion criteria: egg anaphylaxis requiring invasive ventilatio	No systemic allergic reactions (upper 95% CI for population, 1.3%). 8 children experienced mild allergic reaction but self-limiting. 26 (9.4%; 95% CI for population, 6.2% to 13.4%) children experienced lower respiratory tract symptoms within 72 hours, including 13 with parent-reported wheeze. None of these episodes required medical intervention beyond routine treatment.

							n, severe unstable asthma, contraindication to LAIV (other than egg allergy), current salicylate therapy, immunocompromised.	
	Des Roches et al [14] 2014	R1	Prospective, cohort	Canada	123	Children	Prospective cohort, Nov 2013 – Feb 2014 Patient: Children with egg allergy (n=68) and without egg allergy (n=55) Intervention: Flumist LAIV (intranasal, contains <0.24 µg of ovalbumin/dose), 1 hour observation Comparator: None Outcome: Allergic reaction/ anaphylaxis Exclusion criteria: severe persistent asthma	None developed an allergic reaction during the hour of observation. At the 24-hour follow-up, 7 patients (10%) reported non-specific adverse reactions after the first vaccine dose, none of which required medical consultation or treatment. All of the reported adverse reactions (headache, nausea, nasal congestion, abd pain, cough/fever) occurred in the evening or following morning after vaccination except for a patient with a non-pruritic peribuccal rash which occurred 4 hours after vaccination and resolved spontaneously in the evening. None of the 7 patients who received a second dose reported

								an adverse event at the 24-hour follow-up.
	Kelso et al [15] 2014	R1-2	Narrative review		4315	Children & adults	Literature review (28 studies included) Patient: Adults and children with egg allergy (including hx of egg anaphylaxis) Intervention: Influenza vaccination, skin testing prior to vaccination, split dosing Comparator: none, full dosing Outcome: allergic reactions, anaphylaxis	656 of whom had a history of egg anaphylaxis found no severe reactions associated with influenza vaccination. Most studies shown that skin testing prior to vaccination did not predict the reactions. Full dose of vaccination is well tolerated. Therefore, split dosing is unnecessary. Rate of allergic reactions to influenza vaccine in non-egg-allergic individuals was approximately the same as egg-allergic recipients.
	Greenhawt et al [18] 2012	R1-2	RCT (2 phases)	US	143	Children	RCT, 7 sites, Oct 2010 – Mar 2012 Phase 1: RCT (n=31); 2-step approach **Group A**: 0.1 ml vaccine, followed by 30 minutes observation, then remainder of vaccine **Group B**: Normal saline	Phase 1: 45.1% had a history of egg anaphylaxis. Phase 2: 77.6% of participants had a history of egg anaphylaxis. 87 (77.7%) received the single dose and 25 with the split dose. All participants in both phases received TIV without developing

							injection, followed by 30 min observation, then full 100% dose. Phase 2: retrospective, observational (n=112) analysis of single vs split dosing. Patient: Children with egg allergy AND documented history or anaphylaxis or severe allergic reaction to egg Intervention: Fluzone trivalent seasonal influenza vaccine (TIV) [contains ¬0.1µg ovalbumin/dose] Comparator: normal saline injection (phase 1), none (phase 2) Outcome: Allergic reactions	an allergic reaction. Single dosing is well tolerated and graded/split dosing is not necessary. 7/ 31 (22.6%) RCT patients observed or reported some degree of mild, transient induration at the injection site (4 in group A and 3 in group B). No additional local or systemic reaction was observed or reported among the recipients requiring a booster dose of TIV.

Yellow fever vaccination

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Abrams et al 2024[1]	R3	Narrative Review	Canada		Children & adults	Literature Review	Anaphylaxis following yellow fever vaccination in individuals with egg allergy has been reported.

								The CIG recommends that all individuals with egg allergy be referred to an allergist for evaluation prior to vaccine administration. Should an individual with egg allergy require yellow fever vaccination, desensitization protocols exist and recent evidence supports its safety.
	Australasian Society of Allergy & Clinical Immunology (ASCIA)[3] 2022	R3	Clinical Practice Guideline	Australia		Children	Expert consensus	Yellow fever and Q fever vaccines potentially contain higher amounts of egg protein and allergy specialist evaluation is recommended before vaccination.
	Leech et al[4] 2021 (BSACI)	R1	Clinical Practice Guideline	UK		Children & adults	GRADE (A-E)	Yellow Fever vaccines contain detectable, but not quantified amounts of egg protein. If these vaccines are required, the egg-allergic patient should be referred to an allergy specialist with access to a designated yellow fever vaccination centre for assessment and immunization (Grade B recommendation).

	Chua et al[8] 2018	R1, R3	Joint Consensus Statement	Hong Kong		Children & Adults	Expert consensus	Yellow fever vaccine is less commonly administered and is commonly propagated in hens' eggs. Specialist evaluation is recommended prior to vaccination for evaluation of suspected egg allergies with vaccine skin testing or consideration for desensitisation. An egg-free yellow fever formulation is available as an alternative.
	Dreskin et al (WAO)[2] 2016	R3	International consensus statement	Global		Children & Adults	Expert consensus with representatives from WAO, EAACI, AAAAI and ACAAI.	Yellow fever vaccine is prepared in chicken embryos and contains measurable amounts of ovalbumin. The package insert describes a protocol for vaccine skin testing in egg-allergic or chicken-allergic recipients. A skin prick test is performed with the vaccine diluted 1:10, and if negative, an intradermal skin test is performed with the vaccine diluted 1:100. If these skin tests are negative, the vaccine can be administered in the usual manner. If the skin tests are positive, the vaccine can be

								administered in graded doses under observation.
	Tanos et al[21] 2023	R3	Prospective, cross-sectional	Brazil	435	Children	Prospective cohort, Feb 2018 – Jan 2020 Patient: Children with suspected egg allergy Intervention: Single dosing Comparator: skin testing & split dosing Outcome: Allergic reactions	A total of 414 (95.2%) children had no vaccine reactions. Of the 21 (4.8%) children who had some reaction, 10 experienced a local reaction, 9 a mild skin reaction distant from the vaccine site, 1 presented local cutaneous reaction distant to the vaccination site, and 1 patient developed possible anaphylaxis. The vaccine prick test did not predict a vaccine reaction (odds ratio, 1.29; 95% CI, 0.25-6.72; P 5 .67). Conclusions: Yellow fever vaccine can be safely administered as a single dose in children with a confirmed or suspected egg allergy.

Certainty and Magnitude of Effects:

Intervention	Certainty of Evidence
MMR / MMRV vaccination in primary care	High
Influenza (IIV/LAIV) vaccination in primary care	High
Yellow fever vaccination in primary care	High
Special precautions including split dosing, prior allergy testing with the vaccines or eggs, allergy specialist review before	High

	vaccination, or longer observation periods after administration |
Risk/Harm vs Benefit Considerations:	The benefits outweigh the potential harms. Timely administration of routine vaccinations prevents serious and potentially life-threatening infections (e.g. measles, mumps, rubella, varicella, and influenza) and maintains high vaccination rates to prevent disease outbreaks, outweighs the minimal risk of allergic reactions or anaphylaxis. Referring patients with egg allergy to an allergist for routine immunizations or allergy testing with these vaccines will unnecessarily delay vaccination and increase healthcare costs and burden. Due to the higher risk of allergic reactions or anaphylaxis with Yellow Fever vaccination in egg-allergic individuals, it is safer for these patients to be referred to allergy specialist for further evaluation and supervised administration.
Patient/ caregiver values	Most caregivers prioritize timely and safe vaccination for their children. Some patients or caregivers of children with egg allergies may still be concerned about the safety of MMR and influenza vaccinations. **Stakeholder feedback (if available):**
Resource, Cost Considerations:	Singapore citizens are eligible for subsidies (full subsidy or fee cap) for MMR, MMRV or influenza vaccinations at primary care. Avoiding unnecessary specialist referrals optimizes resource allocation and reduces financial/fiscal burden associated with specialist consultations, split dosing or prolonged observation periods.
Equity **Acceptability** **Feasibility**	**Equity** This allows equal and timely access to MMR/MMRV and influenza vaccines for all patients. Egg-allergic patients who require Yellow Fever vaccination will receive appropriate specialist care for equitable and safer outcome due to the higher risk of allergic reaction including anaphylaxis. **Acceptability** Some patients, caregivers or healthcare professionals may still be concerned about the risk of allergic reaction or anaphylaxis with MMR/ MMRV or influenza vaccines in egg-allergic individuals. Thus, education and efforts to address these misconceptions are crucial. **Feasibility** Primary care providers in Singapore are equipped in administering these vaccines and competent in recognizing and managing allergic reactions or anaphylaxis. **Stakeholder feedback (if available):**

Workgroup Consensus Survey (RAND/UCLA):

R 3.10: We strongly recommend that Measles, Mumps and Rubella (MMR) or Measles, Mumps, Rubella and Varicella (MMRV) or influenza vaccine be given in primary care to patients with egg allergy of any severity, with routine precautions.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
1	9	29%	9	0.0	8.4	No Disagreement

R 3.11: We strongly recommend against split dosing, prior allergy testing to vaccines or eggs, prior allergy specialist review or extended observation post administration of MMR, MMRV or influenza vaccines in patients with egg allergy.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
2	9	28%	9	0.0	8.4	No Disagreement

R 3.12: We strongly recommend that patients with egg allergy who require Yellow Fever vaccination should be referred to an allergy specialist for assessment and supervised administration.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
2	9	21%	9	0.6	7.9	No Disagreement

External Review Feedback:

Public Consultation:

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Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-5*
Clinical/PICO Question:	Is baked egg products safe in children with egg allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.13: We strongly recommend that patients with egg allergy should be assessed for tolerance to baked egg products. If tolerated, regular consumption of baked egg products should be recommended.**
Rationale:	Majority (70-80%) of patients with egg allergy are able to tolerate baked egg products.[1-3] The process of baking utilizes high heat (e.g. 180°C for 30 minutes) which alters the conformation of heat-labile proteins, resulting in loss of conformational epitopes and reduced allergenicity of egg proteins. The addition of wheat/grain matrix in baked products creates the matrix effect by decreasing the exposure of egg proteins to the gut's immune system and reduced the allergenicity further.[4-6] Since egg is ubiquitous in our diet, strict avoidance of all forms of eggs can impose significant dietary restrictions and adversely impact the quality of life of patients and their family. Incorporating egg products facilitates liberalization of diet, improves nutritional status and quality of life, and potentially decreases parental anxiety.[7-9] It is safe and well-tolerated with low risk of severe allergic reactions/anaphylaxis (<10%).[1,3] Currently, there is insufficient evidence to draw conclusions that consumption of baked egg products accelerates the resolution of egg allergy (majority are observational studies with high heterogeneity). However, tolerance to baked egg may be used as a marker to identify transient versus persistent phenotype in patients with egg allergy.[9-13]
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Anagnostou et al[10] 2024	R4	Systematic review, meta-analyses	Global		Children (< 18 years)	6 articles included (1 RCT, 3 controlled, observational) Inclusion criteria: RCTs, cohort studies, and case-control and caseseries studies Exclusion criteria: Studies combining DATs with the use of a biologic, non-English language studies, animal studies and mechanistic	No conclusion could be reached regarding if BE ingestion accelerates the development of tolerance due to differences in protocols, patient populations, different study durations, lack of robust controls (including controls

								studies without clinical outcomes Population: children younger than 18 years with IgE-mediated milk or egg allergy. Intervention: the incorporation of the DAT form into the diet Comparator: Strict avoidance Outcomes: rates of desensitization, rates of tolerance, rates of allergic reactions, rates of epinephrine usage, rates of discontinuation, rates of development of eosinophilic esophagitis (EoE), rates of accidental milk or egg reactions during intervention, time to achieve desensitization or tolerance.	where BE or BM tolerance was proven), and lack of clear study design. These estimates are limited by a high degree of heterogeneity . Meta-analysed data showed that tolerance occurred in 43% of patients in BE studies. The single (short-duration) BE RCT study did not demonstrate BE ingestion hastened allergy resolution.
	Cogurlu et al [11] 2022	R4	Prospective cohort	Turkey	65	Children (< 2 years)	OFC-confirmed egg allergic patients underwent OFC to baked egg (2g egg protein, baked 350°F for 30 mins). BE-tolerant group to incorporate baked egg into diet daily with 3-monthly intervals of OFC. BE-reactive group completely avoid all forms of eggs and offered 3-monthly OFC.	75.3% tolerated baked egg at median age of 12 months (IQR, 9.3-15.0) 21/29 (72.4%) children who were BE tolerant acquired regular-egg tolerance at a median age of 14 months (IQR, 12.0-19.0). 16 of 20 children who were BE reactive at baseline and developed tolerance during follow-up acquired regular-egg tolerance at a

								median age of 23 months (IQR, 15.0-30.5). Regular-egg tolerance was acquired at an earlier age among patients who were initially BE tolerant (14 months [IQR, 12.0-19.0]) than among patients who were BE reactive (23 months [IQR, 15.0-30.5]) (P = .009).
	Leech et al 2021[8] (BSACI)	R4	Clinical Practice Guidelines	UK		Children & Adults	GRADE approach (A-E)	Mild egg allergy usually resolves. Attempts to introduce baked egg as an ingredient (e.g. in cake) may be made from the age of 12 months, or 6 months from the last reaction (Grade B) Regular ingestion of baked egg may promote tolerance (Grade C). Resolution occurs gradually over time. Assessment for reintroduction of baked egg in all infants/young children presenting with egg allergy is advised as prolonged total exclusion may lead to more persistent allergy and increases

								dietary and social exclusion (Grade B).
	Netting et al [12] 2017	R4	Randomized Controlled Trial (RCT), double blinded	Australia	43	Children (6 months – 5 years old)	Patient: Children with IgE-mediated egg allergy aged 6 months – 5 years old. Intervention: Inclusion of baked egg products in diet (2-3X/week for 6 months, 1.3g egg protein per serving) Comparator: Strict avoidance of all forms of eggs Outcome: Tolerance to raw egg confirmed by OFC.	23% (4/17) children from the intervention group and 33% (6/18) control group passed the raw egg OFC. There **was no difference** between the groups in rates raw egg tolerance (OR, 0.62; 95% CI, 0.14–2.73; p =0.52), even after age adjustment (OR 0.50; CI, 0.11–2.40; p = 0.39). Both groups demonstrated decreased egg specific serum IgE titres and decreased whole egg specific IgE/IgG4 ratios.
	Lambert et al 2017 [13]	R4	Systematic review	UK	3 studies included	Children (0-18 years)	Systematic review (Medline, Embase, CINAHL). Inclusion criteria: RCTs, case-control or cohort studies). Patient: Children with egg allergy Intervention: baked egg Comparator: strict avoidance, none Outcome: Resolution of egg allergy confirmed by OFC.	There is very weak or little evidence to support that ingestion of BE products accelerates resolution of egg allergy (low quality studies, high heterogeneity and risk of bias).
	Turner et al[3] 2013	R4	Prospective cohort	Australia	236	Children	Population: Children with egg allergy Intervention: Baked egg muffin open food challenge (1g egg protein,	150 (64%) children passed and successfully incorporated baked egg into their diet.

							baked 180°C for 20 mins) Comparator: None Outcome: Allergic reactions or anaphylaxis	36% reacted to the challenge and 12 children (5%) experienced anaphylaxis. 71% children with prior egg anaphylaxis passed BE OFC.
	Leonard et al[2] 2012	R4	Observational (prospective, retrospective matched comparator group)	US	79	Children & Adults (0.5 – 25 years)	Recruitment period: June 2004 – Sep 2007 Population: Children & adults with egg allergy Intervention: Incorporation of baked egg products in diet if BE tolerant Comparator: Strict egg avoidance (retrospective matched comparator group) Outcome: Tolerance to regular egg confirmed via OFC (6.5g egg protein)	89% tolerated baked egg products. Subjects who were initially BE tolerant were 3.3 times more likely to develop regular egg tolerance than initial BE-reactive subjects (hazard ratio, 3.3; 95% CI, 1.2-8.9; P=0.017). Initiation of a baked egg diet accelerates the development of regular egg tolerance compared to strict avoidance. Higher serum egg white-specific IgE level is associated with persistent egg allergy.
	Lemon-Mule et al[1] 2008	R4	Prospective, observational	US	117	Children & adults (0.5 – 25 years)	Recruitment period: June 2004 – Sep 2007 Population: Children & adults with egg allergy Intervention: Incorporation of baked egg products (muffins, waffles) in diet if BE tolerant	70% tolerated baked egg products. 5 subjects (5.5%) experienced anaphylaxis received epinephrine. Conclusions: The majority of subjects with egg allergy were tolerant of heated egg. Continued

							Comparator: Strict egg avoidance Outcome: Tolerance to regular egg confirmed via OFC (6.5g egg protein)	ingestion of heated egg was well tolerated and associated with immunologic changes that paralleled the changes observed with the development of clinical tolerance to regular egg.

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TABLE II. Summary of meta-analyzed outcomes

	Desensitization	Tolerance	Any adverse reaction	Severe reactions	Anaphylaxis	Any updose reactions	Severe updose reactions	Any at-home reactions	Severe at-home reactions	Total epinephrine doses	At-home epinephrine	Discontinuation	EoE	Accidental reactions
Baked Egg														
Konstantinou et al[17]	1 (0.94-1)	0.93 (0.82-0.98)												
Peters et al[18]	0.77 (0.71-0.81)	0.24 (0.19-0.29)										0.41 (0.35-0.47)		
Leonard et al[19]	0.89 (0.79-0.95)	0.53 (0.42-0.64)	0.01 (0.00-0.07)	0	0			0.01 (0-0.07)	0	0	0	0.04 (0.01-0.11)	0	0.01 (0-0.07)
Netting et al[20]	0.81 (0.58-0.95)	0.19 (0.05-0.42)	0.43 (0.22-0.66)	0.10 (0.01-0.30)	0.10 (0.01-0.30)			0.19 (0.05-0.42)	0	0	0	0.19 (0.05-0.42)	0	0.05 (0-0.24)
Kim et al[21]	0.68 (0.48-0.84)	0.11 (0.02-0.28)	0.86 (0.67-0.96)	0	0			0.86 (0.67-0.96)	0	0	0	0.32 (0.16-0.52)	0.04 (0-0.18)	0.11 (0.02-0.28)
Cogurlu et al[22]	0.71 (0.59-0.81)	0.54 (0.41-0.66)										0.06 (0.02-0.14)		
Pooled effect	0.84 (0.71-0.93)	0.43 (0.19-0.68)	0.38 (0-0.96)	0.01 (0-0.08)	0.01 (0-0.08)			0.30 (0-0.90)	No events	No events	No events	0.18 (0.03-0.40)	0.00 (0-0.03)	0.04 (0-0.12)
Egg ladder														
Gotesdyner et al[24]	0.82 (0.66-0.92)	0.56 (0.40-0.72)	0.23 (0.11-0.39)	0.03 (0-0.13)				0.08 (0.02-0.21)	0.03 (0-0.13)	0.03 (0-0.13)		0.03 (0-0.13)		
Cotter et al[25]	0.93 (0.77-0.99)	0.95 (0.77-0.99)	0 (0-0.12)	0 (0-0.12)				0 (0-0.12)	0 (0-0.12)	0.03 (0-0.18)		0.07 (0.01-0.23)		
Thomas et al[26]	0.66 (0.51-0.79)	0.43 (0.28-0.58)	0 (0-0.12)	0.04 (0.01-0.15)					0.04 (0.01-0.15)	0.02 (0-0.11)				
De Vlieger et al[27] (short)	0.90 (0.76-0.9)	0.79 (0.64-0.91)	0.28 (0.15-0.45)	0.13 (0.04-0.27)				0.28 (0.15-0.45)	0.13 (0.04-0.27)			0.21 (0.09-0.36)		
De Vlieger et al[27] (long)	0.79 (0.64-0.91)	0.69 (0.52-0.83)	0.10 (0.03-0.24)	0.03 (0-0.13)				0.10 (0.03-0.24)	0.03 (0-0.13)			0.31 (0.17-0.48)		
Pooled effect	0.82 (0.72-0.91)	0.69 (0.50-0.85)	0.21 (0.04-0.45)	0.04 (0.01-0.08)				0.09 (0.01-0.23)	0.04 (0.01-0.08)	0.03 (0-0.07)		0.14 (0.03-0.29)		
Milk ladder														
Nowak-Wegrzyn et al[28]	0.30 (0.23-0.39)	0.16 (0.10-0.23)		0.04 (0.02-0.09)	0.04 (0.02-0.09)	0.04 (0.02-0.09)	0.04 (0.02-0.09)	0 (0-0.03)	0 (0-0.03)	0.04 (0.02-0.09)	0 (0-0.03)	0.24 (0.17-0.32)		
Effron et al[29]		0.86 (0.72-0.95)	0.30 (0.17-0.46)			0.16 (0.07-0.31)			0.05 (0.01-0.16)	0.05 (0.01-0.16)	0.05 (0.01-0.16)	0.12 (0.04-0.25)		
Ismail-Hadeh et al[30]	1 (0.92-1)	0.88 (0.74-0.96)	0 (0-0.06)	0.05 (0.01-0.16)	0.05 (0.01-0.16)									
D'Art et al[31]		0.52 (0.38-0.65)		0 (0-0.06)	0 (0-0.06)			0 (0-0.06)		0 (0-0.06)	0 (0-0.06)	0.05 (0.01-0.1)		0.02 (0-0.09)
Ball et al[32]		0.81 (0.72-0.89)	0.76 (0.65-0.84)	0 (0-0.04)	0 (0-0.04)				0 (0-0.06)	0 (0-0.04)		0.08 (0.03-0.16)		0.19 (0.11-0.28)
Dunlop et al[33]	0.51 (0.44-0.58)	0.39 (0.32-0.46)	0.32 (0.26-0.39)	0.05 (0.03-0.09)	0.04 (0.02-0.08)	0.09 (0.05-0.13)	0.01 (0-0.04)			0.04 (0.02-0.08)	0.03 (0.01-0.06)	0.25 (0.19-0.32)		0.06 (0.03-0.11)
Weissbrand-Goichberg et al[34]	0.45 (0.34-0.56)	0.38 (0.27-0.49)	0.24 (0.15-0.34)	0.02 (0-0.08)	0.02 (0-0.08)	0.13 (0.07-0.22)	0.02 (0-0.08)	0.24 (0.15-0.34)	0 (0-0.04)	0.02 (0-0.08)	0 (0-0.04)	0.32 (0.22-0.43)		
Pooled effect	0.61 (0.33-0.86)	0.58 (0.36-0.78)	0.25 (0.07-0.49)	0.02 (0.01-0.05)	0.02 (0.01-0.04)	0.09 (0.05-0.15)	0.02 (0.01-0.05)	0.07 (0-0.25)	0 (0-0.02)	0.02 (0.01-0.04)	0.01 (0-0.03)	0.17 (0.09-0.26)		0.08 (0.01-0.18)
Baked egg OIT														
Gruzelle et al[16]	0.89 (0.79-0.95)	0.66 (0.54-0.77)	0.14 (0.07-0.24)	No events	No events	0 (0-0.05)		0.14 (0.07-0.24)	No events	0 (0-0.05)	No events	0.11 (0.05-0.21)		
Zhang et al[17]	0.67 (0.52-0.80)	0.48 (0.33-0.63)	0.06 (0.01-0.17)	No events	No events	0.02 (0-0.11)		0.02 (0-0.11)	No events			0.17 (0.07-0.30)		
Takaoka et al[23]	0.90 (0.70 -0.99)	0.33 (0.15-0.57)	0.24 (0.08-0.47)	No events	No events					0 (0-0.16)	No events	0.10 (0.01-0.30)		
Bravin and Layé[29]	0.53 (0.27-0.79)		0.13 (0.02-0.40)	No events	No events					0 (0-0.22)	No events	0.13 (0.02-0.40)		
Bird et al[36]	0.54 (0.25-0.81)	0.38 (0.14-0.68)	0.62 (0.32-0.86)	No events	No events	0.08 (0-0.36)		0.62 (0.32-0.86)	No events	0.08 (0-0.36)	No events	0.54 (0.25-0.81)		
Pooled effect	0.74 (0.57-0.88)	0.49 (0.33-0.65)	0.20 (0.07-0.35)	0 (0-0.01)	0 (0-0.01)	0.01 (0-0.06)		0.19(0.01-0.49)	0 (0-0.01)	0 (0-0.02)	0 (0-0.01)	0.17 (0.08-0.29)		
Baked milk OIT														
Zhang et al[17]	0.67 (0.41-0.87)	0.17 (0.04-0.41)	0.11 (0.01-0.35)	0.06 (0-0.27)	0.06 (0-0.27)				0.06 (0-0.27)			0.17 (0.04-0.41)		
Gruzelle et al[35]	0.81 (0.70-0.90)	0.42 (0.30-0.55)	0.33 (0.22-0.46)	0.03 (0-0.11)	0.02 (0-0.08)			0.16 (0.08-0.27)	0.03 (0-0.11)	0.02 (0-0.08)	0.02 (0-0.08)	0.19 (0.10-0.30)		
Goldberg et al[41]	0.27 (0.08-0.55)	0 (0-0.22)	0.93 (0.68-1)	0.13 (0.02-0.40)	0.13 (0.02-0.40)			0.13 (0.02-0.40)	0.13 (0.02-0.40)	0.13 (0.02-0.40)	0.13 (0.02-0.40)	0.73 (0.45-0.92)		
Dantzer et al[42]	0.93 (0.68-1)	0.73 (0.45-0.92)	1 (0.78-1)	0.13 (0.02-0.40)	0.13 (0.02-0.40)			0.93 (0.68-1)	0.07 (0-0.32)	0.20 (0.04-0.48)	0.20 (0.04-0.48)	0.07 (0-0.32)		
Anat et al[43]			0.50 (0.29-0.71)	0.29 (0.13-0.51)	0.29 (0.13-0.51)			0.50 (0.29-0.71)	0.29 (0.13-0.51)	0.12 (0.03-0.32)	0.12 (0.03-0.32)	0.04 (0-0.21)		
Pooled effect	0.70 (0.43-0.91)	0.29 (0.05-0.61)	0.61 (0.25-0.91)	0.11 (0.02-0.23)	0.10 (0.01-0.24)			0.42 (0.10-0.79)	0.10 (0.02-0.21)	0.09 (0.01-0.22)	0.09 (0.01-0.22)	0.20 (0.05-0.42)		

Meta-analyzed outcomes listed by study. Only outcomes with 3 or more studies reporting the outcome were meta-analyzed. Outcomes left blank had 2 or fewer studies reporting data for that outcome.
EoE, Eosinophilic esophagitis; *OIT*, oral immunotherapy.

Certainty and Magnitude of Effects:	Safety of baked egg products: High certainty of evidence Acceleration of acquisition of tolerance: very low certainty of evidence Improvement in quality of life and reduction in parental anxiety: very low certainty of evidence
Risk/Harm vs Benefit Considerations:	Benefits outweigh possible harms. Studies have shown that it is safe with low risk of severe allergic reactions/anaphylaxis (<10%). Inclusion of baked egg products into the diet can broaden dietary options, enhance nutrition, and improve social functioning and quality of life.
Patient/ caregiver values	Some children may dislike the taste or texture of baked egg products. Some caregivers may be concerned about high sugar content in baked products. Some may perceive baked goods as an unhealthy option due to the association with processed carbohydrates and fats.

<table>
<tr><td></td><td>Preparing baked egg products at home to meet nutritional requirement may require additional time, effort, and resources. This can be particularly burdensome for some caregivers who have limited cooking skills or busy schedules.

Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>Baked egg goods, such as muffins and cakes, are made with affordable and widely available ingredients, making this approach practical and sustainable for most patients and families.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Incorporation of baked products into diet is socially acceptable and convenient. This allows patients with egg allergy to enjoy more diverse food and participate in social and cultural events. Commercial baked products is readily available in stores and affordable (ensure that egg is listed as third ingredient or further down in the ingredients list).

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 3.13: We strongly recommend that patients with egg allergy should be assessed for tolerance to baked egg products. If tolerated, regular consumption of baked egg products should be recommended.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>22%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

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8. Leech SC, Ewan PW, Skypala IJ, et al. BSACI 2021 guideline for the management of egg allergy [published correction appears in Clin Exp Allergy. 2022 Jan;52(1):211.

9. Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Węgrzyn A. Baked milk- and egg-containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract. 2015;3(1):13-24.
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13. Lambert R, Grimshaw KEC, Ellis B, Jaitly J, Roberts G. Evidence that eating baked egg or milk influences egg or milk allergy resolution: a systematic review. Clin Exp Allergy. 2017;47(6):829-837.

Subgroup/Chapter Evidence Matrix

<table>
<tr><td>Evidence Matrix No.</td><td>EM 3-6</td></tr>
<tr><td>Clinical/PICO Question:</td><td>Are lysozyme-containing products or mucolytics safe in adults or children with egg allergy?</td></tr>
<tr><td>Linked Recommendation Statements:
(Type = R or GPP)
(Chapter no. statement no.)</td><td>GPP 3.14: Lysozyme (muramidase)-containing expectorants and mucolytics should not be used in patients with egg allergy as they are derived from eggs.</td></tr>
<tr><td>Rationale:</td><td>Lysozyme (N-acetyl muramidase) is an enzyme with bactericidal properties that has purported expectorant and mucolytic effects. Since 1989, lysozyme-containing products such as Leftose, Neuflo, Neuzyme and Lyzyme have been available over the counter and used by doctors in Singapore. However, published evidence has not demonstrated the efficacy of lysozyme compared to placebo. As a result, the Health Sciences Authority (HSA) has de-registered lysozyme-containing products as therapeutic products in Singapore in 2018.[1] However, lysozyme continues to be available for use as a health supplement due to its acceptable safety profile.

Lysozyme is derived from hen’s egg white or through biofermentation and is known to cause allergic reactions in patients with egg allergy.[2,3] Hence, it should not be used in patients with egg allergy.[4,5]</td></tr>
<tr><td>Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(* see examples below; or this section can be a narrative summary.)</td><td>
<table>
<tr><th>Study</th><th>Contributed to R/GPP</th><th>Study Type</th><th>Region/ Country</th><th>Total participants</th><th>Age group</th><th>Method</th><th>Outcome</th></tr>
<tr><td>Audicana et al 2011[2]</td><td>GPP1</td><td>Clinical Guideline</td><td>Spain</td><td></td><td>Children & Adults</td><td>Literature review (conducted by Drug Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEAIC)</td><td>The manufacturers should be requested to state in both the patient information leaflet and the summary of product characteristics (SPC) whether lysozyme is used in their products & whether it was obtained from eggs. In this case, the products should include a specific contraindication to its use in patients with egg allergy.

Recommends for individuals</td></tr>
</table>
</td></tr>
</table>

								with egg allergy to systematically avoid medicinal products containing lysozyme and ovalbumin.
	Heath Sciences Authority (HAS) Singapore 2017[1]	GPP1	Update document	Singapore		Children & adults	Literature review	The HSA has conducted a re-evaluation of the benefit-risk profile of lysozyme and concluded that it has failed to show efficacy. Therefore, lysozyme-containing products will be de-registered as therapeutic products in Singapore.
	Artesani et al[3] 2008	GPP1	Case Report	Italy	1	Children (20 months)	Case report	20-month-old child with atopic presented with a severe adverse drug reaction to Narlisim, a nasal decongestant that contains lysozyme. He experienced rhinitis, wheeze, and dysphonia within a few minutes after the nasal instillation of Narlisim. Diagnosis supported by positive skin prick test (SPT) to egg white, egg yolk and Narlisim. Serum specific IgE was detected against egg yolk, egg white, ovalbumin, ovomucoid and lysozyme (1.82 kUa/L). The allergen microarray revealed IgE antibodies against Gal d 4

								(lysozyme) (1.04kUa/L).
	Tan et al[4] 2020 (SMJ)	GPP1	Case report	Singapore	1	Children	Case report	A young girl with eczema, known cow's milk and egg allergy, who developed an allergic reaction to a commonly prescribed lysozyme-containing mucolytic, Leftose. At 3 years of age, she visited her family doctor for an upper respiratory tract infection and was prescribed Leftose®, a lysozyme-containing product,for the first time. Within 30 minutes, she developed generalised urticaria. A subsequent prick-to-prick test to the Leftose syrup was positive with wheal size of 14 mm. SPT to egg white extract was positive (wheal size 9 mm), and serum-specific immunoglobulin E to egg was also positive at 36.30kU/L.
	Goh et al[5] 2022	GPP1	Commentary	Singapore		Children & Adults	Narrative review	Lysozyme (N-acetyl muramidase) is an enzyme with bactericidal activity that is used in expectorants and mucolytics. It is available as a health supplement as it is no longer under the HSA register of

								therapeutic products. Lysozyme is an egg white protein and is known to cause allergic reactions in patients with egg allergy.
Certainty and Magnitude of Effects:	Not graded (GPP)							
Risk/Harm vs Benefit Considerations:	Harms outweigh possible benefits. Evidence from published literature has not demonstrated the efficacy of lysozyme compared to placebo, raising concerns about its therapeutic value. Lysozyme is derived from egg white and can cause allergic reactions including life-threatening reactions in individuals with egg allergy.							
Patient/ caregiver values	Patients and caregivers may value lysozyme as a natural supplement with its purported anti-inflammatory and mucolytic benefits in respiratory infections. They may also value the convenience and affordability since it is available over the counter but may be concerned about their lack of proven efficacy and the risk of allergic reaction in egg-allergic individuals. **Stakeholder feedback (if available):**							
Resource, Cost Considerations:	Cost: Lysozyme-containing products are affordable and accessible especially for patients seeking alternative or natural remedies. Resources: Inadvertent use or prescription of lysozyme-containing products in egg-allergic patients may lead to increased healthcare cost due to consultations or hospitalizations related to allergic reactions.							
Equity **Acceptability** **Feasibility**	<u>Equity</u> Lysozyme-containing products are widely available and affordable across various socioeconomic groups. However, individuals with egg allergies should avoid using these products due to risk of allergic reactions. <u>Acceptability</u> The acceptability of lysozyme-containing products may vary depending on patient education and awareness of their efficacy and risks. Some patients and caregivers who prefers natural remedies are likely to find these products acceptable for use as supplements since they are safe. <u>Feasibility</u> It is feasible to restrict the use of lysozyme-containing products or mucolytics in patients with egg allergy through appropriate ingredient labeling and education for patients and healthcare professionals. **Stakeholder feedback (if available):**							

<table>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 3.14: Lysozyme (muramidase)-containing expectorants and mucolytics should not be used in patients with egg allergy as they are derived from eggs.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>31%</td><td>9</td><td>0.9</td><td>7.7</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

1. Health Sciences Authority Singapore HSA updates on the phasing-out of lysozyme containing products as therapeutic products. Available at: https://www.hsa.gov.sg/docs/default-source/announcements-csg/hsa-updates/hsaupdates_phasing-out-of-lysozyme-containing-products.pdf. [Last accessed on 21 Jul 2023].
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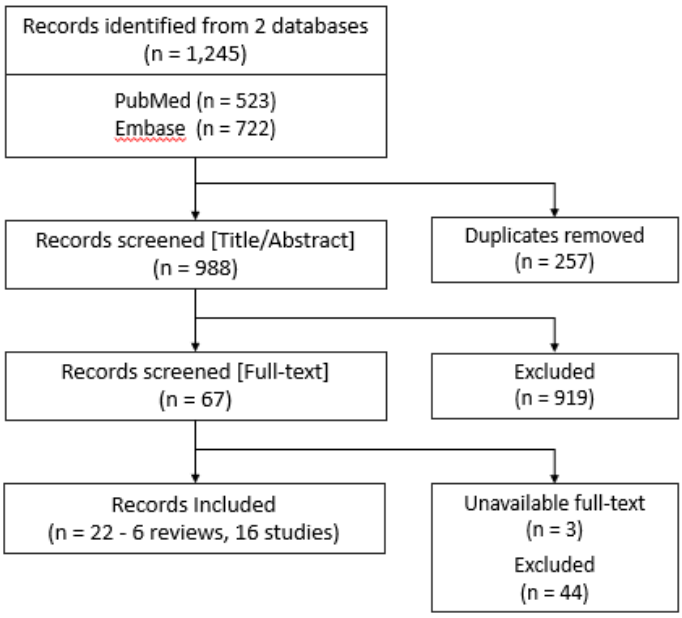
Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Peanut Allergy
Subgroup Members:	Lynette Tan
Main Clinical Question(s):	Is consumption of tree nuts safe in an adult and child with peanut allergy?
Population (age limit, inclusion criteria, excluded groups, special groups):	Adults and children with peanut allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Consumption of tree nuts
Comparator (if applicable):	Strict avoidance of tree nuts
Outcomes (specify critical/primary vs secondary):	Safety – risk of allergic reaction
Publication Dates:	2000 – 2024
Study Designs (specify inclusion/exclusion criteria):	Meta-Analysis ☒ Systematic Review ☒ **Randomised Controlled Trials (RCTs)** ☒ Cohort Study ☒ Case series or Case Report ☐ Animal Research ☐ In Vitro/Lab Research ☐ Editorials, Letters, Opinions ☒
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** 1 Peanut Hypersensitivity/ 2 ((peanut adj2 hypersensitivit*) or (peanut adj2 allerg*) or (Groundnut adj2 Hypersensitivit*) or (Groundnut adj2 allerg*)).ab,ti. 3 1 or 2 7 (consume or consumed or consumption* or cross-react* or react* or co-react* or eat or ate or eaten or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-

	sensiti#ation or cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. (3073382) 10 Nuts/ 11 ("tree nut?" or almond? or hazelnut? or cashew? or pistachio? or walnut? or pecan? or "brazil nut?" or macadamia? or "pine nut?").ab,ti. 12 10 or 11 13 3 and 7 and 12 14 limit 13 to (english language and yr="2000 - 2024")
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches: Number of additional potential studies identified through other sources: Total number of studies screened once duplicates were removed: Number of studies shortlisted for full text review: Number of studies excluded after full text review: Number and type of studies included: 

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-7*
Clinical/PICO Question:	Is consumption of tree nuts safe in an adult and child with peanut allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.15: We conditionally recommend referring peanut-allergic patients to an allergist to for evaluation of potential tree nut co-allergy and to facilitate introduction of untried tree nuts. Blanket avoidance of tree nuts in patients with peanut allergies is not recommended.**
Rationale:	Historically, the main management approach to nut allergy was strict blanket avoidance of all nuts in all peanut and tree nut allergic patients. Although avoiding all nuts simplifies the management and may decrease the risk of reactions secondary to cross-contamination or misidentification, it has pitfalls. Additional and unnecessary dietary restriction may reduce quality of life and lead to development of new allergies[19]. Patients with peanut allergy have a low to moderate risk of reacting to tree nuts. Up to 86% of peanut allergic children can be sensitized to tree nuts[4-5,10,13-16], however the rate of cross-reactivity is lower ranging from 7-60.7%[1-12]. The recent multicentre prospective Pronuts study of 159 patients with at least 1 confirmed nut or sesame seed allergy who underwent sequential diagnostic food challenges to all other nuts and sesame seed, found that the rate of coexistent peanut, tree nut and sesame seed allergy was 60.7%[1]. Skin prick test (SPT) and serum-specific IgE (sIgE) have a good negative predictive value but poor positive predictive value, potentially resulting in false-positive results. Unnecessary dietary restriction may then paradoxically increase risk of developing tree nut allergy. An oral food challenge remains the gold standard for diagnosing food allergy[17,21-22].
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	

Study	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Brough 2020[1]	Prospective study	Europe	159	0-16y	Patients with at least 1 confirmed nut or sesame seed allergy underwent sequential diagnostic food challenges to all other nuts and sesame seed.	The rate of coexistent peanut (PN), tree nut (TN), and sesame seed allergy was **60.7%**.
McWilliam 2019[2]	Prospective study	Australia	5276	1y	At age 1 year, allergies to egg and PN were determined by means of OFC. Challenge-confirmed TN allergy was assessed at age 6 years.	Of the 147 children with PN allergy at age 6 years, **45%** also had 1 or more TN allergies.
Elizur 2018[3]	Prospective study	Israel	83	>3y	Patients with TN allergy were skin-tested to 6 TNs (i.e.	In this TN allergic cohort, the most frequent

						walnut, pecan, cashew, pistachio, hazelnut, or almond), and OFCs were performed to each TN which was not regularly consumed by the patient and to which no IgE-mediated reaction was documented within the last 2 years.	other food allergies reported by the patients was PN (**24.1%**).
	Cousin 2017[4]	12y retrospective study	France	123	Children	Included patients with PN allergy who had a complete work-up for cross-allergy to TN and other legumes	Cross-allergy to TN was identified in 123 patients (**38.8%**).
	Couch 2017[5]	8y retrospective study	USA	109	Children	Open TN OFCs performed from 2007 through 2015 at a referral centre were analysed.	**20%** of patients with peanut allergy were allergic to TN.
	Ball 2011[6]	5y retrospective study	UK	145	Children	94 patients with diagnosed PN allergy were challenged to all TNs (i.e. almonds, cashew nut, Brazil nut, hazelnut and walnut).	In those with PN allergy challenged to TNs, none of the 72 with negative skin prick test (SPT) to TNs reacted on challenge whilst 7 of 22 (31.2%) with positive SPT did (7/94 = **7.4%**).
	Pearlstein 2024[7]	3y retrospective study	USA	600	Infants	We conducted a retrospective chart review on high-risk infants screened for peanut allergy. Infants were followed through age 2 years to establish food allergy diagnoses. Food allergy was defined by meeting any of the following criteria: (1) failed OFC, (2) history of an IgE-mediated reaction and evidence of	Of the patients with PN allergy, 32 (**22.7%**) had a co-allergy with 1 or more tree nuts.

						sensitization, (3) positive SPT result or sIgE testing approaching the 95% positive predictive value for the implicated food (peanut SPT wheal diameter 8 mm or sIgE ≥ 14 kU/L, tree nut SPT wheal diameter 8 mm or sIgE ≥ 15 kU/L).	
	Juel-Berg 2022[8]	Prospective study	Denmark	40	Children, adolescent and adult	43 nut allergic subjects were assessed for clinical reactivity to 6 nuts (i.e. hazelnut, walnut, pistachio, cashew, almond and peanut) by OFCs or convincing history of an immediate allergic reaction or tolerance.	17 (**43%**) had confirmed allergy to peanut.
	Sasaki 2018[9]	Prospective study	Australia	9816	10-14y	Students and their parents were asked to complete a questionnaire regarding the adolescent's food allergy or food-related reactions. Clinic evaluation, which consisted of skin prick tests and OFC where eligible, was undertaken if students were suspected to have current food allergy. Clinic-defined food allergy: 1. Positive OFC results with sensitization 2. Recent or severe reaction with sensitization 3. Highly sensitized (>=8)	Clinic-defined TN allergy and PN allergy coexisted in **41.5%** (56 of 135) of the peanut-allergic students. Self-reported PN and TN allergy was coexistent in 55.1% (70 of 127) of the peanut-allergic students in the questionnaire group.

	Maloney 2008[10]	Prospective study	USA	324	Children, adolescents and adults	Patients referred for evaluation of suspected IgE-mediated PN, TN, or seed (sesame, mustard, poppy, rape, and cotton seed) hypersensitivity were enrolled in the study. A patient was labelled as having a positive diagnosis if he or she had a history of clinical reactivity to the individual food, and when questionable, this reaction was supported by serologic or skin test evidence of IgE-mediated allergy to that food.	The majority of patients with peanut allergy were sensitized to tree nuts (86%), and **34%** had documented clinical allergy.
	Ewan 2001[11]	Prospective study	UK	567	Children and adult	Patients with confirmed PN or TN allergy (diagnosed made from history and confirmed by SPT) were recruited and followed up.	130 (**37%**) of those allergic to PN were also allergic to a TN.
	Sicherer 2001[12]	Voluntary registry	USA	5149	Children and adults	A voluntary registry of individuals with PN and/or TN allergy was established in 1997. The registry was established through use of a structured questionnaire distributed to all members of the Food Allergy and Anaphylaxis Network and to patients by allergists. This study elucidated a variety of features of PN and TN allergy among the first	Isolated peanut allergy was reported by 3482 registrants (68%), isolated tree nut allergy by 464 (9%), and allergy to both foods by 1203 (**23%**).

						5149 registry participants.	
	Lee 2020[13]	5y retrospective study	Singapore	269	Children	Retrospective review of children diagnosed with peanut allergy based on clinical history coupled with a positive skin prick test to peanut or positive OFC.	Amongst the peanut allergic group, **32.3%** were also sensitized to tree nuts; predominantly to cashew nut (17.1%), followed by almond (15.6%), hazelnut (15.6%), and walnut (14.1%).
	Anagnostou 2019[14]	Prospective study	USA	78	Children	Prospective evaluation of peanut allergic children (diagnosed based on a clinical history of allergic reaction and positive IgE or SPT to PN).	Sensitization to at least one tree nut was present in **80%** of our cohort.
	Peters 2015[15]	Prospective study	Australia	100	Children	1-year-old infants with challenge confirmed peanut allergy from the population-based, longitudinal HealthNuts Study were followed up at 4 years of age with repeat OFC.	**64%** of children with persistent peanut allergy at 1 years old had tree nut sensitization. **61%** of children with persistent peanut allergy at 1 years old had tree nut sensitization.
	Green 2007[16]	5y retrospective study	USA	140	Children	We reviewed the medical charts of peanut-allergic patients seen. Diagnosis of peanut allergy was made based on a clinical history of allergic reaction and positive IgE or SPT to PN.	Most patients (68%) demonstrated sensitization or clinical allergy to other foods (53% to eggs, 26% to cow's milk, **20%** to tree nuts, 11% to fish, 9% to shellfish, 7% to soy, 6% to wheat, and 6% to sesame seeds).
	Abrams 2022[17]	Review					NA
	Cox 2021[18]	Review					NA
	Midun 2021[19]	Review					NA
	McWilliam 2020[20]	Review					NA

Chan 2019[21]	Review					NA
Schroer 2019[22]	Review					NA

Certainty and Magnitude of Effects:	Low quality – observational studies (prospective and retrospective)
Risk/Harm vs Benefit Considerations:	Avoiding all nuts simplifies the management of patients with nut allergy and may decrease the risk of reactions secondary to cross-contamination or misidentification. However, it has pitfalls where additional and unnecessary dietary restriction may reduce quality of life and lead to development of new allergies.
Patient/ caregiver values	Different families have different dietary preference on whether they want to include nuts in their diet. **Stakeholder feedback (if available):**
Resource, Cost Considerations:	Screening with SPT and IgE may not be able to accurately differentiate between sensitization and allergy. CRD can improve diagnostic accuracy, however an OFC remains the gold standard for diagnosing food allergy. However, OFCs are personal- and time-consuming, and costly.
Equity **Acceptability** **Feasibility**	Tree nuts are packed with essential nutrients, including healthy fats, protein, vitamins and minerals and have been linked to various positive health benefits including weight management and heart health. However, they are relatively expensive, and not all tree nuts are easily found. Culturally, tree nuts may not be a typical component of some families' diets. In addition, palatability and concerns about choking, especially in young children, can influence whether are they are accepted and consumed. **Stakeholder feedback (if available):**
Workgroup Consensus Survey (RAND/UCLA):	**R 3.15: We conditionally recommend referring peanut-allergic patients to an allergist to for evaluation of potential tree nut co-allergy and to facilitate introduction of untried tree nuts. Blanket avoidance of tree nuts in patients with peanut allergies is not recommended.** *Number voted = 19; Number abstained = 0*

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
3	9	17%	9	0.6	7.9	No Disagreement

External Review Feedback:	
Public Consultation:	

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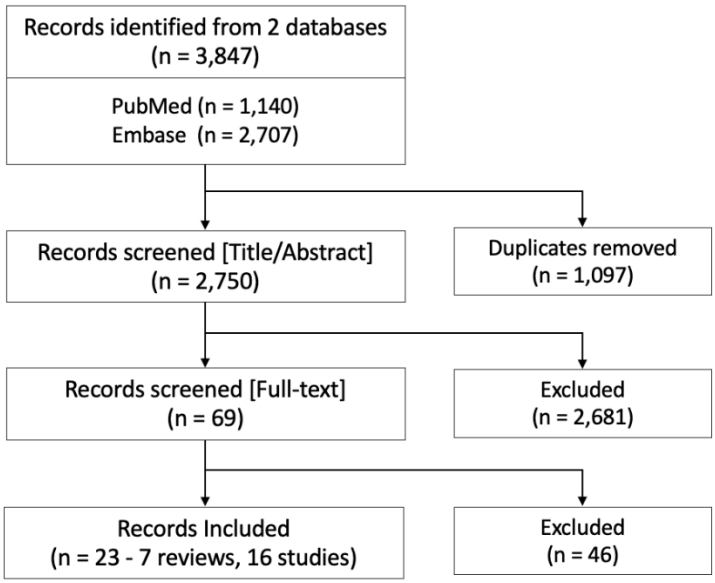
Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Tree Nut Allergy
Subgroup Members:	Lynette Tan
Main Clinical Question(s):	Is consumption of other tree nuts safe in an adult and child with tree nut allergy?
Population (age limit, inclusion criteria, excluded groups, special groups):	Adults and children with tree nut allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Consumption of other tree nuts
Comparator (if applicable):	Strict avoidance of all tree nuts
Outcomes (specify critical/primary vs secondary):	Safety – risk of allergic reaction
Publication Dates:	2000 – 2024
Study Designs (specify inclusion/exclusion criteria):	Meta-Analysis ☒ Systematic Review ☒ **Randomized Controlled Trials (RCTs)** ☒ Cohort Study ☒ Case series or Case Report ☐ Animal Research ☐ In Vitro/Lab Research ☐ Editorials, Letters, Opinions ☒
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** 1 Nut Hypersensitivity/ 2 (allerg* or hypersensitivit*).ab,ti. 3 (consumed or consumption* or cross-react* or react* or co-react* or eat or ate or eaten or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-sensiti#ation or

	cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. 4 ("tree nut?" or almond? or hazelnut? or cashew? or pistachio? or walnut? or pecan? or "brazil nut?" or macadamia? or "pine nut?").ab,ti. 5 1 or 2 6 3 and 4 and 5 7 limit 6 to (english language and yr="2000 - 2024")
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches: Number of additional potential studies identified through other sources: Total number of studies screened once duplicates were removed: Number of studies shortlisted for full text review: Number of studies excluded after full text review: Number and type of studies included: 

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM3-8*
Clinical/PICO Question:	Is consumption of other tree nuts safe in an adult and child with tree nut allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 3.16: We conditionally recommend allergist referral for tree nut-allergic patients to screen for additional tree nut allergies, to facilitate the introduction of untried tree nuts. Blanket avoidance of all tree nuts in patients with a specific tree nut allergy is not recommended.**
Rationale:	Historically, the main management approach to nut allergy was strict blanket avoidance of all nuts in all peanut and tree nut allergic patients. Although avoiding all nuts simplifies the management and may decrease the risk of reactions secondary to cross-contamination or misidentification, it has pitfalls. Additional and unnecessary dietary restriction may reduce quality of life and lead to development of new allergies[10,18]. Most patients with tree nut allergy are allergic to more than 1 tree nut; however, few individuals are allergic to all tree nuts[2,4,5,7]. The Nutcracker study of 83 children who underwent diagnostic food challenges to multiple tree nuts (almond, hazelnut, cashew, pistachio, walnut and pecan), found that although most patients were sensitized to 5 to 6 tree nuts, over 50% were clinically allergic to only 1 to 2 tree nuts. Two-thirds of cashew- and walnut-allergic patients were also allergic to pistachio and pecan, respectively, while all pistachio- and pecan-allergic patients were also allergic to cashew and walnut, respectively[7]. This finding was also seen in the Pronut study of 159 patients with at least 1 confirmed nut or sesame seed allergy who underwent sequential diagnostic food challenges to all other nuts and sesame seed. Most cashew- (83.3%) and walnut-allergic (75%) patients were also allergic to pistachio and pecan, respectively, while almost all pistachio- and pecan-allergic patients (97%) were also allergic to cashew and walnut, respectively. In this study, there was also a walnut-pecan-hazelnut-macadamia cluster[4]. The highly cross-reactive tree nut relationships of cashew-pistachio and walnut-pecan have proven to be clinically relevant in several studies where food challenges have been performed to confirm tree nut allergy[1,2,3,6,8,9]. In addition, Andorf et al[9] found a walnut-pecan-hazelnut cluster and Juel Berg et al[2] found a walnut-hazelnut cluster as seen in the Pronut study[4]. Skin prick test (SPT) and serum-specific IgE (sIgE) have a good negative predictive value but poor positive predictive value, potentially resulting in false-positive results. Component resolved diagnostics (CRD) can improve diagnostic accuracy, however an oral food challenge (OFC) remains the gold standard for diagnosing food allergy. In view of the high rate of co-sensitization amongst tree nuts and difficulty in performing numerous OFCs, tree nut allergic patients are often advised to avoid all tree nuts they are sensitized to. An understanding of patterns of cross-reactivity (cashew-pistachio and walnut-pecan) can guide introduction of individual tree nuts into the diet, which can reduce dietary restriction and may prevent the development of additional tree nut allergy. Elizur et al proposed a different order for OFCs with these nuts, depending on whether there is high or low probability of reaction. In

patients eliminating cashew/pistachio with a high probability for allergy, we challenge to pistachio first. If the pistachio challenge is positive, there is almost 100% chance that the patient is cashew allergic, precluding the need for cashew challenge. In patients with a low probability for cashew allergy, we challenge to cashew first. If the challenge is negative, the chances the patient is pistachio allergic are almost zero and can be introduced. A similar algorithm follows for walnut and pecan. This approach enables a significant reduction in the need for OFC[21]. In addition to the well-described walnut-pecan allergy pair, the walnut-pecan-hazelnut-macadamia cluster described by Brough et al, Andorf et al and Juel-Berg et al can also help rationalize the need for OFCs[2,4,9,21].

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

Study	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Golberg 2024[1]	Prospective study	Israel	125	Children	Children with suspected tree nut (TN) allergy were evaluated with SPT, CRD, basophil activation test (BAT) and OFC. Allergy to cashew and pistachio was determined based on a positive OFC or a recent reaction in the presence of IgE reactivity.	79/125 patients were diagnosed with cashew allergy and 63 (79.7%%) of them were also pistachio allergic. All but 1 pistachio allergic patients was also cashew allergic.
Juel-Berg 2022[2]	Prospective study	Denmark	40	1-23y	TN allergic patients were assessed for clinical reactivity to 6 nuts (peanut/PN, almond, hazelnut, cashew, pistachio and walnut) by OFCs (31/40) or convincing medical history of an immediate allergic reaction or tolerance. 23 participants were assessed for allergy to all six nuts. There was missing information of clinical reactivity for the remaining 17 participants.	Most patients (86%) had confirmed allergy to at least two nuts. 22 (55%), 11 (28%), and 2 patients were confirmed to be allergic to 3, 4, or 5 nuts respectively. None were allergic to all six nuts. There were two independent major allergic phenotypes: hazelnut-walnut and pistachio-cashew nut. Of the 25 hazelnut-allergic patients, 18 were walnut-allergic (72%). 4 hazelnut tolerant patients were

							allergic to walnut. 3 pecan-allergic patients were also walnut-allergic. Only one of the 18 cashew-allergic patient tolerated pistachio (3%). No pistachio allergic patient tolerated cashew.
	Goldberg 2021[3]	Prospective study	Israel	120	Children	Children with suspected TN allergy were evaluated with SPT, BAT and OFC. Allergy to walnut and pecan was determined based on a positive OFC or a recent reaction in the presence of IgE reactivity.	90/120 patients were diagnosed with walnut allergy and 80 (88.8%%) of them were also pecan allergic. All pecan allergic patients were also walnut allergic. All patients not allergic to walnut were pecan tolerant.
	Brough 2020[4]	Prospective study	Europe	159	0-16y	Patients with at least 1 confirmed nut or sesame seed allergy underwent sequential diagnostic food challenges to all other nuts and sesame seed.	The rate of coexistent peanut (PN), tree nut (TN), and sesame seed allergy was 60.7%. Cashew and pistachio were the most highly correlated nut allergies (OR 585), followed by walnut and pecan (OR 150.6). Almost all (97% [n = 35/36]) children with pistachio allergy were allergic to cashew, but only 83.3% of children allergic to cashew were allergic to pistachio. Almost all (97% [n =

							38/39]) children with pecan allergy were allergic to walnut, but only 75% of children with walnut allergy were allergic to pecan. There was also a walnut-pecan-hazelnut-macadamia cluster, with correlation ranging from an OR of 56-11.5.
	McWilliam 2019[5]	Prospective study	Australia	5276	1y	At age 1 year, allergies to egg and PN were determined by means of OFC. Challenge-confirmed TN allergy was assessed at age 6 years.	84 (52.2%) were allergic to only 1 TN, 26.7% to 2 TNs, 12.4% to 3 TNs, and 8.7% to >3 TNs. Of those with cashew allergy, 36% had coexisting pistachio allergy, and if all those with pistachio sensitization results of between 3 and 7 mm who did not have an OFC were deemed allergic, this increased to 46%
	Elizur 2019[6]	Prospective study	Israel	76	>3y	Patients with suspected IgE-mediated allergy to TNs were skin tested for allergy to walnut and pecan. Walnut-sensitized patients were recruited and underwent OFCs to walnut and pecan unless they were regularly consumed.	Of the 61 walnut-allergic patients, 49 were pecan-allergic (80%) whereas 12 were pecan-tolerant. None of the walnut-tolerant patients was allergic to pecan.
	Elizur 2018[7]	Prospective study	Israel	83	>3y	Patients with TN allergy were skin-tested to 6 TNs (i.e. walnut, pecan, cashew,	While most patients were sensitized to 5-6 TNs, over 50% were allergic to

						pistachio, hazelnut, or almond), and OFCs were performed to each TN which was not regularly consumed by the patient and to which no IgE-mediated reaction was documented within the last 2 years.	only 1-2 TNs. Two-thirds of walnut- and cashew-allergic patients were also allergic to pecan and pistachio, respectively, while all pecan- and pistachio-allergic patients were allergic to walnut and cashew, respectively.
	Van der Valk 2017[8]	Prospective study	Netherlands	29	Children	Children were recruited from the IDEAL study, where children with cashew sensitization underwent a DBFCFC with cashew. In this follow-up study, children with co-sensitization to pistachio underwent a DBPCFC with pistachio and mango.	31% (9/29) had coexisting cashew and pistachio allergy. One patient with pistachio allergy was tolerant of cashew.
	Andorf 2017[9]	Prospective study	USA	60	Children	60 participants with multiple food allergies were characterized by clinical history, DBPCFCs, total IgE, specific IgE, and component-resolved diagnostics (IgE and IgG4) data. The food allergens tested were milk, soy, egg, wheat, peanut, almond, hazelnut, cashew, pistachio, walnut, pecan and sesame. Each participant underwent a DBPCFC for between 2 and 8 foods.	All participants who were allergic to pecan (29) were also allergic to walnut and only 3 of 32 walnut-allergic participants (9%) tolerated pecan. The study also identified significant co-occurrences of allergies to hazelnut and pecan or walnut. However, the Jaccard similarity coefficients were much lower for the hazelnut-pecan pair (0.55) and hazelnut-

							walnut pair (0.59) than for a co-occurrence of pecan and walnut allergies (0.91). All of our 42 pistachio-allergic participants were DBPCFC positive against cashew. 4 of 46 cashew-allergic participants (8%) tolerated pistachio.
	Clark 2005[10]	Prospective study	UK	784	Children	Data were collected prospectively after interview with an allergist from 784 children with a typical history of an acute allergic reaction to a nut and evidence of sensitization.	With increasing age, greater proportions were multi-sensitized (19% at 2 yr to 86% at 5–14 yr) and multiallergic (2% at 2 yr to 47% at 14 yr).
	Rance 2003[11]	Prospective study	France	42	Children	42 children with cashew allergy were included. Diagnosis of cashew allergy was based on a clinical history suggestive of cashew allergy, and a positive SPT and/or a positive specific IgE, and/or a positive OFC. Allergy to other TNs were based on clinical history.	Out of the 42 children with cashew allergy, 7 (16.6%) had pistachio allergy and 1 had almond allergy.
	Couch 2017[12]	8y retrospective study	USA	109	Children	Open TN OFCs performed from 2007 through 2015 at a referral centre were analysed.	Among TN allergic patients who were challenged to another TN to which they were sensitized, 76% were tolerant.
	Ball 2011[13]	5y retrospective study	UK	145	Children	51 patients with TN allergy were	In 13 who had a positive PT to the nuts

						challenged to peanuts and/or other TNs (i.e. almonds, cashew nut, Brazil nut, hazelnut and walnut).	being challenged, 5 (38.4%) reacted, whilst in the remaining 38 with negative PT to the nuts challenged, 3 (7.9%) reacted.
	Saba 2020[14]	4y retrospective study	France	147	Children	147 children with positive OFC to cashew nut were included.	Among the 51 children allergic to cashew nut and whose oral tolerance of pistachio was known, 40 (78.4%) were allergic to pistachio (23 had a positive OFC and 17 had a prior history of allergic reaction to pistachio). 20/51 (39.2%) had another TN allergy.
	Chitta 2018[15]	8y retrospective study	Singapore	99	Children	99 children with cashew sensitization (specific IgE≧0.35kU/L) was analysed. Diagnosis of nut allergy was made based on a clinical history of allergic reaction and positive IgE and/or SPT.	All cashew nut allergic patients were cross-reactive (either sensitized or allergic) to pistachio.
	Crealey 2018[16]	5y retrospective study	Ireland	102	Children	102 children with peanut allergy who had cashew sensitization (specific IgE >0.35 kU/L) were included.	Of the 102 children, 55 had a history of prior cashew nut exposure with confirmed clinical reaction, 43 had no prior cashew nut exposure, and 4 were sensitized and tolerating cashew nut. Of those with clinical cashew allergy, 3 (5.4%) had pistachio allergy, 8

							(14.5%) had hazelnut allergy and 5 (9.0%) had peanut allergy.
	Labrosse 2022[17]	Review					NA
	Midun 2021[18]	Review					NA
	Cox 2021[19]	Review					NA
	McWilliam 2020[20]	Review					NA
	Elizur 2020[21]	Review					NA
	Francis 2020[22]	Review					NA
	Greenhawt 2018[23]	Review					NA
Certainty and Magnitude of Effects:	Low quality – observational studies (prospective and retrospective)						
Risk/Harm vs Benefit Considerations:	Avoiding all nuts simplifies the management of patients with nut allergy and may decrease the risk of reactions secondary to cross-contamination or misidentification. However, it has pitfalls where additional and unnecessary dietary restriction may reduce quality of life and lead to development of new allergies						
Patient/ caregiver values	Different families have different dietary preference on whether they want to include nuts in their diet. **Stakeholder feedback (if available):**						
Resource, Cost Considerations:	Screening with SPT and IgE may not be able to accurately differentiate between sensitization and allergy. CRD can improve diagnostic accuracy, however an OFC remains the gold standard for diagnosing food allergy. However, OFCs are personal- and time-consuming, and costly.						
Equity **Acceptability** **Feasibility**	Tree nuts are packed with essential nutrients, including healthy fats, protein, vitamins and minerals and have been linked to various positive health benefits including weight management and heart health. However, they are relatively expensive, and not all tree nuts are easily found. Culturally, tree nuts may not be a typical component of some families' diets. In addition, palatability and concerns about choking, especially in young children, can influence whether are they are accepted and consumed. **Stakeholder feedback (if available):**						
Workgroup Consensus Survey (RAND/UCLA):	**R 3.16: We conditionally recommend allergist referral for tree nut-allergic patients to screen for additional tree nut allergies, to facilitate the introduction of untried tree nuts. Blanket avoidance of all tree nuts in patients with a specific tree nut allergy is not recommended.** *Number voted = 19; Number abstained = 0*						

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
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External Review Feedback:	
Public Consultation:	

References:

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Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Wheat Allergy
Subgroup Members:	Goh Si Hui
Main Clinical Question(s):	Management of food allergy-What food should patients with specific food allergy avoid or what is a safe alternative? Would patients with wheat allergy be able to safely consume other grains?
Population (age limit, inclusion criteria, excluded groups, special groups):	Patients with wheat allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Consumption of other grains e.g. oat, barley, rye.
Comparator (if applicable):	Avoidance
Outcomes (specify critical/primary vs secondary):	Safety
Publication Dates:	2000 – 2024
Study Designs (specify inclusion/exclusion criteria):	Meta-Analysis ☒ Systematic Review ☒ **Randomized Controlled Trials (RCTs)** ☒ Cohort Study ☒ Case series or Case Report ☐ Animal Research ☐ In Vitro/Lab Research ☐ Editorials, Letters, Opinions ☒
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** 1 Wheat Hypersensitivity/ 2 ((wheat adj2 allerg*) or (wheat adj2 hypersensitivit*)).ab,ti. 3 (consumed or consumption* or cross-react* or react* or co-react* or eat or ate or eaten or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co

	allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-sensiti#ation or cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. 4 exp Edible Grain/ or Glutens/ or Avena/ or Hordeum/ or Secale/ 5 (grain? or cereals? or gluten? or Glutelin? or Hordein? or Secalin? or Avena or oat? or hordeum or barley or secale or rye).ab,ti. 6 4 or 5 7 1 or 2 8 3 and 6 and 7 9 limit 8 to (english language and yr="2000 - 2024")
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches:1285 Number of additional potential studies identified through other sources:- Total number of studies screened once duplicates were removed: 1064 Number of studies shortlisted for full text review: 91 Number of studies excluded after full text review: Number and type of studies included:8

Subgroup/Chapter Evidence Matrix

<table>
<tr><td>Evidence Matrix No.</td><td>EM3-9</td></tr>
<tr><td>Clinical/PICO Question:</td><td>Would patients with wheat allergy be able to safely consume other grains?</td></tr>
<tr><td>Linked Recommendation Statements:
(Type = R or GPP)
(Chapter no. statement no.)</td><td>GPP 3.17: Patients with wheat allergy may consume rice, millet, corn and quinoa as alternative grains.

GPP 3.18: We suggest that patients with wheat allergy consult an allergist with regards to consumption of rye, barley and oat, if not already introduced and tolerated, due to risk of cross-reactivity.</td></tr>
<tr><td>Rationale:</td><td>Patients with wheat allergies tend to react to taxonomically similar gluten-containing grains, particularly rye and barley. Risk of reaction is moderate for barley and lower for oat. Rice, millet, corn and quinoa are generally well tolerated.

Grains are an important dietary source and exclusion of all cereals is not warranted in patients with a primary IgE-mediated wheat allergy. Nevertheless, given frequent cereal grain cross-sensitization and poor predictive values of SPT and sIgE levels, clinical tolerance will often need to be assessed by food challenge.[1]</td></tr>
<tr><td>Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(* see examples below; or this section can be a narrative summary.)</td><td>Other Guidelines:

<table>
<tr><th>Study</th><th>Study Type</th><th>Region/ Country</th><th>Total participants</th><th>Age group</th><th>Method</th><th>Outcome</th></tr>
<tr><td>Urisu 2014[2]</td><td>Guidelines</td><td>Japan</td><td>-</td><td>-</td><td>Narrative Review</td><td>Key points for diet therapy: Use rice as the stable food. Avoid processed food containing gluten. Barley tea can be safely drunk by most.</td></tr>
</table>

SRs/MAs:

Other more recent literature or local data:</td></tr>
</table>

Study	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Cox 2021[1]	Clinical management review	-	-	-	Narrative review	<25% risk of cross reactivity to barley and rye. In clinical practice, exclusion of all cereals is not warranted in patients with a primary IgE-mediated wheat or other single grain allergy. Nevertheless, given frequent cereal grain cross-sensitization and poor predictive values of SPT and sIgE levels, clinical tolerance will often need to be assessed by food challenge. Millet, corn, sorghum, teff, and pseudocereals such as amaranth and quinoa are gluten-free and generally safe for those allergic to wheat and gluten-containing grains.
Pourpak 2005[3]	Prospective observational	Iran	18	1-8y	OFC to wheat, barley, rice & corn	55.5% (10/18) patients with wheat allergy had barley allergy. All patients were clinically tolerant to corn and rice.
RodriguezDelRio 2014[4]	Prospective observational	Spain	6	5-11y	OFC oat	33% (2/6) patients were oat allergic, before starting wheat OIT. Authors suggested that every wheat allergic child should be challenged with oat, despite presence of IgE to expand diet.
Takei 2022[5]	Retrospective observational	Japan	128	Med 6.3y	Report	14% were barley allergic, 27% barley tolerant and 59% were never exposed. None were exposed to rye.
Srisuwatchari 2020[6]	Prospective observational	Thailand	10 (9 severe wheat)	5-10y	OFC barley, oat and Job's Tears	In patients with wheat allergy, the cross-reactivity rate for barley, oat, and Job's tears was 60.0%, 33.3%, and 20.0%, respectively.
Yanagida 2022[7]	Prospective observational	Japan	53	5-9y	OFC barley	Half of the wheat-allergic children in this study reacted to barley owing to clinical cross-reactivity.

<table>
<tr><td></td><td>
<table>
<tr><td>Kubota 2022[8]</td><td>Retrospective observational</td><td>Japan</td><td>77</td><td>3-15y</td><td>OFC barley</td><td>36% of patients with wheat allergy, including patients on wheat OIT, had OFC+ barley allergy.</td></tr>
</table>
</td></tr>
<tr><td>Certainty and Magnitude of Effects:</td><td>Not graded (GPP)</td></tr>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td>In patients with wheat allergy, the inclusion of other grain is beneficial nutritionally and improves the quality of life for the patient and family. The potential risk of an allergic reactions is negligible in millet, corn, sorghum, teff, and pseudocereals such as amaranth and quinoa. This list was edited to match local diets. The risk of allergic reaction is low for oat, and moderate for barley and rye. Thus, the suggestion to refer to specialist care for further management.</td></tr>
<tr><td>Patient/ caregiver values</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td></td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>
GPP 3.17: Patients with wheat allergy may consume rice, millet, corn and quinoa as alternative grains.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>7</td><td>9</td><td>8%</td><td>9</td><td>1</td><td>8</td><td>No Disagreement</td></tr>
</table>
GPP 3.18: We suggest that patients with wheat allergy consult an allergist with regards to consumption of rye, barley and oat, if not already introduced and tolerated, due to risk of cross-reactivity.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>6</td><td>9</td><td>12%</td><td>9</td><td>1</td><td>8</td><td>No Disagreement</td></tr>
</table>
</td></tr>
</table>

External Review Feedback:	
Public Consultation:	

References:

1. Cox, A. L.; Eigenmann, P. A.; Sicherer, S. H. Clinical Relevance of Cross-Reactivity in Food Allergy. Journal of Allergy and Clinical Immunology: In Practice 2021;9(1):82-99
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Subgroup/Chapter Name:	Management of Fish Allergy
Subgroup Members:	Goh Si Hui
Main Clinical Question(s):	Management of food allergy-What food should patients with specific food allergy avoid or what is a safe alternative? Would patients with fish allergy be able to safely consume other fish?
Population (age limit, inclusion criteria, excluded groups, special groups):	Patients with fish allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Consumption of other fish
Comparator (if applicable):	Avoidance
Outcomes (specify critical/primary vs secondary):	Safety
Publication Dates:	2000 – 2024
Study Designs (specify inclusion/exclusion criteria):	Meta-Analysis ☒ Systematic Review ☒ **Randomized Controlled Trials (RCTs)** ☒ Cohort Study ☒ Case series or Case Report ☐ Animal Research ☐ In Vitro/Lab Research ☐ Editorials, Letters, Opinions ☒
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** Search Strategy: --- 1 ((fish adj3 allerg*) or (fish adj3 hypersensitivit*)).ab,ti. 2 (consume or consumed or consumption* or cross-react* or react* or co-react* or eat or ate or eaten or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or

	oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-sensiti#ation or cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. 3 1 and 2 4 limit 3 to (english language and yr="2000 - 2024")
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches:942 Number of additional potential studies identified through other sources:- Total number of studies screened once duplicates were removed: 649 Number of studies shortlisted for full text review: 77 Number of studies excluded after full text review:54 Number and type of studies included:23

Subgroup/Chapter Evidence Matrix

<table>
<tr><td>Evidence Matrix No.</td><td>EM3-10</td></tr>
<tr><td>Clinical/PICO Question:</td><td>Would patients with fish allergy be able to safely consume other fish?</td></tr>
<tr><td>Linked Recommendation Statements:
(Type = R or GPP)
(Chapter no. statement no.)</td><td>GPP 3.19: We recommend that patients with a fish allergy may continue to eat the types of fish that they can tolerate. An allergist may be consulted before introducing new types of fish.</td></tr>
<tr><td>Rationale:</td><td>Patients with fish allergy have a 29-67% risk of reaction to other fish, due to the presence of pan-allergens, such as parvalbumin.[3,4,6] Additionally, the real-life difficulty of accurate fish identification puts the patient at risk of accidental ingestion and reaction.

On the other hand, it is important to open up dietary options. Fish-allergic patients are often able to consume certain fish[17-19], particularly tinned fish.[3-5,20,23] Thus patients will benefit from specialist work-up and guidance. This individualized plan is influenced by clinical phenotype, investigation, species of fish and food processing.</td></tr>
<tr><td>Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(* see examples below; or this section can be a narrative summary.)</td><td>
<table>
<tr><th>Study</th><th>Study Type</th><th>Method</th><th>Outcome</th></tr>
<tr><td>Dijkema 2022[1]</td><td>Review</td><td>Narrative review</td><td>Patients with a fish allergy can be divided into three clusters:
(A) poly-sensitized patients who respond to all types of fish,
(B) mono-sensitized patients with a selective allergic reaction to one individual fish species
(C) oligo-sensitized patients who respond to a number of specific fish. Allergens including parvalbumin, enolase and aldolase can be involved.
The majority of patients with a fish allergy can still eat certain fish species. Even poly-sensitized patients generally tolerate fish species low in parvalbumin e.g. tuna (most likely), mackerel, swordfish, flounder, particularly when processed. Evaluation should be strongly considered.</td></tr>
<tr><td>Davis 2020[2]</td><td>Clinical management review</td><td>Narrative review</td><td>Cross reactivity among fish species is 29%-67%. In selected cases, avoidance of fish in fish allergic patients may not be necessary.</td></tr>
<tr><td>Cox 2021[3]</td><td>Clinical management review</td><td>Narrative review</td><td>Cross reactivity with other finned bony fish is 50%, and that to cartilaginous fish is <5%.
High rate of cross-reactivity may warrant class restriction.
Importance of food may warrant individualized challenges. Canned fish less allergenic. There is possible misidentification of type of fish. Stronger sensitization may reflect higher chance to react to multiple types. Those with bony fish allergy will likely tolerate cartilaginous types. Isolated species allergy reported.</td></tr>
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	Kourani 2019[4]	Review	Narrative review	Avoidance is the recommended treatment and is generally extended to all fish species. However, numerous patients who are allergic to 1 fish species can tolerate another species and some patients are mono-sensitised. Patients may be able to tolerate canned fish. The varying reactivity with other bony fish due to different allergen content. There is low cross-reactivity between fish and cartilaginous ray. There are few reports of cross-reactivity to other meats of frog, crocodile, chicken and shellfish.
	Mastrorilli 2023[5]	Review. Consensus (Italy)	Narrative review	The risk of cross-reactivity is high, given the similarity in parvalbumins of various fish and difficulty in accurate identification of fish species. In paediatrics, fish allergy is often diagnosed young and with first intake of fish. In such cases, it is necessary to rigorously exclude fish from the diet at home and follow a specific diagnostic procedure for the progressive reintroduction of some fish into the diet, starting with those with the most significant possibility of tolerance. For this reason, canned tuna is often the first fish species to be reintroduced.
	Ruethers 2018[6]		Narrative review	Description of the taxonomic tree of edible seafood species and related allergen sources.

Study	Study Type	Region/ Country	n	Age group	Method	Outcome
Sorensen 2017[17]	Prospective	Norway	35	5-19	DBPCFC to cod, salmon, mackerel	54% of patients with fish allergy were tolerant of 1 or 2 fish (cod, salmon or mackerel). 43% reacted to all 3 species.
Leung 2024[18]	Retrospective	Hong Kong	249	2-8	Medical records review, sensitisation	40% of fish-allergic participants indicated tolerance to certain fish species by OFC (32%) and history (8%). The most common fish species to which the participants demonstrated tolerance were salmon (28.5%), tuna (9.2%), and halibut (8.0%), whereas tilapia (1.6%), catfish (2.4%), and carp (4.8%) were the least tolerated fish species.
Tan 2023[19]	Retrospective	Singapore	108	2-21	Medical records review	75% of patients with fish allergy can tolerate at least 1 other species of fish. The most common fish that these children could tolerate were salmon (37.0%), tuna (24.1%) and cod (22.2%).
Xepapadaki 2021[23]	Prospective	Greece	58	4-18	OFC to canned tuna, swordfish, cod	Of the 45 fish-allergic children, 39 of 41 (95%) tolerated tuna and 33 of 35 (94%) swordfish.
Kalic 2019[22]	Prospective	Austria	11	7-35	OFC, sensitisation	Tolerance of ray (cartilaginous fish) was observed in 10/11 of patients with reactions to bony fish, by challenge and home introduction.
Carvalho 2017[21]	Retrospective	Portugal	81	Children	Medical records review,	74% of study patients acquired tolerance to at least 1 fish species. The most and earliest tolerated species was tuna (51 patients [63%]), followed by cod (20 [25%]) and salmon (20 [25%]).
Calderon-Rodriguez 2016[20]	Prospective	Spain	34	Children	Medical records review, OFC dogfish	From history, 23.5% of children did not tolerate any type of fish, 23.5% tolerated only canned tuna, 53% tolerated canned tuna and emperor fish. At OFC, all patients tolerated dogfish (cartilaginous shark).

	Main points in older reviews. Content also covered in contemporary reviews[1-5].			
	Stephen 2017[7]		Narrative review	Fish allergens include parvalbumin (isoforms), tropomyosin, collagen, aldolase, enolase. Allergy to bony fish is common. However, that to cartilaginous fish is less common.
	Prester 2016[8]		Narrative review	Important to make accurate diagnosis. Avoid all other fish. But given nutritional importance, balanced approach to complete elimination.
	Mourad 2015[9]		Narrative review	Different types of allergens and the effect of processing. Advised strict avoidance. Recent studies show that fish allergy is not universal. Most can tolerate at least 1 type of fish or even same species processed (canned). The patient may be subjected to testing and challenge.
	Thalayasingam 2015[10]		Narrative review	Major allergens. Cross reactivity between fish-frog. Importance of diagnosis. Strict avoidance as most fish allergic patients are unable to tolerate most fish.
	Leung 2014[11]			Description of fish allergens, epitopes and immunological cross reactivity
	Sharp 2014[12]			Over 1/3 of patients have multiple fish allergy, due to cross reactive PV. Some patients are mono-sensitised to fish, possibly due to species specific allergens. Heat treatment may increase allergenicity. Bony fish, cartilaginous fish, frog. Fish allergic patients have about 50% chance of being cross-reactive to another fish species.
	Hajeb 2012[13]			Regional prevalence of fish and shellfish allergy. Discussion of fish allergens.
	Tsabouri 2012[14]			We suggest that individuals allergic to fish are advised to avoid all fish species, unless clinical tolerance has been proven to a specific species by challenge. Additionally, performing an OFC to canned fish is a useful strategy for allowing the canned fish to be introduced to the diet of children when negative.
	Lopata 2009[15]			Description of fish allergens, epitopes and immunological cross reactivity
	Wild 2005[16]			There is a high rate of cross reactivity among fish, because of pan-allergens such as parvalbumin. It is estimated that 50% of patients that are allergic to some types of fish are at risk of reacting to a second species.
Certainty and Magnitude of Effects:	Not graded (GPP)			
Risk/Harm vs Benefit Considerations:	In patients with fish allergy, it may not be necessary to avoid all fish. The inclusion of other fish is nutritionally beneficial and improves the quality of life for the patient and family. However, the potential risk of an allergic reaction is estimated at 50%. Thus the suggestion to refer to specialist care for further management.			
Patient/ caregiver values	Patients and caregivers would like to reduce the risk, discomfort and potential severity of allergic reactions. They would wish to be able to find choices that can be consumed without reaction, without extensive dietary avoidance.			
Resource, Cost Considerations:	Evaluation would include the time and resources required for consultation with allergy specialist and investigations, including an oral food challenge.			

<table>
<tr><td></td><td></td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>This is equitable and feasible with the local healthcare resources. Depending on patient preferences, most patients interested in evaluating their food allergies would find the standard evaluation acceptable.</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 3.19: We recommend that patients with a fish allergy may continue to eat the types of fish that they can tolerate. An allergist may be consulted before introducing new types of fish.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>23%</td><td>9</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

1. Dijkema, D.; Emons, J. A. M.; Van de Ven, Aajm; Oude Elberink, J. N. G. Fish Allergy: Fishing for Novel Diagnostic and Therapeutic Options Clin Rev Allergy Immunol 2022;62(1):64-71
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16. Wild, L. G.; Lehrer, S. B. Fish and shellfish allergy Current Allergy and Asthma Reports 2005;5(1):74-79
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Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Shellfish Allergy
Subgroup Members:	Goh Si Hui
Main Clinical Question(s):	Management of food allergy-What food should patients with specific food allergy avoid or what is a safe alternative? Would patients with shellfish allergy be able to safely consume other shellfish?
Population (age limit, inclusion criteria, excluded groups, special groups):	Patients with shellfish allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Consumption of shellfish (crustacean or mollusc)
Comparator (if applicable):	Avoidance
Outcomes (specify critical/primary vs secondary):	Safety
Publication Dates:	2000 – 2024
Study Designs (specify inclusion/exclusion criteria):	Meta-Analysis ☒ Systematic Review ☒ **Randomized Controlled Trials (RCTs)** ☒ Cohort Study ☒ Case series or Case Report ☐ Animal Research ☐ In Vitro/Lab Research ☐ Editorials, Letters, Opinions ☒
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** 1 shellfish allergy/ 2 (allerg* or hypersensitivit*).ab,ti. 3 (consume or consumed or consumption* or cross-react* or react* or co-react* or eat or ate or eaten or tolerant or tolerated or co-existent or coexist* or sensiti#ed or sensiti#ation or co-sensiti* or cosensiti* or "co sensiti*" or "mono sensiti*" or mono-sensiti* or monosensiti* or "oligo sensiti*" or oligo-sensiti* or oligosensiti* or "poly sensiti*" or poly-sensiti* or polysensiti* or co-allerg* or coallerg* or "co allerg*" or cross-allerg* or crossallerg* or "cross allerg*" or cross-

	sensiti#ation or cross-sensiti#ed or "cross sensiti#ation" or "cross sensiti#ed" or crosssensiti#ation or crosssensiti#ed).ab,ti. 4 exp shellfish/ 5 (shellfish or crustacean or mollusk or bivalve or gastropod* or cephalopod or prawn or shrimp or crab or lobster or crayfish or abalone or clam or scallop or oyster or mussel or snail or whelk or octopus or squid or conch or limpet or cuttlefish or cockle).ab,ti. 6 4 or 5 7 1 or 2 8 3 and 6 and 7 9 limit 8 to (english language and yr="2000 -2024")
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches:2925 Number of additional potential studies identified through other sources:- Total number of studies screened once duplicates were removed: 2022 Number of studies shortlisted for full text review: 57 Number of studies excluded after full text review: 37 Number and type of studies included: 20

Subgroup/Chapter Evidence Matrix

<table>
<tr><td>Evidence Matrix No.</td><td>EM3-11</td></tr>
<tr><td>Clinical/PICO Question:</td><td>Would patients with shellfish allergy be able to safely consume other shellfish?</td></tr>
<tr><td>Linked Recommendation Statements:
(Type = R or GPP)
(Chapter no. statement no.)</td><td>GPP 3.20: We recommend that patients with shellfish allergy may continue to eat the types of shellfish that they can tolerate. An allergist may be consulted before introducing new types of shellfish.</td></tr>
<tr><td>Rationale:</td><td>Shellfish include crustacean (e.g. shrimp, crab, crayfish, lobster) and mollusc (e.g. oyster, clam, mussel, scallop, limpet, cockle, abalone, snail, octopus, squid). Crustaceans are closely related to mites (house dust mite) and insects (cockroach).[6,9,11,15]

There is a major risk of cross-sensitization and clinical cross-reactivity given the presence of common allergens. Cross-reactivity is highly likely within the crustacean group, and lower between crustacean and mollusc.[3,4,9,18] There is clinical heterogeneity and some patients may be able to tolerate certain shellfish.[1,2,10,14] We would suggest an allergy work-up for patients with shellfish allergy interested in exploring dietary options.</td></tr>
<tr><td>Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(* see examples below; or this section can be a narrative summary.)</td><td>
<table>
<tr><th>Study</th><th>Study Type</th><th>Method</th><th>Outcome</th></tr>
<tr><td>Cox 2021[1]</td><td>Clinical Management Review</td><td>Narrative review</td><td>In primary crustacean allergy, there is a 75% risk of cross-reactivity to other crustaceans and <50% to molluscs.
In primary mollusc allergy, there is >70% risk of cross-reactivity to crustaceans.
Risk of multiple reactions may warrant class restriction, but importance of food may warrant individualized challenges. Allergy to isolated species is reported. Caution regarding ingesting edible insects. No comprehensive studies but risk appears lower between Crustacean and mollusc than within Crustacean</td></tr>
<tr><td>Davis 2020[2]</td><td>Clinical Management Review</td><td>Narrative Review</td><td>Shellfish constitutes a diverse group subdivided into crustaceans and molluscs Crustaceans are closely related arthropods such as insects and mites, and all contain cross-reactive allergens.
Although there is not much data on crustacean and mollusc allergy cross-reactivity, many physicians recommend avoidance of both because of the risk of cross-contamination. Although cross-reactivity is common in shellfish-allergic patients (75%), studies have shown that crustacean-allergic patients are not always allergic to molluscs, which could be a potential source of protein for a child’s diet.</td></tr>
<tr><td>Faber 2017[3]</td><td>Review</td><td>Narrative Review</td><td>Shellfish are classified into mollusc and crustaceans, the latter belonging to a class of arthropods. Cross-reactivity between shellfish species is a common phenomenon and involves several components of major allergens, particularly tropomyosin, and minor allergens.
The amino acid homology between the tropomyosins of phylogenetically related crustaceans attains up to 98%. The homology between the different Mollusca classes varies from 68 to 100%. In contrast, amino acid homology between crustacean and mollusc tropomyosin is lower, 56–68%.</td></tr>
</table>
</td></tr>
</table>

Gelis 2020[4]	Review	Narrative Review	Major shellfish allergens: tropomyosin, myosin light chain, sarcoplasmic calcium-binding protein. Cross reactivity is due to sequence homology between crustaceans, dust mites, cockroaches, and mollusc.
Giannetti 2023[5]	Review	Narrative Review	There is a major risk of cross-sensitization and clinical cross-reactivity between crustaceans, molluscs, house dust mites and insects. Tropomyosin is the major allergen implicated in cross-reactivity. Approximately 45% of individuals with a crustacean allergy are also allergic to mollusc, while 70–80% of mollusc-allergic patients also experienced allergic reactions to crustaceans. Some patients may have species-specific allergy.
Giovannini 2023[6]	Review	Narrative Review	Cross-reactivity has been reported in >75% of shellfish-allergic patients. Due to allergen sequence homology, patients allergic to one type of crustacean may also react to other crustaceans. Of note, patients with crustacean allergy do not always react to molluscs, which may be an alternative protein source. In general, an allergic workup is recommended for different types of shellfish allergens if the patient does not consume these allergens safely. On the other hand, if a type of shellfish is tolerated, testing for this type is not required.
Kamath 2023[9]	Review	Narrative Review	Many diverse species with homologous allergens are consumed in different regions of the world. In individuals with crustacean allergy, clinical or immunologic cross-reactivity has been observed to molluscs, inhaled insects, edible insects, mites, and anisakis. Several cross-reactive crustacean allergens have been identified and characterized.
Lopata 2016[11]	Review	Narrative	Discussion of allergen and epitope homology. Advice that patients with proven shellfish allergy should avoid a broad range of related shellfish species unless they have already tolerated other species. This cautious approach takes into account that allergic subjects may not be familiar with the variety of shellfish species, their biological relationship and the composition in non-self-prepared mixed seafood dishes.
Wong 2019[14]	Review	Systematic review	A common perception is that all patients with shellfish allergy should avoid all shellfish, as the risk of pan- shellfish cross-reactivity is high. However, some may be allergic to crustaceans but tolerate molluscs, or exhibit species-specific allergy. There is also significant heterogeneity in mollusc allergy. Several studies have shown high rates of IgE cross-reactivity between crustaceans and molluscs. Cross- sensitization rates appear to be highest within the crustacean group, followed by molluscs, and then cephalopods. This serological cross-sensitization does not correlate as closely with clinical cross-reactivity and is therefore unreliable for diagnosis.
Wai 2021[16]	Review	Narrative review	Discussion of the major allergens in shellfish – crustaceans, mollusc and arthropods, the diversity in food consumption (various parts of the shellfish) and preparation (raw, cooked, fermented) in Asia.
Lee 2012[10]	Review	Systematic review	Despite the establishment of molecular homology and allergenic cross reactivity between allergens of the same class, clinical cross-reactivity is more variable between patients, with unique clinical manifestation and wide spectrum of severity.
Wong 2016[15]	Review	Narrative	Discussion of allergens and correlation of house dust mite and shrimp allergy – similar to more recent review. [14]

	Leung 2014[12]	Review	Narrative	Discussion of allergen and epitope homology – similar to more recent reviews. [3-4, 11]
	Lopata 2009[13]	Review	Narrative	Discussion of allergen and epitope homology – similar to more recent reviews. [3-4, 11]
	Hajeb 2012[7]	Review	Narrative	Discussion of cross-reactivity between crustacean, mollusc and arthropods.
	Ho 2014[8]	Review	Narrative	Cross reactivity within shellfish: crustation, insects and mollusc. In Asia, people consume shellfish in diverse ways, various cooking methods and body parts consumed.
	Tsabouri 2012[17]	Review	Systematic review	Discussion of allergens and clinical reactivity – similar to recent reviews.
	Ruethers 2018[18]	Review	Narrative	Seafood refers to several distinct groups of edible aquatic animals including fish, crustacean, and mollusc. The two invertebrate groups of crustacean and mollusc are, for culinary reasons, often combined as shellfish but belong to two different phyla. The evolutionary and taxonomic diversity of the various consumed seafood species poses a challenge in the identification and characterisation of the major and minor allergens critical for reliable diagnostics and therapeutic treatments. Many allergenic proteins are very different between these groups; however, some pan-allergens, including parvalbumin, tropomyosin and arginine kinase, seem to induce immunological and clinical cross-reactivity.
	Prester 2016[19]	Review	Narrative	Discussion of allergens and clinical reactivity – similar to recent reviews. Due to the high cross-reactivity within shellfish group, all patients with shellfish allergy are advised to avoid all shellfish in the absences of evidence for tolerance.
	Pedrosa 2015[20]	Review	Narrative	Cross-reactivity among shellfish is common, and thus avoidance of all crustaceans and molluscs after the first reaction is mandatory until clinical tolerance is confirmed. In vitro cross- reactivity with other species, such as mites, is frequent, as they share common allergens. Nevertheless, clinical cross-reactivity is still a matter of debate.

Certainty and Magnitude of Effects:	Not graded (GPP)
Risk/Harm vs Benefit Considerations:	In patients with shellfish allergy, there is a high risk of clinical reactions within the crustacean group and lower between crustacean and mollusc. Clinical manifestation is heterogenous. If patients are interested in exploring dietary options, we would suggest specialist referral and work-up.
Patient/ caregiver values	Patients and caregivers would like to reduce the risk, discomfort and potential severity of allergic reactions. They also value the importance of finding options that can be safely consumed as extensive dietary avoidance impacts on their quality of life.
Resource, Cost Considerations:	Evaluation would include the time and resources required for consultation with allergy specialist and possible investigations including oral food challenge.
Equity **Acceptability** **Feasibility**	This is equitable and feasible with the local healthcare resources. Depending on patient preferences, most patients interested in evaluating their food allergies would find the standard evaluation acceptable.

Workgroup Consensus Survey (RAND/UCLA):	**GPP 3.20: We recommend that patients with shellfish allergy may continue to eat the types of shellfish that they can tolerate. An allergist may be consulted before introducing new types of shellfish.** *Number voted = 18; Number abstained = 1*

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
1	9	30%	9	1.0	7.6	No Disagreement

External Review Feedback:	
Public Consultation:	

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15. Wong, L.; Huang, C. H.; Lee, B. W.Shellfish and house dust mite allergies: Is the link tropomyosin?Allergy, Asthma and Immunology Research 2016;8(2):101-106
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Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Acute Food-induced Allergic Reactions
Subgroup Members:	Samuel Lee, Bernard Thong
Main Clinical Question(s):	1. What are effective treatments for minor acute food-induced immediate hypersensitivity reactions? 2. What drugs can be given to prevent an allergic reaction in patients with existing food-induced immediate hypersensitivity? 3. What are effective treatments for food-induced anaphylaxis? 4. Who is at greater risk of food anaphylaxis and should be prescribed adrenaline autoinjectors?
Population (age limit, inclusion criteria, excluded groups, special groups):	1. Children and adults 2. Diagnosed with immediate-type food allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Q1. H1 antagonists (1st and 2nd generation) and glucocorticoids. Q2. Antihistamines, Mast cell stabilisers, Leukotriene receptor antagonists, Omalizumab Q3. Therapeutic modalities including Adrenaline, Beta2-agonists, H1 antihistamines, H2 antihistamines, Glucocorticoids Q4. Exposures: Food-related factors, Non-food factors
Comparator (if applicable):	Q1. Placebo or standard-of-care Q2. Placebo or standard-of-care Q3. Placebo or standard-of-care Q4. Not applicable
Outcomes (specify critical/primary vs secondary):	Q1. Efficacy, Safety Q2. Prevention of an allergic reaction Q3. Efficacy, Safety Q4. Anaphylaxis
Publication Dates:	2000 – 2023

Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria - Existing CPGs, SRs, MAs, RCTs Exclusion criteria - Case reports, Case series, Observational studies, Non-English
Search Strategy:	**Clinical Question 1** **Databases Searched:** Medline, Medline in-process, Embase, PubMed, CINAHL, Cochrane **Grey Literature Sources?** No Hand-search bibliographies for relevant articles **Search Terms:** **Search Strategy:** **1** exp Food Hypersensitivity/ **2** ((food or egg? or milk or nut? or peanut? or wheat or shellfish or seafood) adj1 (hypersensitivit* or allerg*)).ab,ti. **3** 1 or 2 **4** exp histamine h1 antagonists/ or exp histamine h1 antagonists, non-sedating/ or exp Glucocorticoids/ **5** ("H1 antihistamine?" or "H1 antagonist?" or glucocorticoid? or Antazoline or Brompheniramine or Chlorpheniramine or Cinnarizine or Clemastine or Cyclizine or Cyproheptadine or Dimenhydrinate or Dimethindene or Diphenhydramine or Doxylamine or Flunarizine or Hydroxyzine or Ketotifen or Meclizine or Methapyrilene or Mianserin or Mirtazapine or Pheniramine or Promethazine or Pyrilamine or Tripelennamine or Triprolidine or Astemizole or Cetirizine or Loratadine or "Olopatadine Hydrochloride" or Terfenadine or Beclomethasone or Betamethasone or "Betamethasone Valerate" or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or "Fluocinolone Acetonide" or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Fluticasone-Salmeterol or "Melengestrol Acetate" or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or "Tobramycin Dexamethasone" or Tobramycin-Dexamethasone or Triamcinolone).ab,ti. **6** 4 or 5 **7** 3 and 6 **8** limit 7 to (english language and yr="2000 - 2023") **Clinical Question 2** **Databases Searched:** Medline, Medline in-process, Embase, PubMed, CINAHL, Cochrane **Grey Literature Sources?** No Hand-search bibliographies for relevant articles **Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review &**

Other Non-Indexed Citations, Daily and Versions <1946 to December 27, 2023>
Search Strategy:
1 exp Food Hypersensitivity/ (24202)
2 ((food or egg? or milk or nut? or peanut? or wheat or shellfish or seafood) adj1 (hypersensitivit* or allerg*)).ab,ti. (20270)
3 1 or 2 (30665)
4 exp histamine antagonists/ or exp butyric acid/ or exp doxepin/ or exp mast cell stabilizers/ or exp cromolyn sodium/ or exp nedocromil/ or Leukotriene Antagonists/ or Omalizumab/ (73325)
5 ("histamine antagonist?" or Antihistamine? or "butyric acid" or doxepin or "mast cell stabiliser?" or "mast cell stabilizer?" or "cromolyn sodium" or nedocromil or "Leukotriene Antagonist?" or "Leukotriene Receptor Antagonist?" or montelukast or Omalizumab).ab,ti. (32608)
6 4 or 5 (92160)
7 3 and 6 (958)
8 limit 7 to (english language and yr="2000 - 2023") (571)

Clinical Question 3

Databases Searched:
Medline, Medline in-process, Embase, PubMed, CINAHL, Cochrane

Grey Literature Sources? No
Hand-search bibliographies for relevant articles

Search Terms:
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to December 27, 2023>
Search Strategy:
1 Anaphylaxis/
2 (Anaphylaxis or Anaphylactic or Anaphylactoid).ab,ti.
3 (food? or "food? induced" or food-induced).ab,ti.
4 1 or 2
5 3 and 4
6 exp histamine h1 antagonists/ or exp histamine h1 antagonists, non-sedating/ or exp Glucocorticoids/ or exp Epinephrine/ or exp adrenergic beta-2 receptor agonists/ or exp albuterol/ or exp fenoterol/ or exp formoterol fumarate/ or exp hexoprenaline/ or exp isoetharine/ or exp metaproterenol/ or exp procaterol/ or exp ritodrine/ or exp salmeterol xinafoate/ or exp terbutaline/
7 ("H1 antihistamine?" or "H1 antagonist?" or glucocorticoid? or Antazoline or Brompheniramine or Chlorpheniramine or Cinnarizine or Clemastine or Cyclizine or Cyproheptadine or Dimenhydrinate or Dimethindene or Diphenhydramine or Doxylamine or Flunarizine or Hydroxyzine or Ketotifen or Meclizine or Methapyrilene or Mianserin or Mirtazapine or Pheniramine or Promethazine or Pyrilamine or Tripelennamine or Triprolidine or Astemizole or Cetirizine or Loratadine or "Olopatadine Hydrochloride" or Terfenadine or Beclomethasone or Betamethasone or "Betamethasone Valerate" or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or "Fluocinolone Acetonide" or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Fluticasone-Salmeterol or "Melengestrol Acetate" or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or "Tobramycin Dexamethasone" or Tobramycin-Dexamethasone or Triamcinolone or adrenaline or Epifrin or Epinephrine or Epitrate or Lyophrin or Medihaler-

	Epi or beta-2-agonist? or albuterol or fenoterol or "formoterol fumarate" or hexoprenaline or isoetharine or metaproterenol or procaterol or ritodrine or "salmeterol xinafoate" or terbutaline).ab,ti. **8** 6 or 7 **9** 5 and 8 **10** limit 9 to (english language and yr="2000 - 2023")
	Clinical Question 4:
	Databases Searched: Medline, Medline in-process, Embase, PubMed, CINAHL, Cochrane **Grey Literature Sources?** No Hand-search bibliographies for relevant articles **Search Terms:** **Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to December 29, 2023>** **Search Strategy:** **1** Food Hypersensitivity/ (18750) **2** (food adj1 (allerg* or hypersensitivit* or anaphylaxis)).ab,ti. (16096) **3** 1 or 2 (25286) **4** Epinephrine/ (56397) **5** ("adrenaline autoinjector?" or epipen? or Epinephrine or Adrenaline or Epifrin or Epitrate or Lyophrin or Medihaler-Epi).ab,ti. (56235) **6** 4 or 5 (81107) **7** 3 and 6 (991) **8** limit 7 to (english language and yr="2000 - 2023") (843)
Search Outcomes:	
	Clinical Question 1:
	Number of potential studies identified by database searches: 3907 Number of additional potential studies identified through other sources: 2 Total number of studies screened once duplicates were removed: 3280 Number of studies shortlisted for full text review: 13 Number of studies excluded after full text review: 8 Number and type of studies included: 5
	Clinical Question 2:
	Number of studies: Number of potential studies identified by database searches: 6088 Number of additional potential studies identified through other sources: 2 Total number of studies screened once duplicates were removed: 4765 Number of studies shortlisted for full text review: 25 Number of studies excluded after full text review: 19 Number and type of studies included: 6

	Clinical Question 3: **Number of studies:** Number of potential studies identified by database searches: 4975 Number of additional potential studies identified through other sources: 10 Total number of studies screened once duplicates were removed: 3104 Number of studies shortlisted for full text review: 30 Number of studies excluded after full text review: 15 Number and type of studies included: 15 **Clinical Question 4:** Number of potential studies identified by database searches: 4885 Number of additional potential studies identified through other sources: 5 Total number of studies screened once duplicates were removed: 3004 Number of studies shortlisted for full text review: 41 Number of studies excluded after full text review: 31 Number and type of studies included: 10

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM4-1*
Clinical/PICO Question:	What are effective treatments for minor acute food-induced immediate hypersensitivity reactions?
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**R 4.1: We strongly recommend using non-sedating H1 antihistamines to treat patients experiencing mild allergic reactions, such as urticaria, angioedema, or oral itch.**
Rationale:	Antihistamines are the first-line treatment for mild allergic reactions, such as urticaria, mild angioedema, and oral itch, which are primarily mediated by histamine release from mast cells. Orally administered non-sedating antihistamines are preferred over their sedating counterparts for their better safety profile and longer duration of action. While effective for cutaneous and mucosal symptoms, antihistamines are not adequate for systemic or life-threatening reactions, such as anaphylaxis, where adrenaline is the treatment of choice. While there are limited large-scale studies focusing specifically on food allergies and H1 antihistamines, existing research on allergies unrelated to food supports the effectiveness of these medications in treating allergic symptoms. Guidelines from organizations such as the American Academy of Allergy, Asthma, and Immunology, as well as the European Academy of Allergy & Clinical Immunology, advocate for the use of H1 antihistamines in managing mild allergic reactions. Second-generation H1 antihistamines are preferred over first-generation ones because they are less likely to block muscarinic receptors or cross the blood-brain barrier. They are also longer acting and tend to have fewer clinically significant drug interactions. For conditions with persistent symptoms requiring regular treatment, an oral non-sedating antihistamine should be used to minimise the risk of sedation and psychomotor impairment associated with sedating antihistamines. There is insufficient evidence to recommend the routine use of glucocorticoids for treating minor allergic symptoms.
Evidence Summaries (include GRADE SoF Tables and	**<u>Glucocorticoids</u>**: No good-quality studies evaluated the effectiveness of glucocorticoids in relieving minor food-related immediate-type allergic reactions.

EtD Frameworks if available):

(see examples below; or this section can be a narrative summary.)*

Antihistamines:

Study	Contributed to R/GPP	Study Type	Age group	Outcome
Muraro et al. 2021.[1]	R1	Clinical Practice Guideline (EAACI)	Children & adults	**Antihistamines** There is evidence to support the benefits of antihistamines (evidence level III, grade C).
Boyce et al. 2010.[2]	R1	Clinical Practice Guideline (NIAID)	Children & adults	**Antihistamines, H1 and H2** Milder forms of allergic reactions, such as flushing, urticaria, isolated mild angioedema, or symptoms of oral allergy syndrome, can be treated with H1 and H2 antihistamine medications.
De Silva. 2014.[3]	R1	Systematic Review (EAACI)	Children & adults	**Antihistamines** The systematic review included three randomised trials (RCTs) and two non-randomised comparisons found that antihistamines may reduce immediate symptoms or severity in children and adults. Only one study was published between 2000 - 2023.
Lin et al. 2000.[4]	R1	Randomised double-blind placebo-controlled	Adults	**Diphenhydramine with Placebo versus Diphenhydramine with Ranitidine** This RCT studied 91 adults with acute allergic syndromes, half of which tested positive for food allergy. Subjects were randomised to two groups: 50 mg of diphenhydramine and saline solution (H1 antagonist control group) versus 50 mg of diphenhydramine and 50 mg ranitidine (H1 & H2). The primary outcome was symptomatic improvement. Results: Two hours after treatment, the H1 + H2 antagonist group was less likely to have urticarial or both urticaria and angioedema. There were no differences between groups in the absence of erythema or angioedema, blood pressure and other symptoms.
Park et al. 2011.[5]	R1	Randomised double-blind controlled trial	Children and adults	**Cetirizine vs Diphenhydramine** This RCT studied children and adults with oral food challenge-related allergic reactions. Subjects were randomly assigned to either receive liquid diphenhydramine (1mg/kg) or liquid cetirizine (0.25mg/kg). The primary outcome was the percentage of patients experiencing sedation. The secondary outcome was the mean time for the resolution of urticaria and pruritus. Results: There was no statistically significant difference in the medial sedation scores between the two groups, but there was a trend towards a higher percentage of sedation with diphenhydramine. Both treatment groups had no significant difference in the mean time to resolution of urticaria and pruritus nor the mean time to onset of relief.

Certainty and Magnitude of Effects:

Intervention	Certainty of Evidence	Magnitude
H1 antihistamines	Very low	Small
H2 antihistamines	Very low	Small
Glucocorticoids	Very low	Small

Risk/Harm vs Benefit Considerations:

Non-sedating second-generation H1 antihistamines have a good safety profile.

In contrast, sedating first-generation H1 antihistamines can lead to various short- and long-term effects on the central nervous system, including drowsiness, impaired motor skills, and potential cognitive decline with prolonged used. Because of these risks, sedating antihistamines should be used cautiously and generally only when non-sedating alternatives are not available.

Patient/ caregiver values

Stakeholder feedback (if available):

Resource, Cost Considerations:

Equity

Acceptability

Feasibility

Stakeholder feedback (if available):

Workgroup Consensus Survey (RAND/UCLA):

R 4.1: We strongly recommend using non-sedating H1 antihistamines to treat patients experiencing mild allergic reactions, such as urticaria, angioedema, or oral itch.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	5%	9	0.0	8.4	No Disagreement

External Review Feedback:

Public Consultation:

References:

1. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, Riggioni C, de Silva D, Angier E, Arasi S, Bellou A, Beyer K, Bijlhout D, Bilò MB, Bindslev-Jensen C, Brockow K, Fernandez-Rivas M, Halken S, Jensen B, Khaleva E, Michaelis LJ, Oude Elberink HNG, Regent L, Sanchez A, Vlieg-Boerstra BJ, Roberts

G; European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022 Feb;77(2):357-377. doi: 10.1111/all.15032. Epub 2021 Sep 1. PMID: 34343358.
2. NIAID-Sponsored Expert Panel; Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58. doi: 10.1016/j.jaci.2010.10.007. PMID: 21134576; PMCID: PMC4241964.
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5. Park JH, Godbold JH, Chung D, Sampson HA, Wang J. Comparison of cetirizine and diphenhydramine in the treatment of acute food-induced allergic reactions. J Allergy Clin Immunol. 2011 Nov;128(5):1127-8. doi: 10.1016/j.jaci.2011.08.026. Epub 2011 Sep 25. PMID: 21945608; PMCID: PMC3205335.

Subgroup/Chapter Evidence Matrix

<table>
<tr><td>Evidence Matrix No.</td><td>EM4-2</td></tr>
<tr><td>Clinical/PICO Question:</td><td>What drugs can be given to prevent an allergic reaction in patients with existing food-induced immediate hypersensitivity (secondary prophylaxis)?</td></tr>
<tr><td>Linked Recommendation Statements:
(Type = R or GPP)
(Chapter no. statement no.)</td><td>GPP 4.2: Medications are not routinely recommended to prevent allergic reactions from occurring in individuals with established IgE-mediated food allergies.</td></tr>
<tr><td>Rationale:</td><td>The prophylactic use of antihistamines, glucocorticoids, or mast cell stabilisers does not consistently prevent IgE-mediated reactions or anaphylaxis when exposure to allergens occurs. Relying on pre-treatment may create a false sense of security and encourage risk-taking behaviour. Omalizumab, a monoclonal anti-IgE antibody, is a treatment option for patients with existing IgE-mediated food allergies who are at risk of reactions resulting from accidental exposure. Patients taking omalizumab for food allergies should continue avoiding foods they are allergic to. Omalizumab is associated with an increase in the tolerated doses of food allergens, improved quality of life, and a reduction in the frequency of allergic reactions. Omalizumab can be used alone or as an adjunct treatment during oral immunotherapy. The appropriateness of oral immunotherapy and/or omalizumab for individuals with food allergies should be determined in consultation with an experienced allergist.</td></tr>
<tr><td>Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(* see examples below; or this section can be a narrative summary.)</td><td>
<table>
<tr><th>Study</th><th>Contributed to R/GPP</th><th>Study Type</th><th>Age group</th><th>Outcome</th></tr>
<tr><td>Boyce et al. 2010.[1]</td><td>GPP1</td><td>Clinical Practice Guideline (NIAID)</td><td>Children and adults</td><td>Cromolyn
Anti-IgE therapy

There are no medications currently recommended to prevent IgE-mediated food-induced allergic reactions from occurring in an individual with existing food allergy.

However, drug therapy has been used to treat food allergy in cases where allergen avoidance is extremely difficult or results in nutritional deficiencies. Randomised controlled trials in anti-IgE therapy showed positive results (cromolyn results were negative), supporting the continued evaluation of the role of anti-IgE therapy.</td></tr>
<tr><td>Sampson et al. 2011.[2]</td><td>GPP1</td><td>Randomised Controlled Trial</td><td>Children and adults</td><td>Omalizumab

Omalizumab did not increase the proportion of children and adults able to tolerate 1000mg peanut protein at 24 weeks (44% omalizumab vs 20% placebo, p > 0.05). There was no no statistically significant improvement from omalizumab in the maximum dose of peanut tolerated by children and adults compared to baseline, but there were positive trends (p>0.05). There was no difference in mild to moderate adverse events reported in children and adults taking omalizumab versus placebo (77% vs 89% placebo, p>0.05). There was no systemic adverse events in children and adults taking omalizumab or placebo.

Moderate risk of bias. The study was terminated early due to the recommendation of the Data Safety Monitoring Committee because of the severity of 2</td></tr>
</table>
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					anaphylactic reactions that occurred during oral food challenges before the administration of the study drug.
	De Silva et al. 2021.[3]	GPP1	Systematic Review and Meta-analysis	Children and adults	**Omalizumab** There were too few studies (3 studies, with only one on omalizumab [Sampson 2011]) to draw meaningful conclusions about biologicals alone in the management of food allergy.
	De Silva et al. 2022. [4]	GPP1	Systematic Review	Children and adults	**Omalizumab** This paper concluded that there was not yet enough certainty to support offering omalizumab widely for food allergy (one RCT, Sampson 2011, rated as moderate risk of bias).
	Matsui et al. 2023.[5]	GPP1	Randomised Controlled Trial	Children	**Prednisolone with antihistamines** Investigators administered prednisolone 1mg/kg in addition to antihistamines immediately after oral food challenge tests (OFCs) provoked mild skin symptoms in 103 patients with food allergies. The primary outcome (worsening of allergic reaction) did not differ significantly between the prednisolone and no-prednisolone groups, even when stratified according to allergen type. Overall, prednisolone (with antihistamines) did not exert rapid effects to protect from exacerbation of food allergy symptoms.
	Zuberbier et al. 2023.[6]	GPP1	Systematic Review and Meta-analysis	Children and adults	**Omalizumab** In a meta-analysis of 4 studies (n=210) showed that omalizumab (duration 9-22 weeks) significantly increased the tolerated dose of multiple foods versus pre-omalizumab over a period of 17 to 22 weeks (RR 24.88; P < .001). In patients with severe and persistent allergy (n=7, 1 study), omalizumab monotherapy did not significantly increase the tolerated dose of cow's milk and eggs compared to pre-omalizumab at week 16 as assessed in a single-blind food challenge test (RR 10.38; P = 0.09) A significant increase in the threshold of tolerated dose for multiple foods (milk, egg, wheat, and baked milk) was observed with omalizumab at 17 weeks versus pre-omalizumab in a single study (n=15) (MD 2,794.89; P < 0.001). Analysis from 1 study demonstrated that omalizumab significantly reduced accidental or intentional food-induced allergic reactions (urticaria, atopic dermatitis, rhinosinusitis, asthma, and anaphylaxis; RR 16.21; P < 0.001) at 52 weeks in patients with multiple food allergies (n=22) versus pre-omalizumab. Also, a reduction in allergic reactions (MD 5.21; P < 0.001) was noted at 18 weeks in patients with an allergy to peanuts (n= 14) receiving omalizumab compared with pre-omalizumab.
Certainty and Magnitude of Effects:	Not graded (GPP)				

	Omalizumab	Very low	Small

Risk/Harm vs Benefit Considerations:

Medications used for secondary prophylaxis should not be regarded as a substitute for the active avoidance of food allergens. They do not entirely eliminate the inherent risk associated with such reactions. Furthermore, reliance on pharmacological interventions may foster a false sense of security, leading individuals to underestimate the importance of avoiding known triggers. Consequently, it is imperative for individuals at risk of food allergies to prioritize allergen avoidance as the principal strategy for protecting their health.

Patient/ caregiver values

Stakeholder feedback (if available):

Resource, Cost Considerations:

Equity

Acceptability

Feasibility

Stakeholder feedback (if available):

Workgroup Consensus Survey (RAND/UCLA):

GPP 4.2: Medications are not routinely recommended to prevent allergic reactions from occurring in individuals with established IgE-mediated food allergies.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
5	9	17%	9	1.0	7.6	No Disagreement

External Review Feedback:

Public Consultation:

References:

1. NIAID-Sponsored Expert Panel; Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Schneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58. doi: 10.1016/j.jaci.2010.10.007. PMID: 21134576; PMCID: PMC4241964.
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Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022 Jun;77(6):1852-1862. doi: 10.1111/all.15211. Epub 2022 Jan 19. PMID: 35001400; PMCID: PMC9303769.
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7. Wood RA, Togias A, Sicherer SH, Shreffler WG, Kim EH, Jones SM, Leung DYM, Vickery BP, Bird JA, Spergel JM, Iqbal A, Olsson J, Ligueros-Saylan M, Uddin A, Calatroni A, Huckabee CM, Rogers NH, Yovetich N, Dantzer J, Mudd K, Wang J, Groetch M, Pyle D, Keet CA, Kulis M, Sindher SB, Long A, Scurlock AM, Lanser BJ, Lee T, Parrish C, Brown-Whitehorn T, Spergel AKR, Veri M, Hamrah SD, Brittain E, Poyser J, Wheatley LM, Chinthrajah RS. Omalizumab for the Treatment of Multiple Food Allergies. N Engl J Med. 2024 Mar 7;390(10):889-899. doi: 10.1056/NEJMoa2312382. Epub 2024 Feb 25. PMID: 38407394; PMCID: PMC11193494.

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM4-3*
Clinical/PICO Question:	What are effective treatments for food-induced anaphylaxis?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 4.3: We strongly recommend that patients suspected of having food-related anaphylaxis be treated as an emergency with the immediate administration of intramuscular adrenaline as the first-line intervention.** **R 4.4: We strongly recommend administering additional doses of intramuscular adrenaline every 5 to 15 minutes based on the patient's clinical response, for those who do not show improvement while awaiting transfer to an emergency facility.** **GPP 4.5: We recommend that the following treatments be administered as adjunctive measures to intramuscular adrenaline if clinically indicated:** • **High-flow supplemental oxygen for respiratory distress** • **Intravenous fluids for hypotension/shock** • **Inhaled beta-2-agonists for bronchoconstriction** • **Non-sedating antihistamines for cutaneous symptoms.** **R 4.6: We conditionally recommend against the routine use of glucocorticoids for the prevention of biphasic anaphylaxis.**
Rationale:	The pharmacological treatment of food-induced anaphylaxis is based on therapies used for cardiac arrest and asthma, as well as findings from uncontrolled human trials involving insect sting challenges and studies conducted in animal models of anaphylaxis. No randomised controlled trials (RCTs) have been conducted in humans to thoroughly evaluate therapeutic interventions for anaphylaxis. Adrenaline is the first-line and most critical treatment for food-induced anaphylaxis and should be administered promptly when signs of systemic allergic reaction are present, including respiratory compromise and cardiovascular symptoms. Multiple clinical guidelines uniformly endorse early administration of intramuscular (IM) adrenaline as the single most effective intervention in anaphylaxis. IM injection into the mid-anterolateral thigh is the recommended route as it gives higher plasma adrenaline levels. Delays in giving adrenaline can lead to increased morbidity and mortality. Adrenaline mitigates the pathophysiologic cascade of anaphylaxis by causing vasoconstriction, increasing cardiac output, relaxing bronchial smooth muscle, and reducing mast cell mediator release. Dosing should be weight-based and may be repeated every 5–15 minutes if symptoms persist whilst awaiting transfer to an emergency facility. H1 and H2 antihistamines, along with corticosteroids, are commonly used in managing anaphylaxis, though the evidence supporting their effectiveness is limited. H1 antihistamines can help relieve itching and urticaria but do not address stridor, shortness of breath, wheezing, gastrointestinal symptoms, or shock. Minimal evidence supports the use of H2 antihistamines in the emergency treatment of anaphylaxis. Corticosteroids are not effective for acute anaphylaxis due to their slow onset of action (4 to 6 hours). Additionally, there is very low certainty evidence suggesting that antihistamines and glucocorticoids do not prevent biphasic anaphylaxis, as demonstrated in a meta-analysis.[5]

Inhaled beta-2 adrenergic receptor agonists do not relieve airway oedema and should not replace intramuscular adrenaline in the treatment of anaphylaxis. However, they can be used as an adjunct to help alleviate bronchospasm. Similarly, high-flow supplemental oxygen and intravenous fluids address specific life-threatening manifestations of anaphylaxis — namely hypoxaemia and haemodynamic instability — that adrenaline alone may not fully resolve. In each case, the decision to administer these therapies is guided by the patient's clinical presentation, and the net benefit in the appropriate context is clear. As the supporting evidence is largely indirect and not readily amenable to quantitative synthesis, these adjunctive measures are classified as GPPs rather than formal recommendations.

Adrenaline IM dose (Use 1 mg/mL [1:1000] adrenaline)

The recommended dosage of adrenaline for treating anaphylaxis is 0.01 mg/kg, up to a maximum of 0.3 mg for children (12 years and under) and 0.5 mg for adults.

UK NICE and Resuscitation Council UK	
Age	Intramuscular dose (1mg/mL of 1:1000 adrenaline)
Infants aged under 6 months	0.1mg to 0.15mg (0.1 to 0.15 mL)
Child aged 6 months to 6 years	0.15mg (0.15 mL)
Child aged 6 years to 12 years	0.3 mg (0.3 mL)
Adult or child older than 12 years	0.5mg (0.5 mL)

EAACI guidelines: Anaphylaxis (2021 update)	
Age	Intramuscular dose (1mg/mL of 1:1000 adrenaline)
Children < 25 - 30 kg	0.15 mg (0.15 mL)
Adults and children ≥ 25 - 30kg	0.3 mg (0.3 mL)

WAO 2020 guidelines	
Age	Intramuscular dose 1mg/mL (1:1000) adrenaline
Infants under 10kg	0.01 mg/kg = 0.01 mL/kg
Children aged 1 - 5 years	0.15 mg (0.15 mL)
Children aged 6 - 12 years	0.3 mg (0.3 mL)
Teenagers and adults	0.5 mg (0.5 mL)

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

Study	Contributed to R/GPP	Study Type	Age group	Outcome
Boyce et al. 2010.[1]	R 4.3, R 4.4, GPP 4.5	Clinical Practice Guideline (NIAID)	Children and adults	This recommendation was based on moderate evidence quality with significant expert opinion contribution. Prompt treatment with intramuscular adrenaline is recommended as first-line therapy, and other treatments are recommended as adjunctive to adrenaline dosing. IV adrenaline (1:10,000 solution) is recommended for patients who do not respond to an initial (or repeated) IM injection of adrenaline. Adjunctive treatment: •Supplemental oxygen •H1 and H2 antihistamines and corticosteroids may be used, but little or no data demonstrate their functional role or effectiveness. •Bronchodilator medications such as nebulised salbutamol • Glucagon may be used in those with inadequate response to adrenaline due to beta-adrenergic receptor antagonists. •Patients who have persistent hypotension despite the administration of adrenaline and IV fluids should receive vasopressor medications
Simons et al. 2014.[2]	R 4.3, R 4.4, GPP 4.5	Clinical Practice Guideline (ICON)	Children and adults	Collaborating organisations' guidelines concur about recommendations for prompt initial treatment of anaphylaxis with adrenaline injected intramuscularly in the mid-outer thigh and repeating the adrenaline dose after 5-15 minutes if the response to the first injection is not optimal. At any time, supplemental oxygen, intravenous fluid resuscitation, and cardiopulmonary resuscitation should be started without delay, and H1-antihistamines, H2-antihistamines, and glucocorticoids are not initial medications of choice.
Simons et al. 2015.[3]	R 4.3, R 4.4, GPP 4.5	Clinical Practice Guideline (WAO)	Children and adults	Adrenaline is the medication of first choice. H1, H2 antihistamines and glucocorticoids are non-life-saving and should not be used as initial or sole treatment.
Cardona et al. 2020.[4]	R 4.3, R 4.4, GPP 4.5, R 4.6	Clinical Practice Guideline (WAO)	Children and adults	IM adrenaline 0.01mg/kg body weight (max 0.5mg), repeated every 5-15 minutes if symptoms are refractory. IV adrenaline is not recommended as an initial treatment and requires administration by experienced personnel. Administer high-flow oxygen for patients in respiratory distress and intravenous crystalloids (20ml/kg bolus) for patients with cardiovascular instability. Adjunctive inhaled short-acting beta-2 agonists can be given to patients with bronchoconstriction.

					H1 antihistamines have a limited role in treating anaphylaxis, but they may be helpful with cutaneous symptoms. However, they should not delay the administration of adrenaline. Second-generation H1 antihistamines are less sedating, but only first-generation drugs may be available for parenteral use. There is increasing evidence that glucocorticoids may not benefit the acute management of anaphylaxis. There is limited evidence, but parenteral glucagon may be used in patients with no optimal response to adrenaline, particularly, in patients taking beta-blockers.
	Shaker et al. 2020.[5]	R 4.6	Clinical Practice Guidelines (AAAAI/ACAAI)) with meta-analysis published	Children and adults	Suggest against administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Strength of recommendation: conditional. Certainty of evidence: very low.

Glucocorticoids to prevent biphasic anaphylaxis

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Biphasic	Uniphasic		
Biphasic anaphylaxis	Based on data from 15,633 participants in 26 observational studies Biphasic 616 of 871 (70.7%) Uniphasic 10,270 of 14,762 (69.6%)	Relative: OR 0.87 (0.74-1.02) Absolute: 30 fewer per 1000 (from 4 more to 67 fewer)		**Low** Very serious risk of bias. Serious inconsistency. Serious indirectness. Serious imprecision.	Very low certainty evidence that treatment with glucocorticoids as part of initial anaphylaxis management does not prevent biphasic anaphylaxis.

H1 Antihistamines to prevent biphasic anaphylaxis

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Biphasic	Uniphasic		
Biphasic anaphylaxis	Based on data from 3549 participants in 16 observational studies Biphasic 210 of 245 (85.7%) Uniphasic 2875 of 3304 (87.0%)	Relative: OR 0.71 (0.47-1.06) Absolute: 44 fewer per 1000 (from 6 more to 111 fewer)		**Very Low** Very serious risk of bias. Serious inconsistency. Serious indirectness. Serious imprecision.	Very low certainty evidence that treatment with H1 antihistamines as part of initial anaphylaxis management does not prevent biphasic anaphylaxis.

H2 Antihistamines to prevent biphasic anaphylaxis

	Outcome	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
			Biphasic	Uniphasic		
	Biphasic anaphylaxis	Based on data from 2128 participants in 10 observational studies Biphasic 60 of 173 (34.7%) Uniphasic 763 of 1955 (39.0%)	Relative: OR 1.21 (0.80-1.83) Absolute: 46 more per 1000 (from 52 fewer to 149 more)		**Very Low** Very serious risk of bias. Not serious inconsistency. Serious indirectness. Serious imprecision.	Very low certainty evidence that treatment with H2 antihistamines as part of initial anaphylaxis management does not prevent biphasic anaphylaxis.

Sargent et al. 2021.[6]	R 4.4	Clinical Practice Guideline (Resuscitation Council UK)	Children and adults	Refractory anaphylaxis is defined as a reaction requiring ongoing treatment (no improvement in respiratory or cardiovascular symptoms) despite two appropriate doses of intramuscular adrenaline. The authors recommend a low-dose intravenous adrenaline infusion in all patients whose reaction is refractory to initial adrenaline.
Muraro et al. 2021.[7]	R 4.3, R 4.4, GPP 4.5	Clinical Practice Guideline (EAACI)	Children and adults	Recommends prompt use of intramuscular adrenaline in mid-thigh as first-line management of anaphylaxis. Suggests using adrenaline autoinjectors for the first-line management of anaphylaxis in the community. Suggests prescribing 0.15mg adrenaline autoinjectors for children from 7.5kg to 25-30kg, and 0.3mg adrenaline autoinjectors for children from 25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis. The systematic review found no eligible randomised controlled trials assessing the effectiveness of other interventions in the acute management of anaphylaxis. The guideline acknowledges that H1 and H2 antihistamines, glucocorticoids, inhaled beta2-agonists and inhaled adrenaline (for laryngeal oedema) may be useful as concomitant therapy with intramuscular adrenaline,
Dodd et al. 2021.[8]	R 4.3, R 4.4, GPP 4.5, R 4.6	Clinical Practice Guideline {Resuscitation Council UK)	Children and adults	Recommend adrenaline as the first line treatment for anaphylaxis (strong recommendation, moderate certainty evidence) <u>Recommended doses of IM adrenaline</u> Adults • 500 micrograms (0.5 mg) IM (0.5 mL of 1 mg/ml [1:1000] adrenaline) Children • >12 years: 500 micrograms IM (0.5 mL), i.e., same as adult dose; 300 micrograms (0.3 mL) if the child is small or prepubertal • 6- 12 years: 300 micrograms IM (0.3 mL)

					• 6 months - 6 years: 150 micrograms IM (0.15 mL) • <6 months: 100 - 150 micrograms IM (0.1 - 0.15 mL) Titrate the administration of adrenaline (by any route) against clinical response (strong recommendation, very low certainty evidence). Suggest that antihistamines are not used as part of the initial emergency treatment for anaphylaxis (weak recommendation, low certainty evidence) as they have no role in treating respiratory or cardiovascular symptoms of anaphylaxis Suggest antihistamines are used to treat skin symptoms which often occur as part of allergic reactions, including anaphylaxis (weak recommendation, very low certainty evidence) - their use must not delay the management of respiratory or cardiovascular symptoms of anaphylaxis with adrenaline and IV fluids. Suggest against the routine use of corticosteroids to treat anaphylaxis (weak recommendation, very low certainty evidence). Corticosteroids may be used as a third-line intervention to treat underlying asthma or shock (weak recommendation, very low certainty evidence). Beta-2 agonists (such as salbutamol) may be useful as an adjunct treatment for lower respiratory symptoms caused by anaphylaxis following initial treatment with IM adrenaline (weak recommendation, very low certainty evidence). In the presence of persisting respiratory symptoms in anaphylaxis, beta-2 agonists (whether inhaled or parenteral) should not be used as an alternative to further parenteral treatment with adrenaline (strong recommendation, very low certainty evidence).
	Sheikh et al. 2007.[9]	GPP 4.5	Systematic Review	Children and adults	**H1 antihistamines** No eligible studies for inclusion in a systematic review performed of randomised and quasi-randomized-controlled trials comparing H1-antihistamines with placebo or no intervention were in patients with anaphylaxis.
	Sheikh et al. 2008.[10]	Nil	Systematic Review	Children and adults	**Adrenaline** No eligible studies for inclusion in a systematic review performed of randomised controlled trials and quasi-randomized controlled trials comparing adrenaline with no intervention in patients with anaphylaxis.
	Choo et al. 2010.[11]	R 4.6	Systematic Review	Children and adults	**Glucocorticoids** No eligible studies for inclusion in a systematic review were performed of randomised controlled trials and quasi-randomized controlled trials comparing glucocorticoids with any control (either

					placebo, adrenaline, an antihistamine, or any combination) in patients with anaphylaxis.
	De Silva et al. 2014.[12]	GPP 4.5	Systematic Review (EAACI)	Children and adults	**Antihistamines** Three randomised trials and two nonrandomised comparisons found that antihistamines may reduce immediate symptoms or severity in children and adults.
	Nurmatov et al. 2014.[13]	GPP 4.5	Systematic Review	Children and adults	**H2 antihistamines** No eligible studies for inclusion in a systematic review performed of randomised controlled trials and quasi-randomized controlled trials comparing H2-antihistamines with placebo or no intervention in patients with anaphylaxis.
	Alqurashi et al. 2017.[14]	R 4.6	Systematic Review	Children and adults	**Corticosteroids** Because of the potential detrimental adverse effects of corticosteroids and the lack of compelling evidence demonstrating an effective role in reducing anaphylaxis severity or preventing biphasic anaphylaxis, the authors do not advocate for their routine use in anaphylaxis.
	De Silva et al. 2020.[15]	R 4.3, R 4.4	Systematic Review	Children and adults	**Biphasic anaphylaxis and Adrenaline** Very low certainty evidence that adrenaline reduces the risk of biphasic reactions in anaphylaxis and, in its intramuscular form, carries a lesser risk of overdose and cardiovascular events than as an intravenous bolus.

Outcome	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)
		Biphasic	Uniphasic	
Biphasic anaphylaxis associated with adrenaline.	Based on data from 269 participants in 2 case-control studies Children	Relative: OR 0.08 (0.014 - 0.43) Absolute: Range 9% (P >0.05) to 18% (P < 0.05) reduction		**Very Low**
Hospital admissions associated with adrenaline administered before vs at ED	Based on 384 participants in 1 case-control study Children	Relative: OR 0.25 (0.10 to 0.62) Absolute: 26% reduction if administered before ED (P <0 .05)		**Very low**
Overdose associated with intravenous bolus compared to intramuscular adrenaline.	Based on data from 301 participants in 1 case series Adults and children	Relative: OR 61.3 (7.5 to infinity) Absolute: 13% increase (P < .05)		**Very low**

Certainty and Magnitude of Effects:

Intervention	**Certainty of Evidence**	**Magnitude**
IM Epinephrine	Very low	Large

	Nebulised beta-2-agonists	Very low	Small
	H1 antihistamines	Very low	Small
	H2 antihistamines	Very low	Small
	Glucocorticoids	Very low	Small
Risk/Harm vs Benefit Considerations:	The benefits of early treatment of anaphylaxis with intramuscular adrenaline greatly outweigh its risks, as delays in its administration are linked to mortality and morbidity. Administration of intramuscular adrenaline should not be delayed by the administration of adjunctive treatments (such as antihistamines, glucocorticoids, et cetera).		
Patient/ caregiver values	**Stakeholder feedback (if available):**		
Resource, Cost Considerations:			
Equity **Acceptability** **Feasibility**	**Stakeholder feedback (if available):**		

Workgroup Consensus Survey (RAND/UCLA):

R 4.3: We strongly recommend that patients suspected of having food-related anaphylaxis be treated as an emergency with the immediate administration of intramuscular adrenaline as the first-line intervention.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
3	9	17%	9	0.0	8.4	No Disagreement

R 4.4: We strongly recommend administering additional doses of intramuscular adrenaline every 5 to 15 minutes based on the patient's clinical response, for those who do not show improvement while awaiting transfer to an emergency facility.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	8%	9	0.6	7.9	No Disagreement

GPP 4.5: We recommend that the following treatments be administered as adjunctive measures to intramuscular adrenaline if clinically indicated:

- **High-flow supplemental oxygen for respiratory distress**
- **Intravenous fluids for hypotension/shock**
- **Inhaled beta-2-agonists for bronchoconstriction**
- **Non-sedating antihistamines for cutaneous symptoms.**

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
4	9	17%	9	1.0	7.6	No Disagreement

R 4.6: We conditionally recommend against the routine use of glucocorticoids for the prevention of biphasic anaphylaxis.

Number voted = 18; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus

	2	9	24%	9	1.0	7.6	No Disagreement	

External Review Feedback:	
Public Consultation:	

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Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM4-4*
Clinical/PICO Question:	Who should be prescribed adrenaline autoinjectors? / Which patients are at increased risk for anaphylaxis?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 4.7: We strongly recommend the prescription of adrenaline autoinjectors for individuals with a history of food-induced anaphylaxis.** **GPP 4.8: We suggest that adrenaline autoinjectors may be considered for individuals with a history of mild-to-moderate allergic reactions to foods, particularly if there are additional risk factors for anaphylaxis. Risk factors include but are not limited to:** • **Unstable or moderate-to-severe persistent asthma** • **Previous reaction to trace amounts of food allergens** • **Allergies to peanuts or tree nuts** • **History of risk-taking behaviour** • **Limited/ remote access to medical care** • **Underlying systemic mastocytosis** • **Oral immunotherapy for food allergy** • **Unable to avoid further exposure to the allergen consistently.**
Rationale:	Adrenaline autoinjectors are life-saving devices for individuals at risk of food-induced anaphylaxis. They should be prescribed to all patients with an IgE-mediated food allergy who have a history of anaphylaxis or possess risk factors for severe reactions. These devices deliver a fixed dose of intramuscular adrenaline, typically 0.3 mg for children weighing between 15 and 30 kg, and 0.3 mg for patients above 30kg, and are designed for rapid administration into the mid-anterolateral thigh. Autoinjectors should be prescribed alongside a written anaphylaxis action plan, which provides clear instructions for recognising symptoms and responding appropriately. This plan should outline when to administer adrenaline and when to call emergency services. Education and hands-on training for patients and caregivers are required to ensure they can confidently and correctly recognise anaphylaxis and use the autoinjector. Regular review of the action plan and technique during follow-up visits enhances preparedness for any potential allergic reactions.

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

Study	Contributed to R/GPP	Study Type	Age group	Outcome
Muraro et al. 2007.[1]	R4, GPP3	Clinical Practice Guideline (EAACI)	Children	Absolute indications for adrenaline autoinjector: •Previous cardiovascular or respiratory reaction to a food, insect sting or latex. •Exercise-induced anaphylaxis. •Idiopathic anaphylaxis. •Child with food allergy and co-existent persistent asthma. Relative indications: •Any reaction to small amounts of food (e.g. airborne food allergen or contact only via skin). •History of a previous mild reaction to peanut or a tree nut. •Remoteness of home from medical facilities. •Food allergic reaction in a teenager.
Sicherer et al. 2007.[2]	R4, GPP3	Review/ Guidance (American Academy of Paediatrics)	Children	Factors that may indicate the need to prescribe adrenaline for persons "at risk" of anaphylaxis: Reaction history: •Reaction to trace allergen exposure •Repeat exposures likely •Specific food triggers known to be associated with severe/fatal reactions (e.g. peanut, tree nut, seafood, milk) Certain comorbidities: •Asthma •Use of nonselective beta-blockers Additional factors: •Initial reaction details unclear (possibility of anaphylaxis) •Remote from medical care/access
Boyce et al. 2010.[3]	R4, GPP3	Clinical Practice Guideline (NIAID)	Children and adults	All patients experiencing anaphylaxis should be provided directly with an adrenaline autoinjector. Other patients who should be prescribed an adrenaline autoinjector include •Patients with a history of prior systemic allergic reactions, •Food allergy and asthma, and •Patients with a known food allergy to peanut, tree nuts, fish and crustacean shellfish (i.e. allergens known to be associated with more fatal and near-fatal allergic reactions). Consideration should be given to prescribing an adrenaline autoinjector for all patients with food allergies having IgE-mediated reactions because it is impossible to predict the severity of any subsequent reactions with accuracy. Adrenaline auto-injector dose: •Children weighing less than 25 kg should receive the 0.15 mg dose •Children over 25 kg through adults should receive the 0.3 mg dose autoinjector. Education for patient and family on: •Allergen avoidance •Early recognition of signs and symptoms of anaphylaxis •Anaphylaxis emergency action plan implementation •Appropriate IM adrenaline administration

					•Medical identification jewellery or an anaphylaxis wallet card
	Lieberman et al. 2010.[4]	R4, GPP3	Clinical Practice Guidelines (AAAAI/ ACAAI/ JCAAI)	Children and adults	The most commonly implicated foods responsible for food-induced anaphylaxis include peanuts, tree nuts, fish, shellfish, cow's milk, soy, eggs and sesame. Common themes associated with fatal food anaphylaxis include the following: •Reactions commonly involve peanuts and tree nuts •Teenagers and young adults •Previous history of food allergy and asthma •Failure to administer adrenaline promptly.
	Stiefel et al. 2017.[5]	R4, GPP3	Clinical Practice Guidelines (BSACI, Peanut & Tree nut)	Children and adults	Clear indications to provide injectable adrenaline include any previous episodes of anaphylaxis to a nut. Patients with pollen food syndrome usually do not require an adrenaline autoinjector unless there has been a severe reaction.
	Muraro et al. 2021.[6]	R4, GPP3	Clinical Practice Guideline (EAACI)	Children and adults	The task force suggests using adrenaline autoinjectors for the first-line management of anaphylaxis in the community (very low certainty of evidence) The task force suggests prescribing 0.15mg adrenaline autoinjectors for children weighing 7.5kg to 25-30kg, 0.3mg adrenaline autoinjectors for children weighing 25-30kg, and at least 0.3mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis (very low certainty of evidence). The task force recommends providing structured, comprehensive training to improve recognition of anaphylaxis and the use of adrenaline autoinjectors in people at risk of anaphylaxis. This is in addition to basic instructions about autoinjector use (low certainty of evidence). Absolute indications for adrenaline autoinjectors: •Previous anaphylaxis triggered by food. •Co-existing unstable or moderate to severe, persistent asthma and a food allergy. •Underlying systemic mastocytosis in adults with any previous systemic reaction. Consider prescribing adrenaline autoinjectors with any of the following additional factors: •Previous mild-to-moderate allergic reaction to foods known to be associated with anaphylaxis in the patient's region (e.g. peanut and/or tree nut, cow's milk, seafood). •Teenagers or young adults with a food allergy with previous mild-to-moderate reactions. •Remote from medical help or prolonged travel abroad in the context of previous mild-to-moderate allergic reaction to a food. •Previous mild-to-moderate allergic reaction to traces of food. •Oral immunotherapy for food allergy.
	Turner et al. 2022.[7]	R4, GPP3	Evidence review and meta-analysis (GA2LEN)	Children and adults	Potential risk factors for more severe reactions in food allergy: <u>Increased risk</u> Low certainty evidence: •Prior anaphylaxis is not a good predictor of future anaphylaxis. The absence of prior anaphylaxis does not exclude future risks.

					•Specific food triggers, e.g. persistent cow's milk allergy, peanut, seafood, wheat •LTP sensitisation without pollen co-sensitization •Risk-taking behaviour; poor situational awareness. •Exercise •Concomitant use of ACE inhibitors and beta-blockers. High certainty evidence: •Adolescence/ adults <40 years old <u>Decreased risk</u> Low certainty evidence: •Specific food triggers e.g. egg. •Disease-modifying treatment, e.g. allergen immunotherapy. High certainty evidence: •Bet v 1-mediated pollen food allergy syndrome. <u>Risk unknown</u> •Active atopic disease (allergic rhinitis, eczema). •Suboptimal asthma control, asthma severity. •IgE sensitisation to specific components/ basophil activation test. •Mastocytosis. •Dose of allergen.
	Skypala et al. 2022.[8]	R4, GPP3	Clinical Practice Guidelines (BSACI, Pollen food)	Children and adults	Pollen food syndrome: self-injectable adrenaline devices are rarely required (for rare cases with severe reactions).
	Angier et al. 2023.[9]	R4, GPP3	Clinical Practice Guidelines (BSACI, adrenaline autoinjector)	Children and adults	For individuals who cannot reliably avoid re-exposure to the allergen, adrenaline autoinjector is recommended in those with a history of a severe (e.g. airway involvement or hypotension) reaction. It is also recommended if the reaction was mild (e.g. urticaria without airway involvement) or moderate (e.g. generalised urticaria with mild airway involvement) but with an added risk factor (e.g. asthma, trace exposure, raised baseline tryptase, teenager/young adult, remoteness from medical help). Adrenaline autoinjectors could be considered in individuals with a history of a moderate reaction without an added risk factor. Prescribe two autoinjectors for those at significant risk of anaphylaxis. Training should be specific to the device, ongoing and be incorporated into the prescribing process alongside an individualised action plan.
Certainty and Magnitude of Effects:	**R 4.7** : Certainty of Evidence: High Magnitude: High GPP 4.8: Not graded (GPP)				

<table>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td>The benefits of early treatment of anaphylaxis with an adrenaline autoinjector outweigh its risks and cost, as delays in adrenaline administration are linked to poor outcomes.</td></tr>
<tr><td>Patient/ caregiver values</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td></td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 4.7: We strongly recommend the prescription of adrenaline autoinjectors for individuals with a history of food-induced anaphylaxis.
Number voted = 18; Number abstained = 1
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<tr><td>7</td><td>9</td><td>8%</td><td>9</td><td>0.9</td><td>7.7</td><td>No Disagreement</td></tr>
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GPP 4.8: We suggest that adrenaline autoinjectors may be considered for individuals with a history of mild-to-moderate allergic reactions to foods, particularly if there are additional risk factors for anaphylaxis. Risk factors include but are not limited to:

Unstable or moderate-to-severe persistent asthma
Previous reaction to trace amounts of food allergens
Allergies to peanuts or tree nuts
History of risk-taking behaviour
Limited/ remote access to medical care
Underlying systemic mastocytosis
Oral immunotherapy for food allergy
Unable to avoid further exposure to the allergen consistently.

Number voted = 19; Number abstained = 0
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<tr><td>2</td><td>9</td><td>21%</td><td>9</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
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<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

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8. Skypala IJ, Hunter H, Krishna MT, Rey-Garcia H, Till SJ, du Toit G, Angier E, Baker S, Stoenchev KV, Luyt DK. BSACI guideline for the diagnosis and management of pollen food syndrome in the UK. Clin Exp Allergy. 2022 Sep;52(9):1018-1034. doi: 10.1111/cea.14208. Epub 2022 Aug 17. PMID: 35975576.
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Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Nutritional Counselling and Evaluation
Subgroup Members:	Chong Yan Fong
Main Clinical Question(s):	1. Are children with food allergies at an increased risk of nutritional deficiencies and poor growth? 2. When should children with food allergies be referred to a dietitian? 3. What are the recommendations for measurement and monitoring of nutritional biomarkers in food allergic children? 4. Are there any nutritional supplements required for children with food allergies?
Population (age limit, inclusion criteria, excluded groups, special groups):	Included: Children with food allergies Excluded: Other allergic disorders
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Q1. Nutritional deficiencies and poor growth Q2. Dietitian referral Q3. Nutritional biomarkers Q4. Nutritional supplements
Comparator (if applicable):	N/A
Outcomes (specify critical/primary vs secondary):	Q1. Rates of nutritional deficiencies and poor growth Q2. Indications for dietitian referral Q3. Recommendations for measurement and monitoring of nutritional biomarkers Q4. Nutritional supplementation advice
Publication Dates:	2000 – 2025
Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria – Systematic review, meta-analysis, reviews, guidelines, practice guidelines Exclusion criteria- Other study designs

Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No
Search Outcomes:	**Number of guidelines and studies reviewed: 10**

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM5-1*
Clinical/PICO Question:	1. Are children with food allergies at an increased risk of nutritional deficiencies and poor growth? P: Children with food allergies E: Nutritional deficiencies and poor growth O: Rates of nutritional deficiencies and poor growth 2. When should children with food allergies be referred to a dietitian? P: Children with food allergies E: Dietitian referral O: Indications for dietitian referral 3. What are the recommendations for measurement and monitoring of nutritional biomarkers in food allergic children? P: Children with food allergies E: Nutritional biomarkers O: Recommendations for measurement and monitoring of nutritional biomarkers 4. Are there any nutritional supplements required for children with food allergies? P: Children with food allergies E: Nutritional supplements O: Nutritional supplementation advice
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**GPP 5.1: We recommend regular growth monitoring and nutritional counselling for all children with food allergies.** **GPP 5.2: Referral to a dietitian should be made for patients who present with poor growth or suspected malnutrition, including obesity. Other considerations for further nutritional evaluation include patients with:** • **Cow's milk allergy** • **Multiple (more than 2) food allergies** • **Multiple elimination diets lacking appropriate nutritional substitutes** • **Feeding difficulties, child and/or parental anxiety around feeding, delayed weaning progression in infants and/ or difficulties transiting to more textured foods** • **History of multiple accidental exposures or anaphylaxis indicating an inability to manage food avoidance** • **Additional dietary restrictions such as vegetarianism or personal food beliefs**

	GPP 5.3: Targeted nutritional biomarkers for micronutrient assessment should be considered after evaluating dietary intake, foods eliminated, growth patterns and physical signs. **GPP 5.4: Vitamin and mineral supplementation in children with food allergies should be guided by both the evaluation of nutritional biomarkers and the assessment of dietary intake.**
Rationale:	Children with food allergies are at higher risk of nutritional inadequacy and deficiencies, feeding problems and faltering growth, particularly low height for age. A prolonged elimination diet, especially when involving multiple and major food groups, must be regularly monitored as the risk of suboptimal intake increases with increasing number of food allergen avoidance and could also affect quality of life with long term effects on eating behaviours. Early childhood is characterised by rapid growth with unique requirements during various stages, a critical period for cognitive and motor development and establishing feeding patterns. Evidence has shown that individualised dietary interventions from a dietitian improves growth and nutritional biomarkers, dietary diversity, feeding behaviours, oral motor skill development and has positive effects on mental health and wellbeing of the child and family.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines:** 【1】 Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. Nutrition 2011;27:253-67. 【2】Muraro A, de Silva D, Halken S, Worm M, Khaleva E, Arasi S, et al. Managing food allergy: GA2LEN guideline 2022. World Allergy Organ J 2022;15:100687. 【3】Ebisawa M, Ito K, Fujisawa T; Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology; Japanese Society of Allergology. Japanese guidelines for food allergy 2020. Allergol Int. 2020 Jul;69(3):370-386. 【4】Santos AF, Riggioni C, Agache I, et al. EAACI guidelines on the management of IgE-mediated food allergy. Allergy. 2025; 80: 14-36. doi:10.1111/all.16345 【5】World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines update – XVI - Nutritional management of cow's milk allergy. Venter, CarinaAnsotegui, Ignacio et al. World Allergy Organization Journal, Volume 17, Issue 8, 100931 **SRs/MAs:** Nil

	Other more recent literature or local data: 【6】Venter C, Meyer R, Bauer M, Bird JA, Fleischer DM, Nowak-Wegrzyn A, Anagnostou A, Vickery BP, Wang J, Groetch M. Identifying Children at Risk of Growth and Nutrient Deficiencies in the Food Allergy Clinic. J Allergy Clin Immunol Pract. 2024 Mar;12(3):579-589. 【7】Leone L, Mazzocchi A, Maffeis L, De Cosmi V, Agostoni C. Nutritional management of food allergies: Prevention and treatment. Front Allergy. 2023 Jan 6;3:1083669. doi: 10.3389/falgy.2022.1083669. PMID: 36686963; PMCID: PMC9853442. 【8】Durban R, Groetch M, Meyer R, Coleman Collins S, Elverson W, Friebert A, Kabourek J, Marchand SM, McWilliam V, Netting M, Skypala I, Van Brennan T, Vassilopoulou E, Vlieg-Boerstra B, Venter C. Dietary Management of Food Allergy. Immunol Allergy Clin North Am. 2021 May;41(2):233-270. 【9】Wright, K., Feeney, M., Yerlett, N. et al. Nutritional Management of Children with Food Allergies. Curr Treat Options Allergy 2022; 9, 375–393 【10】Venter C, Groetch M, Netting M, Meyer R. A patient-specific approach to develop an exclusion diet to manage food allergy in infants and children. Clin Exp Allergy. 2018 Feb;48(2):121-137.
Certainty and Magnitude of Effects:	Not graded (GPP)
Risk/Harm vs Benefit Considerations:	There is no significant risk in providing nutritional counselling and regular growth monitoring. Early identification and nutritional intervention may help to prevent and improve outcomes such as nutritional status, growth, child's oral motor development, feeding pattern and quality of life. Over-use of blood test and assessment of nutritional biomarkers may be associated with increased costs with no improvement in outcome, unnecessary venipuncture and patient discomfort, increasing burden on lab resources.
Patient/ caregiver values	Increased anxiety, mental distress and fear of allergic reactions among families with food allergy, coupled with food allergy misinformation impacts personal food beliefs and thus effectiveness of nutrition intervention and compliance. **Stakeholder feedback (if available):**
Resource, Cost Considerations:	Increase accessibility to paediatric dietetic services Costs of dietetic consultation, additional blood tests and supplements may be adding to financial burden among families of children with food allergy

<table>
<tr><td>Equity

Acceptability

Feasibility</td><td>Dietetic consultation can be easily accessed at major paediatric hospitals in Singapore. Increased awareness among healthcare professionals regarding red flags which warrants nutrition assessment and intervention will reduce unnecessary referrals as well as laboratory-testing.

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 5.1: We recommend regular growth monitoring and nutritional counselling for all children with food allergies.
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>7</td><td>9</td><td>7%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table>
GPP 5.2: Referral to a dietitian should be made for patients who present with poor growth or suspected malnutrition, including obesity. Other considerations for further nutritional evaluation include patients with:

Cow’s milk allergy
Multiple (more than 2) food allergies
Multiple elimination diets lacking appropriate nutritional substitutes
Feeding difficulties, child and/or parental anxiety around feeding, delayed weaning progression in infants and/ or difficulties transiting to more textured foods
History of multiple accidental exposures or anaphylaxis indicating an inability to manage food avoidance
Additional dietary restrictions such as vegetarianism or personal food beliefs

Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>3</td><td>9</td><td>17%</td><td>9</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
</table></td></tr>
</table>

GPP 5.3: Targeted nutritional biomarkers for micronutrient assessment should be considered after evaluating dietary intake, foods eliminated, growth patterns and physical signs.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
2	9	22%	9	1.0	7.6	No Disagreement

GPP 5.4: Vitamin and mineral supplementation in children with food allergies should be guided by both the evaluation of nutritional biomarkers and the assessment of dietary intake.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
6	9	9%	9	1.0	8.0	No Disagreement

External Review Feedback:	
Public Consultation:	

References:

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. Nutrition 2011;27:253-67.
2. Muraro A, de Silva D, Halken S, Worm M, Khaleva E, Arasi S, et al. Managing food allergy: GA2LEN guideline 2022. World Allergy Organ J 2022;15:100687.
3. Ebisawa M, Ito K, Fujisawa T; Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology; Japanese Society of Allergology. Japanese guidelines for food allergy 2020. Allergol Int. 2020 Jul;69(3):370-386.
4. Santos AF, Riggioni C, Agache I, et al. EAACI guidelines on the management of IgE-mediated food allergy. Allergy. 2025; 80: 14-36. doi:10.1111/all.16345
5. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines update – XVI - Nutritional management of cow's milk allergy. Venter, Carina, Ansotegui, Ignacio et al. World Allergy Organization Journal, Volume 17, Issue 8, 100931
6. Venter C, Meyer R, Bauer M, Bird JA, Fleischer DM, Nowak-Wegrzyn A, Anagnostou A, Vickery BP, Wang J, Groetch M. Identifying Children at Risk of Growth and Nutrient Deficiencies in the Food Allergy Clinic. J Allergy Clin Immunol Pract. 2024 Mar;12(3):579-589.
7. Leone L, Mazzocchi A, Maffeis L, De Cosmi V, Agostoni C. Nutritional management of food allergies: Prevention and treatment. Front Allergy. 2023 Jan 6;3:1083669. doi: 10.3389/falgy.2022.1083669. PMID: 36686963; PMCID: PMC9853442.

8. Durban R, Groetch M, Meyer R, Coleman Collins S, Elverson W, Friebert A, Kabourek J, Marchand SM, McWilliam V, Netting M, Skypala I, Van Brennan T, Vassilopoulou E, Vlieg-Boerstra B, Venter C. Dietary Management of Food Allergy. Immunol Allergy Clin North Am. 2021 May;41(2):233-270.
9. Wright, K., Feeney, M., Yerlett, N. et al. Nutritional Management of Children with Food Allergies. Curr Treat Options Allergy 2022; 9, 375–393
10. Venter C, Groetch M, Netting M, Meyer R. A patient-specific approach to develop an exclusion diet to manage food allergy in infants and children. Clin Exp Allergy. 2018 Feb;48(2):121-137.

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Management of Food Allergies in Schools, Pre-schools and Childcare Facilities
Subgroup Members:	Loh Wenyin
Main Clinical Question(s):	1. What is the impact of food allergy on school teachers? 2. Is training of school staff on the management of food allergy effective?
Population (age limit, inclusion criteria, excluded groups, special groups):	Included: School staff caring for children with food allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Q1. Impact on school staff Q2. Efficacy of food allergy management training
Comparator (if applicable):	Control
Outcomes (specify critical/primary vs secondary):	Risk of allergic reaction and anaphylaxis in school
Publication Dates:	2000 – 2023
Study Designs (specify inclusion/exclusion criteria):	Inclusion criteria – Existing clinical guidelines; Systematic reviews (SRs'); Randomised controlled trials (RCT) will be favoured over non-randomised clinical trials (in the systematic reviews, and to supplement SRs' if newer information changes existing impression of evidence), Case reports
Search Strategy:	**Databases Searched:** Medline, Embase, PubMed, Cochrane Library, CINAHL **Grey Literature Sources?** No **Search Terms:** 1 school teacher/ (3126) 2 teacher?.ab,ti. (69843) 3 1 or 2 (70302) 4 food allergy/ (34137) 5 ("food allerg*" or "food hypersensitivit*").ab,ti. (28302) 6 4 or 5 (41546) 7 3 and 6 (141) 8 limit 7 to (english language and yr="2000 - 2023") (119) 1 school teacher/ (3126) 2 (teacher? or educator? or "school personnel" or "school staff").ab,ti. (115065) 3 1 or 2 (115446) 4 food allergy/ (34137) 5 ("food allerg*" or "food hypersensitivit*").ab,ti. (28302) 6 4 or 5 (41546)

	7 3 and 6 (237) 8 limit 7 to (English language and yr="2000 - 2023") (208) Filters applied as per inclusion criteria above.
Search Outcomes:	1. Impact of food allergy on school teachers No. of citations retrieved from Medline (Ovid): 52 No. of citations retrieved from Embase (Ovid): 119 No. of citations retrieved from PubMed: 57 No. of citations retrieved from Cochrane Library: 3 No. of citations retrieved from CINAHL: 36 Total: 267, After de-duplication: 139 2. Efficacy of training school staff on management of food allergy No. of citations retrieved from Medline (Ovid): 86 No. of citations retrieved from Embase (Ovid): 208 No. of citations retrieved from PubMed: 93 No. of citations retrieved from Cochrane Library: 7 No. of citations retrieved from CINAHL: 56 Total: 450, After de-duplication: 234

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM6-1*
Clinical/PICO Question:	Should schools implement training for school personnel? Should schools require parents of students with food allergy to provide allergy action plans?
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**GPP 6.1: Schools and childcare centres should have at least one, or more if possible, member of staff trained in the prevention, recognition and management of allergic reactions.** **GPP 6.2: Parents of students with a diagnosed food allergy should provide the childcare centre, school and after school care facilities with an up-to-date allergy action plan.**
Rationale:	A median 375 allergic reactions occur per 100 000 students per year with 3-20% of these reactions happening at childcare centres or schools. Fatal allergic reactions, although rare, have also occurred in schools and have been reported to be associated with a delay in administering intramuscular adrenaline.[1,4,5] Studies have shown that teachers and school personnel have limited knowledge, skills, and confidence related to the prevention and treatment of allergic reactions.[6] Training has been reported to be associated with short-term improvements in allergy-related test scores or knowledge, confidence and self-efficacy among teachers and school personnel.[1,6,7] There is lack of data on the effect of training on long-term improvements and reducing frequency of allergic reactions and/or anaphylaxis in childcare centres and schools. Allergy action plans are emergency care plans that outline the recommended emergency response to a suspected allergic reaction. There is some data that suggests allergy action plans may help reduce frequency of allergic reactions or adrenaline use in students.[1]
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines:** 1. Waserman et al. Prevention and management of allergic reactions to food in child care centers and schools: Practice Guidelines JACI 2021. 2. Vale et al. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. J Paeds Child Health 2015. 3. Muraro et al. EAACI/GALEN Task force on the allergic child at school. Allergy 2010. **SRs/MAs:** NIL **Other more recent literature or local data:** 4. Bock et al. Further fatalities caused by anaphylactic reactions to food, 2001-2006. JACI 2007;119:1016 5. Turner et al. Keeping food allergic children safe in our schools – time for urgent action. JACI 2015;125:95 6. Santos et al. Improvement in knowledge, food allergy-related attitudes and beliefs, self-efficacy and confidence levels. Allergy, Asthma Clin Immunol 2022;18. 7. Chong KW et al. Improving school teachers' self-efficacy and knowledge on food allergy and management of anaphylaxis using a virtual multidisciplinary workshop. Annals Academy of Medicine 2024

	8. Gonzalez Perez R et al. Development of an educational strategy to improve school teachers' management on food allergy and anaphylaxis. Allergy 2018;73: 351. 9. Polloni L et al. What do schools know, think and feel about food allergy? PAI 2009;20:65 10. Padua I et al. Welcoming patients with food allergy: what is the preparation of schools and restaurants? Allergy 2019;74:588.
Certainty and Magnitude of Effects:	Not graded (GPP)
Risk/Harm vs Benefit Considerations:	Given there is limited harm associated with both interventions, it is reasonable to recommend both with some considerations given to their implementation (see below).
Patient/ caregiver values	Patients and their caregivers value safety and support for children with food allergy in schools. **Stakeholder feedback (if available):** NIL
Resource, Cost Considerations:	Training, action plans and protocols: • Evidence-based and standardized. (Waserman 2021) • Designed, reviewed and regularly updated by healthcare professionals with expertise in food allergy. (Waserman 2021) • ASCIA recommends training of all staff by appropriately qualified professionals (eg. trained nurse educators and first aid trainers) every 1-2 years. (ASCIA 2015) Action plans: • May be personalized with student's name, emergency contact information, list of allergy triggers and other information. (Waserman 2021) • Should be completed and signed by a registered medical practitioner. (ASCIA 2015) • Ask parents of students with known food allergy to regularly review their action plans and report any changes. (Waserman 2021) • Should be updated when the AAI is replaced or approximately every 12-18 months (ASCIA 2015) • Should be kept in locations that child care and school personnel can easily access in the case of an allergic reaction but not in areas visible to the general public to protect student privacy. (Waserman 2021) • Childcare and school personnel should be familiar with the plans of students under their supervision. (Waserman 2021)
Equity **Acceptability** **Feasibility**	**Equity** Given that children are expected to spend significant amounts of time in schools, pre-schools and childcare settings, the school environment needs to be safe and inclusive for all food-allergic children. **Acceptability** School staff may still have concerns with regards to managing allergic reactions in school. There is evidence there this can improve with training and education. **Feasibility** A comprehensive approach involving the affected family, community, school staff and medical team is necessary to ensure that the above recommendations are implemented in all schools. **Stakeholder feedback (if available):** NIL

Workgroup Consensus Survey (RAND/UCLA):

GPP 6.1: Teachers and other personnel in childcare centres and schools should be trained in the prevention, recognition and treatment of allergic reactions to food.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	6%	9	0	8	No Disagreement

GPP 6.2: Parents of students with a diagnosed food allergy should provide the childcare centre, school and after school care facilities with an up-to-date allergy action plan.

Number voted = 18; Number abstained = 1

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	4%	9	0	8	No Disagreement

External Review Feedback:

Public Consultation:

References:

1. Waserman et al. Prevention and management of allergic reactions to food in child care centers and schools: Practice Guidelines JACI 2021.
2. Vale et al. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. J Paeds Child Health 2015.
3. Muraro et al. EAACI/GALEN Task force on the allergic child at school. Allergy 2010.
4. Bock et al. Further fatalities caused by anaphylactic reactions to food, 2001-2006. JACI 2007;119:1016
5. Turner et al. Keeping food allergic children safe in our schools – time for urgent action. JACI 2015;125:95
6. Santos et al. Improvement in knowledge, food allergy-related attitudes and beliefs, self-efficacy and confidence levels. Allergy, Asthma Clin Immunol 2022;18.
7. Chong KW et al. Improving school teachers' self-efficacy and knowledge on food allergy and management of anaphylaxis using a virtual multidisciplinary workshop. Annals Academy of Medicine 2024
8. Gonzalez Perez R et al. Development of an educational strategy to improve school teachers' management on food allergy and anaphylaxis. Allergy 2018;73: 351.
9. Polloni L et al. What do schools know, think and feel about food allergy? PAI 2009;20:65
10. Padua I et al. Welcoming patients with food allergy: what is the preparation of schools and restaurants? Allergy 2019;74:588.

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Natural History of Food Allergy
Subgroup Members:	Elizabeth Tham Huiwen, Lydia Wong Su Yin, Nur Farah Addina Lee Binte Zailan
Main Clinical Question(s):	What is the natural history of specific food allergies? (E.g. milk, egg, peanut, treenuts, shellfish, wheat, soy, fish) • What are the rates of outgrowing/persistence of each of the allergenic foods? • How to follow up food allergic children longitudinally? • How to manage very mild food allergic patients – e.g. tolerates cooked egg but reacts with mild peri oral rash with less cooked egg? Can they be managed in primary care?
Population (age limit, inclusion criteria, excluded groups, special groups):	Adults and children with IgE-mediated food allergies (Excluded: Other allergic disorders)
Interventions or Screening/Diagnostic Tools or Management Evaluated:	NA
Comparator (if applicable):	Persistence of specific food allergy by the end of the follow up period
Outcomes (specify critical/primary vs secondary):	Outgrown food allergy by end of observation or follow-up period
Publication Dates:	2000 – 2023
Study Designs (specify inclusion/exclusion criteria):	**Inclusion criteria –** Existing CPGs, SRs, MAs, RCTs (control arm without intervention to change natural history of food allergy), long-term follow-up studies, prospective studies, retrospective studies, reviews, prognostic studies **Exclusion criteria –** Preclinical studies, Phase 1 studies, Case reports, commentaries and letters, consensus reports
Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **Search Terms:** **PubMed** ("Natural History"[MeSH Terms] OR "Prognosis"[MeSH Terms] OR "Patient Outcome Assessment"[MeSH Terms] OR ("natural histor*"[Title/Abstract] OR "natural course"[Title/Abstract] OR "prognos*"[Title/Abstract] OR "outcome assessment"[Title/Abstract:~3] OR "outcome assessments"[Title/Abstract:~3]

	OR "outgrow*"[Title/Abstract] OR "persist*"[Title/Abstract] OR "remiss*"[Title/Abstract])) AND ("Immunoglobulin E"[MeSH Terms] OR ("Immunoglobulin E"[Title/Abstract] OR "ige mediated"[Title/Abstract] OR "ige specific"[Title/Abstract] OR "ige related"[Title/Abstract] OR "ige dependent"[Title/Abstract])) AND ("Food Hypersensitivity"[MeSH Terms] OR (("food"[Title/Abstract] OR "nut"[Title/Abstract] OR "nuts"[Title/Abstract] OR "peanut*"[Title/Abstract] OR "treenut*"[Title/Abstract] OR "seafood*"[Title/Abstract] OR "shellfish*"[Title/Abstract] OR "wheat*"[Title/Abstract] OR "soy"[Title/Abstract] OR "soybean*"[Title/Abstract] OR "seed*"[Title/Abstract] OR "legume*"[Title/Abstract] OR "milk"[Title/Abstract] OR "multiple food*"[Title/Abstract] OR "egg"[Title/Abstract] OR "eggs"[Title/Abstract]) AND ("allerg*"[Title/Abstract] OR "hypersensitivit*"[Title/Abstract] OR "anaphyla*"[Title/Abstract]))) **Embase** ('history'/exp OR 'prognosis'/exp OR 'outcome assessment'/exp OR 'natural histor*':ab,ti OR 'natural course':ab,ti OR prognos*:ab,ti OR ((assessment* NEAR/3 outcome*):ab,ti) OR outgrow*:ab,ti OR persist*:ab,ti OR remiss*:ab,ti) AND ('immunoglobulin e'/exp OR 'immunoglobulin e':ab,ti OR 'ige mediated':ab,ti OR 'ige specific':ab,ti OR 'ige related':ab,ti OR 'ige dependent':ab,ti) AND ('food allergy'/exp OR ((food:ab,ti OR nut*:ab,ti OR peanut*:ab,ti OR treenut*:ab,ti OR milk:ab,ti OR seafood*:ab,ti OR shellfish*:ab,ti OR wheat*:ab,ti OR soy*:ab,ti OR seed*:ab,ti OR legume*:ab,ti OR 'multiple food*':ab,ti OR egg*:ab,ti) AND (allerg*:ab,ti OR hypersensitivit*:ab,ti OR anaphyla*:ab,ti)))
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches: 4,073 Number of additional potential studies identified through other sources: NA Total number of studies screened once duplicates were removed: 3241 Number of studies shortlisted for full text review: 134 Number of studies excluded after full text review: 48 Number and type of studies included: 86 (12 cohort studies, 3 guidelines, 3 longitudinal studies, 25 prospective studies, 21 retrospective studies, 17 reviews, 1 retrospective + prospective, 2 presumed retrospective studies, 1 cross-sectional study, 1 letter)

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM7-1*
Clinical/PICO Question:	What is the natural history of specific food allergies? (E.g. milk, egg, peanut, tree nuts, shellfish, wheat, soy, fish) P: Adults and Children with IgE-mediated food allergies I: NA C: Persistence of specific food allergy by the end of the follow up period O: Outgrown food allergy by end of follow-up period
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**GPP 7.1: We recommend that all patients with food allergies should be reviewed regularly by an allergist to reassess allergy status. Children younger than 5 years old should have at least yearly monitoring of food allergies.** <u>*Natural resolution and follow-up*</u> The rate and time-course of natural resolution vary depending upon the food and may occur as late as adolescence. NIAID guidelines recommend yearly monitoring of egg, milk, soy and wheat allergies; and 2-3 yearly monitoring of peanut, tree nut, shellfish and fish allergies.[1] Children less than 5 years old should have at least yearly monitoring of food allergies, especially of egg, milk, soy, wheat and peanut allergies. If food allergy is not outgrown by 5 years of age, monitoring may be extended to 2-3 yearly.[2] <u>*Egg and milk*</u> Egg and milk allergies are associated with a high chance of natural resolution of up to 80%. The median age of natural resolution varies according to geographical region - studies of egg allergic patients in Australia[3] and Japan[4] found 73-89% outgrew their allergies by 6 years of age, and a local Singaporean retrospective review[5] found 81.8% of milk allergic children were tolerant by 6 years of age. Prognostic factors associated with higher likelihood of natural resolution include the ability to tolerate baked egg and baked milk products, and lower initial sIgE level at baseline. <u>*Peanut and tree nut allergy*</u> The rate of resolution of peanut allergy is 25-30% by age 6-10 years in various cohorts[3, 6], but resolution of tree nut allergy is only around 10%.[7] <u>*Soy and wheat allergy*</u> Soy and wheat allergy are also associated with high rates of resolution, with 69% of soy allergies resolving by age 10 years and 65% of wheat allergies by age 12 years. High peak wheat or soy IgE levels of >50 kU/L at baseline are associated with persistent allergy.[8, 9] <u>*Sesame allergy*</u> The rate of resolution of sesame allergy was 20-30% in 2 Israeli-based cohorts.[10, 11] <u>*Fish and shellfish allergy*</u> Fish and shellfish allergies are generally more likely to be persistent. A retrospective review of fish-allergic Singaporean children found a 25.9% rate of resolution by median age of 60 months.[12] A follow-up study of challenge proven Thai prawn-allergic patients found that 46% tolerated a repeat challenge at 10 years, however this study was

	significantly biased by a high attrition rate as challenges could only be repeated in only 37% of the original cohort.[13] **GPP 7.2: We recommend that skin prick tests (SPT) and/or food-specific IgE (sIgE) should be performed regularly, as a declining trend of sIgE level and size of SPT wheal is a good prognostic marker for development of tolerance.** **GPP 7.3: We recommend that patients with a trend of declining sIgE and/or SPT wheal size and no recent clinical reactions, should be re-evaluated for possible natural resolution, by an allergist to enable reintroduction of tolerated food.** *Biomarkers associated with natural resolution* Decrease in sIgE levels over time, particularly in the first 4 years of life, are significantly associated with the development of natural tolerance. Decline in skin prick test wheal size is also associated with development of tolerance, although to a lesser degree. Borderline skin prick tests (SPT 3-5mm) may persist even after clinical tolerance has developed.[1] *Clinical factors associated with persistent allergy* Clinical factors associated with persistent food allergy include high initial or peak sIgE levels, history of severe atopic dermatitis (especially early onset), multiple food allergies, and severe anaphylactic reactions.[14] *Natural resolution should be confirmed by reintroduction of food, under supervision of allergist* Determination of food allergy resolution requires reintroduction of the food into the diet as loss of sensitization alone does not guarantee tolerance, and low levels of sIgE or small SPT wheals may be persistent even after tolerance develops. Reintroduction is associated with risk of food allergic reactions, including risk of anaphylaxis – thus these should be done under guidance of an allergist.[1] **GPP 7.4: The use of egg and milk ladders for reintroduction of egg and milk, in patients with mild egg and milk allergy, can be considered. This should be done under guidance of an allergist as appropriate patient selection and preparation is essential to minimize the risk of anaphylaxis.** *Egg and milk ladders (under allergist supervision) may be appropriate for low-risk children with mild reactions* Egg and milk ladders are used to introduce less allergenic forms of baked egg and milk in very small quantities (grain or pea-sized amount), with gradual staged reintroduction of more allergenic forms of egg and milk to assess **existing tolerance** to less allergenic forms of the food allergen in low-risk patients. It is important to note that 40-80% of children experience adverse reactions on the egg and milk ladder, including a low rate of anaphylaxis events.[15-18] For this reason, home based reintroduction should be performed under guidance of an allergist, with careful patient selection of low-risk children with previously mild reactions. For higher-risk patients, reintroduction of the allergen should be done in the hospital in the form of a supervised oral food challenge. **Egg and milk ladders are not a form of oral immunotherapy and should not be used as such.**

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available):
(see examples below; or this section can be a narrative summary.)*

Other guidelines:
NIAID guidelines for the diagnosis and management of food allergy, 2010.[1]

SRs/MAs:
Narrative review:
Jeong K and Lee S. Natural course of IgE-mediated food allergy in children. *Clin Exp Pediatr* 2023; 66: 504-511. 20230614.[19]

Table 1. Studies of the natural course of cow's milk, hen's egg, and wheat allergy in children

Food	Age or rates of resolution	Criteria for resolution	Study type, country	Year
Cow's milk	19% by 4 ears, 42% by 8 years, 64% by 12 years, and 79% by 16 years[25]	Passed OFC or sIgE <3 kU/L with no symptoms within 12 months	Retrospective, US	2007
	57.4% during 48- to 60-month follow-up[69]	Passed OFC or successful consumption history	Prospective, Israel	2012
	52.6% at a median age of 63 months[9]	Passed OFC or ingestion of uncooked milk products in serving size quantities	Observational cohort, USA	2013
	57% after 1 year from the diagnosis[32]	Passed OFC	Birth cohort, Europe	2015
	25% by 43 months, 50% by 104.8 months[33]	Passed OFC or successful consumption history	Retrospective, Korea	2020
	81.8% by 6 years[70]	Passed OFC or successful consumption history	Retrospective, Singapore	2022
Hen's egg	11% by 4 years, 41% by 8years, 65% by 12 years, 82% by 16 years[8]	Passed OFC or sIgE < 2 kU/L with no symptoms within 12 months	Retrospective, USA	2007
	49.3% at a median age of 74 months[71]	Passed OFC or ingestion of whole, concentrated egg products in serving size quantities	Observational cohort, USA	2014
	30% by 3 years, 59% by 5 years, and 73% by 6 years[35]	Passed OFC	Retrospective, Japan	2016
	83.9% by 4 years[26]	Passed OFC	Longitudinal cohort, Australia	2019
	25% by 46.7 months, 50% by 67.6 months[33]	Passed OFC or successful consumption history	Retrospective, Korea	2020
	14.6% by 7 years, 40.8% by 9 years, 60.5% by 12 years[a,36]	Passed OFC	Prospective, Japan	2022
	89% by 6 years[34]	Passed OFC or SPT < 3 mm or SPT 3–7 mm with successful consumption history	Longitudinal cohort, Australia	2022
Wheat	29% by 4 years, 56% by 8 years, 65% by 12 years[27]	Passed OFC or successful consumption history	Retrospective, USA	2009
	20% by 4 years, 52% by 8years, 66% by 12 years, 76% by 18 years[38]	Passed OFC	Prospective, Poland	2014
	14.7% at 2 years, 27% at 4 years, 45.7% at 5 years, 69% at 9 years[37]	Passed OFC	Prospective, Thailand	2017

OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test.
[a]Among children with a definitive immediate-type reaction to hen's eggs at 6 years of age.

Table 2. Studies of the natural course of legume, tree nut, seed, and seafood allergies in children

Food	Age or rates of resolution	Criteria for resolution	Study type, country	Year
Peanut	13.2% at 3 years, 21.4% at 5 years, 34.2% at 7 years[72]	Passed OFC	Longitudinal cohort, Australia	2008
	10% by 4 years, 18% by 6 years, 22% by 8 years, 26% by 10 years[73]	Passed OFC	Prospective, Canada	2013
	22% by 4 years[29]	Passed OFC	Longitudinal cohort, Australia	2015
	10.3% by 6 years, 32.8% by 10 years[39]	Passed OFC or successful consumption history	Retrospective, Korea	2021
	29% by 6 years[34]	Passed OFC or SPT <3 mm or SPT 3–7 mm with successful consumption history	Longitudinal cohort, Australia	2022
Tree nuts	8.9% among children with previous clinical reactivity and evidence of tree nut sensitization[30]	Passed OFC	Retrospective, USA	2005
Soy	25% by 4 years, 45% by 6 years, 69% by 10 years[28]	Passed OFC or successful consumption history	Retrospective, USA	2010
Sesame	20% during 6.4-year follow-up[42]	Successful consumption history	Retrospective, Israel	2007
	32.1% during 3.86±4.43-year follow-up[43]	Passed OFC or successful consumption history	Retrospective, Israel	2022
Seafood	0.6% per person-year for fish, 0.8% per person-year for shellfish[a,46]	Successful consumption history or decision of resolution by a physician	Longitudinal cohort, Canada	2019
	Complete fish tolerance 3.4% in preschool children, 45% in adolescents[45]	Passed OFC	Prospective, Greece	2021

OFC, oral food challenge; SPT, skin prick test.
[a]The study population was composed of 49 children and 14 adults.

Other more recent literature or local data:
Chong et al, 2022[5] in a retrospective review of 355 Singaporean children with IgE mediated cow's milk protein allergy found that 81.8% acquired natural tolerance by 6 years.

In a similar retrospective review of 108 Singaporean children with IgE mediated fish allergy, Tan et al, 2023[12] found a resolution rate of 25.9% at the mean age of 60 months.

Certainty and Magnitude of Effects:

Not graded (GPP)

<table>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td>Benefits of regular monitoring and guided food reintroduction significantly outweigh risks when managed by allergists. Unsupervised reintroduction may lead to adverse events, including anaphylaxis. Food ladders carry a risk of reactions but offer developmental and quality-of-life benefits if successful.</td></tr>
<tr><td>Patient/ caregiver values</td><td>Not explicitly provided in current version; can be updated after stakeholder consultation.

Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>Regular allergist reviews and diagnostic testing (SPT, sIgE) may be resource intensive. Food ladders may reduce cost of prolonged elimination diets, improve nutrition, and reduce healthcare use if successful.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Equity:
Access to allergist care and diagnostic testing may be limited in underserved areas. Home ladder introduction may offer an equitable alternative when guided appropriately.

Acceptability:
High among caregivers when there is clear explanation and allergist support.

Feasibility:
Feasible in tertiary allergy clinics with trained staff. May be more challenging in primary care settings without specialist access.

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 7.1: We recommend that all patients with food allergies should be reviewed regularly by an allergist to reassess allergy status. Children younger than 5 years old should have at least yearly monitoring of food allergies.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>7</td><td>9</td><td>8%</td><td>9</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
</table>
GPP 7.2: We recommend that skin prick tests (SPT) and/or food-specific IgE (sIgE) should be performed regularly, as a declining trend of sIgE level and size of SPT wheal is a good prognostic marker for development of tolerance.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>7</td><td>9</td><td>8%</td><td>8</td><td>1.0</td><td>7.6</td><td>No Disagreement</td></tr>
</table>
GPP 7.3: We recommend that patients with a trend of declining sIgE and/or SPT wheal size and no recent clinical reactions, should be re-evaluated for possible natural resolution, by an allergist to enable reintroduction of tolerated food.</td></tr>
</table>

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	8%	9	1.0	7.6	No Disagreement

GPP 7.4: The use of egg and milk ladders for reintroduction of egg and milk, in patients with mild egg and milk allergy, can be considered. This should be done under guidance of an allergist as appropriate patient selection and preparation is essential to minimize the risk of anaphylaxis.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
6	9	11%	9	0.6	7.9	No Disagreement

External Review Feedback:	
Public Consultation:	

References:

1. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; 126: S1-58.
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12. Tan LL, Lee MP, Loh W, et al. IgE-mediated fish allergy in Singaporean children. *Asian Pac J Allergy Immunol* 2023 20230211.
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14. Sicherer SH and Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *Journal of Allergy and Clinical Immunology* 2018; 141: 41-58.
15. Ball HB and Luyt D. Home-based cow's milk reintroduction using a milk ladder in children less than 3 years old with IgE-mediated cow's milk allergy. *Clinical & Experimental Allergy* 2019; 49: 911-920.
16. Chomyn A, Chan ES, Yeung J, et al. Safety and effectiveness of the Canadian food ladders for children with IgE-mediated food allergies to cow's milk and/or egg. *Allergy, Asthma & Clinical Immunology* 2023; 19: 94.
17. Gotesdyner L, Zeldin Y, Machnes Maayan D, et al. A structured graduated protocol with heat denatured eggs in the treatment of egg allergy. *Pediatric Allergy and Immunology* 2019; 30: 824-832.
18. Thomas L, Belcher J, Phillips R, et al. Use of an egg ladder for home egg introduction in children with IgE-mediated egg allergy. *Pediatric Allergy and Immunology* 2021; 32: 1572-1574.
19. Jeong K and Lee S. Natural course of IgE-mediated food allergy in children. *Clin Exp Pediatr* 2023; 66: 504-511. 20230614.

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Oral immunotherapy (OIT) for Food Allergy
Subgroup Members:	Soh Jian Yi
Main Clinical Question(s):	1. What is the efficacy of OIT? 2. What are the side effects of OIT? 3. Does OIT improve the quality of life of patients?
Population (age limit, inclusion criteria, excluded groups, special groups):	Included: Human children and adults diagnosed with food allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	Oral immunotherapy (OIT) for food allergy
Comparator (if applicable):	Placebo or avoidance
Outcomes (specify critical/primary vs secondary):	Safety and feasibility
Publication Dates:	2000 – 2023
Study Designs (specify inclusion/exclusion criteria):	*Inclusion criteria – Study types: Existing clinical guidelines on OIT; systematic reviews (SRs'). Randomised controlled trials (RCT) will be favoured over non-randomised clinical trials (in the systematic reviews, and to supplement SRs' if newer information changes existing impression of evidence)* *Exclusion criteria – Case reports, clinical trials without randomisation; non-oral immunotherapy; studies comparing adjuncts or methods of immunotherapy without placebo/elimination diet.*
Search Strategy:	**Databases Searched:** *PubMed, Embase, Cochrane Library, CINAHL* **Grey Literature Sources?** No *- Systematic reviews and clinical guidelines are unlikely to be found in gray literature* **Search Terms:** PubMed: ([Food allergy AND (desens* OR immunotherapy)) OR (["Food Hypersensitivity"[Mesh] AND ("Immunotherapy"[Mesh] OR "Desensitization, Immunologic"[Mesh])). Filters applied as per inclusion criteria above. Embase: (**'food allergy'**/exp OR **'food hypersensitivity'**) AND (**immunotherapy** OR **'desensitization'**/mj) AND (**'randomized controlled trial'**/mj OR **'systematic review'**) AND [2000-2023]/py

	Cochrane Library: Food allergy immunotherapy CINAHL: ([Food allergy OR Food hypersensitivity] AND (desens* OR immunotherapy)
Search Outcomes:	**Number of studies:** Number of potential studies identified by database searches: 390 + 174 + 491 +159 = 1293 Number of additional potential studies identified through other sources: 2 Total number of studies screened once duplicates were removed: 918 Number of studies shortlisted for full text review: 94 Number of studies excluded after full text review: 89 Number and type of studies included: 5 Systematic reviews and meta-analyses will be prioritised first. Existing guidelines may reveal further references or perspectives. Recent guidelines in the last 5 years (2019-2023) were considered the most relevant for this purpose. Only the CSACI guidelines (comprehensive, covered ethics, public consultation, etc) qualify.

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM8-1*
Clinical/PICO Question:	What is the efficacy of OIT? P: Patients with food allergy I: Food allergen administered through Oral route (not sublingual or other routes) C: Placebo or elimination diet (no food allergen) O: Reach target dose (Desensitisation) and/or increase in Threshold of Reactivity
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 8.1: We strongly recommend offering OIT under specialist supervision to children with persistent IgE-mediated peanut allergy to achieve desensitisation (increase the amount of peanut tolerated while on therapy), in centres with expertise and infrastructure in OIT. Informed shared decision making is key in patient's choice to take up OIT.** **R 8.2: We conditionally recommend offering OIT under specialist supervision to children with persistent IgE-mediated hen's egg, cow's milk, tree nut and wheat allergy to achieve desensitisation (increase the amount of allergen tolerated while on therapy), in centres with expertise and infrastructure in OIT.** **R 8.3: We conditionally recommend OIT be offered as a treatment option for adults.** **GPP 8.4: OIT should be discussed with, and provided by, a specialist in allergy who is experienced in providing OIT to patients.** **GPP 8.5: Uncontrolled asthma is an absolute contraindication to OIT. Asthma must be controlled before beginning OIT and pro-actively managed during OIT.** **GPP 8.6: Given the potentially higher risk of anaphylaxis during OIT, carrying an adrenaline autoinjector is good practice.**
Rationale:	The included meta-analyses consistently show a large magnitude of benefit of OIT for peanut allergy, with high certainty of evidence. This is consistent with the older CSACI guidelines. The included meta-analyses consistently show benefit of OIT for hen's egg and cow's milk allergy, with very low to moderate certainty of evidence. One meta-analysis also included an RCT on wheat OIT, with evidence of benefit (low certainty of evidence). This is consistent with the older CSACI guidelines. The primary studies enrolled infants up to young adults (21 years of age), with almost all subjects across these studies being of toddler through to 17 years of age. This is consistent with the older CSACI guidelines. The CSACI guidelines included other study types, which included studies with adult subjects. There is no evidence suggesting that OIT is not effective in adults.
Evidence Summaries (include GRADE	**Other guidelines:** CSACI guidelines 2020[1]

SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	*OIT indications* - An accurate diagnosis of IgE-mediated food allergy is essential before proceeding with OIT - OIT is recommended as a treatment to achieve desensitization. It is indicated in toddlers through to adolescent age. (Level of evidence: high. 3 meta-analyses [Nurmatov et al 2017[2], Romantsik et al 2018[3], Chu et al 2019[4]]; 3 additional RCTs'.) - OIT may be indicated for adults. (Level of evidence: low) - The notion of severity is inadequate for determining eligibility for OIT. OIT should be available as an option for all patients wishing to receive it, provided there is no contraindication and a clear understanding of individual risks and benefits *Contraindications* - Uncontrolled asthma is an absolute contraindication to OIT. Asthma must be controlled before beginning OIT and pro-actively managed during OIT (Level of evidence: high) - Patient- or caregiver-specific contexts that may jeopardize the safe administration of therapy must be assessed. These include but are not limited to unreliable adherence to protocol, reluctance to use epinephrine, language barrier, severe anxiety, psychiatric barriers, non-collaborative family dynamics, lack of schedule flexibility for proper dosing, and lack of commitment from patient or caregivers. If these cannot be satisfactorily addressed, they constitute contraindications for OIT - Conditions such as active severe atopic dermatitis, pre-existing eosinophilic esophagitis, heart disease, and those requiring the use of beta-blockers or ACE inhibitors are relative contraindications for OIT. A decision to pursue OIT in these patients should be based on clinical judgment, provider expertise and shared decision-making *Provision of OIT* - Empowerment of patients and families should be promoted through shared responsibility with the healthcare system, in respect and support of patient choices - Informed consent must be obtained before initiating OIT. This should include clear discussion of potential outcomes, risks and benefits, as well as of patients' and their caregivers' concerns, expectations and goals. Patients should be informed on how to recognize and manage reactions during therapy **SRs/MAs:** Lodge et al 2023[5] – RCTs, 18 studies, until Oct 2022. Must have data for numerical analysis (ITT). Egg (6), milk (4), peanut (8, including AR101). English only (n=7 non-English excluded). No mention of or check for publication bias. Age up to 21 years of age in included subjects - Must have Oral food challenge (OFC) at baseline and at end. Evidence for efficacy, anaphylaxis, and improvement in QoL. Authors cited methodological concerns with their meta-analysis being highly select populations, often excluded patients with severe anaphylaxis, severe asthma. 20% of subjects in RCTs' were still excluded because they passed baseline OFC.

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT for egg, milk or peanut	no OIT	Relative (95% CI)	Absolute (95% CI)		
Peanut efficacy (assessed with: Desens)												
8	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected strong association[a]			**RR 11.32** (5.93 to 21.60)	**11 fewer per 1,000** (from 22 fewer to 6 fewer)	⊕⊕⊕⊕ High	CRITICAL
Milk efficacy (assessed with: Desens)												
4	randomised trials	serious[c]	not serious	not serious	serious[d]	publication bias strongly suspected strong association[a]			**RR 13.98** (3.51 to 55.65)	**14 fewer per 1,000** (from 56 fewer to 4 fewer)	⊕⊕◯◯ Low	
Egg Desens												
5	randomised trials	serious[c]	serious[f]	not serious	not serious	publication bias strongly suspected strong association[a]			**RR 4.67** (2.66 to 8.21)	**5 fewer per 1,000** (from 8 fewer to 3 fewer)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No check for or mention of publication bias. Search methodology was of concern, such as excluding non-English studies (n=7)
b. Significant statistical heterogeneity
c. Some studies have concerns or high risk of bias
d. Small studies, CI did cross line of no significance
e. Huge CI
f. Point estimate had no significance

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Bognanni et al 2022[6] (Milk) – RCTs (13) and NR (109) trials, until Feb 2021. 8 RCTs' (children) analysed for fresh milk. OFC not required for diagnosis in 2 of the 13 RCTs'.

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT for cow's milk	no OIT	Relative (95% CI)	Absolute (95% CI)		
Ability to drink cow's milk and eat dairy products without a reaction (follow-up: range 4 months to 11 months; assessed with: passing a supervised graded food challenge with >150ml of cow's milk and/or ability to drink cow's milk and eat dairy products with no symptoms)												
10[a]	randomised trials	not serious[b]	not serious	Serious[c]	not serious[d]	publication bias strongly suspected strong[e,f]	107/158 (67.7%)	3/135 (2.2%)	**RR 12.34** (5.86 to 25.99)	**25 more per 1,000** (from 11 more to 56 more)	⨁⨁◯◯ Low	CRITICAL
Ability to accidentally consume a small amount of cow's milk without a reaction (follow-up: range 4 months to 11 months; assessed with: passing a supervised graded food challenge with ≥5ml of cow's milk.												
10[a]	randomised trials	not serious[b]	not serious	serious	not serious	publication bias strongly suspected strong[e,f]	107/137 (87.1%)	4/122 (3.3%) 13.0%	**RR 8.67** (4.66 to 16.12)	**25 more per 1,000** (from 12 more to 50 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. One study (Morisset 2007) explicitly included only children that could tolerate at least 60ml of cow's milk at baseline and found a smaller effect of OIT RR 1.44 (95% CI: 0.96-2.11). Another RCT published as a conference abstract only reported tolerance in 4/11 children receiving OIT but did not report how many children achieved tolerance in the control group (n=4) (Fiho 2015).

b. In some studies, participants were not blinded but the results were consistent across studies. Although the true effect might be smaller than the presented estimate, we did not rate down the certainty of evidence for risk of bias given the very strong association.

c. It is not certain whether all of those passing a graded food challenge in a clinic will also be able to tolerate an equivalent total amount of milk without a graded challenge.

d. Total 85 events among 217 patients.

e. There was some suggestion of publication bias as all studies were small and all showed very large effect. We did not reduce the certainty of evidence because we already reduced it for indirectness.

f. There was a very large associated which does increase the confidence in the estimated effect on an indirect outcome. However, because of this indirectness we thought that very strong association may not apply to the outcome of interest.

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de Silva et al 2022[7] – RCTs', peanut (7), milk (8), egg (7). Until Apr 2021. Must have OFC at baseline. Found 1 study for wheat (Nowak-Wegrzyn 2019[8], n=46), showing increased likelihood to tolerate 4.4 grams of wheat protein, increased rate of mild/moderate reactions, no increase in severe adverse reactions (all low or very low certainty)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT	no OIT	Relative (95% CI)	Absolute (95% CI)		
Efficacy of peanut OIT (assessed with: Desens)												
7	randomised trials	serious[a]	not serious	not serious	not serious	strong association			**RR 9.9** (4.5 to 21.4)	**10 fewer per 1,000** (from 21 fewer to 5 fewer)	⊕⊕⊕⊕ High	CRITICAL
Efficacy peanut (assessed with: Tolerated 300mg)												
5	randomised trials	serious[a]	not serious	not serious	not serious	none			**RR 5.7** (4.0 to 7.9)	**6 fewer per 1,000** (from 8 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Efficacy peanut (assessed with: Tolerated 1000mg)												

5	randomised trials	serious[a]	not serious	not serious	not serious	strong association			**RR 16.6** (8.0 to 34.4)	**17 fewer per 1,000** (from 34 fewer to 8 fewer)	⊕⊕⊕⊕ High	CRITICAL

Egg desens (assessed with: Desens)

6	randomised trials	very serious[a]	not serious	not serious	not serious	strong association			**RR 8.9** (4.4 to 18.0)	**9 fewer per 1,000** (from 18 fewer to 4 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

Milk desens (assessed with: Desens)

7	randomised trials	very serious[f]	not serious	not serious	not serious[e]	strong association			**RR 5.7** (1.9 to 16.7)	**6 fewer per 1,000** (from 17 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Not all studies at low risk of bias
b. high statistical heterogeneity
c. small sample sizes and significant statistical heterogeneity in meta-analysis
d. inconsistent findings, likely due to different measurements
e. small sample sizes
f. most studies at moderate or high risk of bias
g. variations in studies include inclusion criteria, severity

Other systematic reviews/meta-analyses that were excluded for this clinical question:

Jie Chen 2022[9] – RCTs' in children only, milk, 11 trials, until Apr 2021. Excluded because less robust methodology, less generalisable, very high statistical heterogeneity, less detailed and relevant information compared to Bognanni et al 2022.

PACE (Chu et al 2019[4]) – RCTs' for peanut, 12 trials, children, until Dec 2018. Excluded because older; findings do not change the conclusions of Lodge et al[5], recommendations or GPP.

<table>
<tr><td></td><td>Other more recent literature or local data:
Nil</td></tr>
<tr><td>Certainty and Magnitude of Effects:</td><td>R8.1 - 8.3:
The certainty of the evidence is high for peanut OIT, and low-to-moderate for egg, cow's milk and wheat OIT.
The magnitude of effect for desensitisation, is large for peanut, egg and cow's milk OIT.

GPP 8.4 - 8.5: Not graded (GPP)</td></tr>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td></td></tr>
<tr><td>Patient/ caregiver values</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>Cost of treatment depends on provider</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 8.1: We strongly recommend offering OIT under specialist supervision to children with persistent IgE-mediated peanut allergy to achieve desensitisation (increase the amount of peanut tolerated while on therapy), in centres with expertise and infrastructure in OIT. Informed shared decision making is key in patient's choice to take up OIT.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>2</td><td>9</td><td>24%</td><td>8</td><td>1.0</td><td>6.1</td><td>No Disagreement</td></tr>
</table>
R 8.2: We conditionally recommend offering OIT under specialist supervision to children with persistent IgE-mediated hen's egg, cow's milk, tree nut and wheat allergy to achieve desensitisation (increase the amount of allergen tolerated while on therapy), in centres with expertise and infrastructure in OIT.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>4</td><td>9</td><td>20%</td><td>8</td><td>2.0</td><td>6.9</td><td>No Disagreement</td></tr>
</table></td></tr>
</table>

R 8.3: We conditionally recommend OIT be offered as a treatment option for adults.
Number voted = 17; Number abstained = 2

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	10%	8	1.0	7.6	No Disagreement

GPP 8.4: OIT should be discussed with, and provided by, a specialist in allergy who is experienced in providing OIT to patients.
Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
8	9	4%	9	0.0	8.4	No Disagreement

GPP 8.5: Uncontrolled asthma is an absolute contraindication to OIT. Asthma must be controlled before beginning OIT and pro-actively managed during OIT.
Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	10%	9	0.0	8.4	No Disagreement

GPP 8.6: Given the potentially higher risk of anaphylaxis during OIT, carrying an adrenaline autoinjector is good practice.
Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
3	9	20%	9	0.6	7.9	No Disagreement

External Review Feedback:	
Public Consultation:	

References:

1. Bégin P, Chan ES, Kim H, Wagner M, Cellier MS, Favron-Godbout C, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food

allergy. Allergy Asthma Clin Immunol. 2020 Mar 18;16:20. doi: 10.1186/s13223-020-0413-7. PMID: 32206067; PMCID: PMC7079444.
2. Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy. 2017;72(8):1133-1147. doi:10.1111/all.13124
3. Romantsik O, Tosca MA, Zappettini S, Calevo MG. Oral and sublingual immunotherapy for egg allergy. Cochrane Database Syst Rev. 2018;4(4):CD010638. Published 2018 Apr 20. doi:10.1002/14651858.CD010638.pub3
4. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019;393(10187):2222-2232. doi:10.1016/S0140-6736(19)30420-9
5. Lodge CJ, Waidyatillake N, Peters RL, Netting M, Dai X, Burgess J, et al. Efficacy and safety of oral immunotherapy for peanut, cow's milk, and hen's egg allergy: A systematic review of randomized controlled trials. Clin Transl Allergy. 2023 Jul;13(7):e12268. doi: 10.1002/clt2.12268. PMID: 37488726; PMCID: PMC10314278.
6. Bognanni A, Chu DK, Firmino RT, Arasi S, Waffenschmidt S, Agarwal A, et al; WAO DRACMA Guideline Group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XIII - Oral immunotherapy for CMA - Systematic review. World Allergy Organ J. 2022 Sep 8;15(9):100682. doi: 10.1016/j.waojou.2022.100682. PMID: 36185550; PMCID: PMC9474924.
7. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022 Jun;77(6):1852-1862. doi: 10.1111/all.15211. Epub 2022 Jan 19. PMID: 35001400; PMCID: PMC9303769.
8. Nowak-Węgrzyn A, Wood RA, Nadeau KC, et al. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. J Allergy Clin Immunol. 2019;143(2):651-661.e9. doi:10.1016/j.jaci.2018.08.041
9. Tang L, Yu Y, Pu X, Chen J. Oral immunotherapy for Immunoglobulin E-mediated cow's milk allergy in children: A systematic review and meta analysis. Immun Inflamm Dis. 2022;10(10):e704. doi:10.1002/iid3.704

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM8-2*
Clinical/PICO Question:	What are the side effects of OIT? P: Patients with food allergy I: Food allergen administered through Oral route (not sublingual or other routes) C: Placebo or elimination diet (no food allergen) O: Reach target dose (Desensitisation) and/or increase in Threshold of Reactivity
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 8.1: We strongly recommend offering OIT under specialist supervision to children with persistent IgE-mediated peanut allergy to achieve desensitisation (increase the amount of peanut tolerated while on therapy), in centres with expertise and infrastructure in OIT. Informed shared decision making is key in patient's choice to take up OIT.** **R 8.2: We conditionally recommend offering OIT under specialist supervision to children with persistent IgE-mediated hen's egg, cow's milk, tree nut and wheat allergy to achieve desensitisation (increase the amount of allergen tolerated while on therapy), in centres with expertise and infrastructure in OIT.** **R 8.3: We conditionally recommend OIT be offered as a treatment option for adults.**
Rationale:	*Concise summary and explanation of why the recommendations were being made.* Meta-analyses show that side effects for OIT are common. Most reactions are mild, and involve the oral, skin or gastrointestinal systems. Lodge et al[1] found a much higher rate of Adrenaline use in cow's milk OIT (RR 8.45) and peanut OIT (RR 2.96) compared to no intervention. de Silva et al[2] reported that anaphylaxis and use of Adrenaline is rare. de Silva et al[2] included a study on wheat OIT by Nowak-Wegrzyn[3], which showed an increased rate of side effects, but no severe reactions (all very low certainty of evidence). Lodge et al[1] did not report on side effects being a reason to discontinue OIT. Bognanni et al[4] reported an increased risk of side effects causing milk OIT discontinuation, the estimate ranging from 6 to 9 more per 100 patients, compared to placebo. De Silva et al[2] reported similar rates of side effects in the peanut OIT and placebo groups, and discontinuation of milk and egg OIT due to side effects, being rare. However, a research setting is different from a clinical setting for the basis of discontinuation of OIT. Patients must also invest money in a clinical setting, which becomes an extra factor to weigh for starting or continuing OIT. Research subjects may face constraints with the research schedule for doses, reporting, and location (such as if they migrate to another area that can provide clinical OIT, but the research study cannot continue due to this). Thus, the individual patient and family setting comprises several factors that require consideration by the patient for decisions regarding OIT, which forms the basis for ensuring informed consent, discussion and exploration by the OIT provider if side effects arise along the way. The strength of evidence for OIT to the above foods, balanced against the evidence for frequency and severity of side effects, forms the basis for the above recommendations.

	The findings above are consistent with the older CSACI guidelines.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines:** CSACI guidelines 2020[5] (Safety data: Page 29-31/45) **SRs/MAs:** Lodge et al 2023[1] – RCTs, 18 studies, until Oct 2022. Must have data for numerical analysis (ITT). Egg (6), milk (4), peanut (8, including AR101). English only (n=7 non-English excluded). No mention of or check for publication bias. - Must have OFC at baseline and at end. Evidence for efficacy, anaphylaxis, and improvement in QoL. Authors cited methodological concerns with their meta-analysis being highly select populations, often excluded patients with severe anaphylaxis, severe asthma, and noted 20% of subjects in RCTs' were still excluded because they passed baseline OFC.

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT for egg, milk or peanut	no OIT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Peanut AE (assessed with: AE)												
8	randomised trials	not serious	serious[b]	not serious	not serious	publication bias strongly suspected[a]			**RR 1.11** (1.03 to 1.20)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT
Peanut parenteral Adrenaline use												
8	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected[a]			**RR 2.96** (1.63 to 5.35)	**3 fewer per 1,000** (from 5 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Milk AE												

2	randomised trials	serious[c]	serious[b]	not serious	serious[e]	publication bias strongly suspected[a]			**RR 3.75** (0.28 to 49.93)	**4 fewer per 1,000** (from 50 fewer to 0 fewer)	⊕◯◯◯ Very low	

Milk parenteral Adrenaline use

4	randomised trials	serious[c]	not serious[d]	not serious	serious[d]	publication bias strongly suspected strong association [a]			**RR 8.45** (2.02 to 35.27)	**8 fewer per 1,000** (from 35 fewer to 2 fewer)	⊕⊕◯◯ Low	

Egg AE

1	randomised trials	not serious	not serious	not serious	very serious[e]	publication bias strongly suspected[a]			**RR 9.17** (0.55 to 152.78)	**9 fewer per 1,000** (from 153 fewer to 1 fewer)	⊕◯◯◯ Very low	

Egg parenteral adrenaline use

6	randomised trials	serious[c]	not serious	not serious	serious[d]	publication bias strongly suspected[a]			**RR 1.71** (0.42 to 6.92)	**2 fewer per 1,000** (from 7 fewer to 0 fewer)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No check for or mention of publication bias. Search methodology was of concern, such as excluding non-English studies (n=7)
b. Significant statistical heterogeneity
c. Some studies have concerns or high risk of bias
d. Small studies, CI did cross line of no significance
e. Huge CI
f. Point estimate had no significance

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Bognanni et al 2022[4] (Milk) – RCTs (13) and NR (109) trials, until Feb 2021. 8 RCTs' analysed for fresh milk. OFC not required for diagnosis in 2 of the 13 RCTs'.

Author(s): JLB, AB
Question: OIT with cow's milk compared to no IT for IgE-mediated CMA [SR]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT with cow's milk	no IT	Relative (95% CI)	Absolute (95% CI)		
Anaphylaxis (follow-up: range 6 to 17 months)												
7[1,2,3,4,5,6,11]	randomised trials	not serious[g]	serious[h]	not serious	not serious[i]	none	6 studies reported anaphylaxis but only one (De Schryver 2019) used current definition of anaphylaxis. Based on this study the rate of anaphylaxis was 0.01 per 1 person-year (i.e. 1 per 100 persons per year) without OIT and 5.5 per 1 person-year with OIT (rate ratio: 60.0; 95% CI: 15 to 244; rate difference: 5 more anaphylactic reactions per 1 person per year (95% CI: 4 to 6)). One study (Skripak 2008) defined anaphylaxis as "some combination of respiratory, gastrointestinal, and/or skin reaction" and reported similar results. Maeda 2021 reported that "the annual rate of anaphylactic symptoms was about one per patient" among those receiving OIT. The 4 remaining studies reported that there were no anaphylactic reactions, however, Salmviesi 2013 equaled anaphylaxis with epinephrine use and the other 3 studies did not provide the definition of anaphylaxis that was used.				⊕⊕⊕◯ Moderate	CRITICAL
Use of IM epinephrine (follow-up: range 4 to 12 months)												
9[1,2,3,4,5,6,7,8,11]	randomised trials	not serious[i]	not serious	not serious	not serious	none	85/134	2/120	**Rate ratio 35.16** (9.00 to 136.50)	**268 more per 100 patient(s) per year** (from 203 more to 333 more)[k]	⊕⊕⊕⊕ High	CRITICAL
Gastrointestinal symptoms (severe) (follow-up: range 4 to 17 months)												
5[1,3,4,5,6]	randomised trials	not serious[i]	not serious	serious[l]	serious[m]	none	45/91 (49.5%)	4/84 (4.8%)	**RR 6.9** (1.6 to 30.9)[n]	**28 more per 100** (from 3 more to 100 more)	⊕⊕◯◯ Low	CRITICAL
Severe respiratory symptoms/wheezing (follow-up: 12 months; assessed with: "nebulized epinephrine for respiratory symptoms")												
1[4]	randomised trials	not serious[i]	not serious	not serious	serious[o]	none	24/30 (80.0%)	0/30 (0.0%)	**RR 49.00** (3.12 to 770.59)	**77 more per 100** (from 62 more to 92 more)[k]	⊕⊕⊕◯ Moderate	CRITICAL
Generalized erythema or urticaria (follow-up: range 4 to 17 months)												
5[1,3,4,5,6]	randomised trials	not serious[i,p]	not serious	serious[q]	serious[r]	none	27/89 (30.3%)	7/82 (8.5%)	**RR 2.72** (0.76 to 9.68)[s]	**15 more per 100** (from 2 fewer to 74 more)	⊕⊕◯◯ Low	CRITICAL
Emergency department visit												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT with cow's milk	no IT	Relative (95% CI)	Absolute (95% CI)		
3[1,4,8]	randomised trials	serious[t]	not serious	not serious	very serious[u]	none	There were 4 events among 62 children in OIT group and no events in control groups. Six series of cases (Berti 2019, Longo 2012, Mantyla 2018, Ono 2018, Barbi 2012, Sugiura 2020) reported that a mean of 3.3% (95% CI: 0.5% to 6.2%) children receiving OIT required at least one ED visit.				⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. One study (Morisset 2007) explicitly included only children that could tolerate at least 60 ml of milk at baseline and found a smaller effect of OIT RR: 1.44 (95% CI: 0.98 to 2.11). Another RCT published as a conference abstract only reported tolerance in 4/11 children receiving OIT but did not report how many children achieved tolerance in control group (n = 4) (Filho 2015).
b. In some studies participants were not blinded but the results were consistent across all studies. Although the true effect might be smaller than the presented estimate, we did not rate down the certainty of evidence for risk of bias given the very strong association.
c. It is not certain whether all those passing a graded food challenge in a clinic will also be able to tolerate an equivalent total amount of milk without a graded challenge.
d. Total 85 events among 217 patients
e. There is some suggestion of publication bias as all studies were small and all showed very large effect. We did not reduce the certainty of evidence because we already reduced it for indirectness.
f. There was a very large association that does increase the confidence in the estimated effect on an indirect outcome. However, because of this indirectness we thought that very strong association may not apply to the outcome of interest.
g. The only study (De Schryver 2019) that reported direct evidence was not blinded and was stopped early because of apparent benefit. However, both of those biases are likely to underestimate adverse effects.
h. 2 studies reported the rate of anaphylaxis with OIT between 4.7 and 5.5 per person per year and other 4 studies reported no anaphylactic reactions with OIT. This difference could not be explained with population characteristics or the type of OIT. It is possible that the difference is related to the definition of anaphylaxis used in individual studies; 3 studies did not report what definition was used. We did not reduce the certainty because of indirectness (one study provided a direct outcome measure) but rather because of inconsistency, as they seem to be related.
i. We did not lower the certainty because of imprecision, because the results of one study that could be used provided precise estimates. If data from other studies could be used then the judgment about precision might change.
j. Most studies were not blinded but it is unlikely that this would overestimate the risk of adverse effects.
k. There were no events in control groups; 95% CI around the risk difference was estimated from risk difference meta-analysis.
l. Studies did not report GI symptoms consistently – some may have had very different importance for patients than the others.
m. The CI does not exclude an appreciably increased risk of GI symptoms or no difference.
n. In 2 studies the rate of reactions per patient was reported. Across these studies the rate of GI symptoms was 21.4 times higher (95% CI: 8.9 to 51.8) with OIT than without.
o. Only 24 events; 95% confidence interval does not exclude an appreciable benefit or an appreciable harm.
p. Few studies reported this outcome that we considered obvious to measure and report; in general adverse effects were reported inconsistently, using variable definitions, and sometimes precluding meaningful conclusions.
q. The severity of symptoms was not reported in any of the relevant included studies.
r. There were only 34 events and the pooled confidence interval does not exclude harm from OIT or no difference.
s. Two additional studies measured urticaria as rate of events per patient. Rate of generalized urticaria was 8.3 times higher (95% CI: 3.2 to 21.1) with OIT than without.
t. Only 2 of 7 studies reported this outcome.
u. Only 2 events in one study.

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de Silva Allergen IT 2022[2] – RCTs', peanut (7), milk (8), egg (7), others (3) for OIT. Until Apr 2021. Must have OFC at baseline. Found 1 study for wheat (Nowak-Wegrzyn 2019, n=46), showing increased likelihood to tolerate 4.4 grams of wheat protein, increased rate of mild/moderate reactions, no increase in severe adverse reactions (all low or very low certainty)

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OIT	no OIT	Relative (95% CI)	Absolute (95% CI)		
Peanut adverse (assessed with: Adverse reaction rate)												
7	randomised trials	serious[a]	serious[b]	not serious	not serious	none			**RR 1.1** (1.0 to 1.2)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ Low	IMPORTANT

Peanut SAE (assessed with: Serious AE)

6	randomised trials	serious[a]	not serious	not serious	serious[c]	none			**RR 1.6** (0.7 to 3.5)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⊕⊕◯◯ Low	IMPORTANT

Egg AE (assessed with: AE)

6	randomised trials	serious[a]	not serious	not serious	serious[b,c]	strong association			**RR 7.0** (2.4 to 19.8)	**7 fewer per 1,000** (from 20 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Egg SAE (assessed with: Serious AE)

4	randomised trials	serious[a]	serious[d]	not serious	serious[e]	none			**RR 3.4** (9.6 to 19.6)	**3 fewer per 1,000** (from 20 fewer to 10 fewer)	⊕◯◯◯ Very low	IMPORTANT

Milk AE (assessed with: AE)

6	randomised trials	serious[a]	not serious	serious[g]	serious[e]	strong association			**RR 3.9** (2.1 to 7.5)	**4 fewer per 1,000** (from 8 fewer to 2 fewer)	⊕⊕◯◯ Low	IMPORTANT

Milk SAE (assessed with: serious AE)

4	randomised trials	serious[a]	not serious	serious[g]	serious[e]	none			**RR 7.0** (0.4 to 124.8)	**7 fewer per 1,000** (from 125 fewer to 0 fewer)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio; **AE**: adverse effects; **SAE**: serious adverse effects

Explanations

a. Not all studies at low risk of bias
b. high statistical heterogeneity
c. small sample sizes and significant statistical heterogeneity in meta-analysis
d. inconsistent findings, likely due to different measurements
e. small sample sizes
f. most studies at moderate or high risk of bias
g. variations in studies include inclusion criteria, severity

Other systematic reviews/meta-analyses that were excluded for this clinical question:

Jie Chen 2022[6] – RCTs' in children only, milk, 11 trials, until Apr 2021. Excluded because less robust methodology, less generalisable, very high statistical heterogeneity, less detailed and relevant information compared to Bognanni et al 2022.

Chataway et al 2020[7] – on peanut OIT side effects. High statistical and methodological heterogeneity, included uncontrolled studies; thus excluded.

PACE (Chu et al 2019)[8] – RCTs' for peanut, 12 trials, children, until Dec 2018. Excluded because older; findings do not change the conclusions of Lodge et al, recommendations or GPP.

Other more recent literature or local data:

Certainty and Magnitude of Effects:	Certainty: Moderate Magnitude: Moderate
References:	

1. Lodge CJ, Waidyatillake N, Peters RL, Netting M, Dai X, Burgess J, et al. Efficacy and safety of oral immunotherapy for peanut, cow's milk, and hen's egg allergy: A systematic review of randomized controlled trials. Clin Transl Allergy. 2023 Jul;13(7):e12268. doi: 10.1002/clt2.12268. PMID: 37488726; PMCID: PMC10314278.
2. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022 Jun;77(6):1852-1862. doi: 10.1111/all.15211. Epub 2022 Jan 19. PMID: 35001400; PMCID: PMC9303769.
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4. Bognanni A, Chu DK, Firmino RT, Arasi S, Waffenschmidt S, Agarwal A, et al; WAO DRACMA Guideline Group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XIII - Oral immunotherapy for CMA - Systematic review. World Allergy Organ J. 2022 Sep 8;15(9):100682. doi: 10.1016/j.waojou.2022.100682. PMID: 36185550; PMCID: PMC9474924.
5. Bégin P, Chan ES, Kim H, Wagner M, Cellier MS, Favron-Godbout C, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol. 2020 Mar 18;16:20. doi: 10.1186/s13223-020-0413-7. PMID: 32206067; PMCID: PMC7079444.
6. Tang L, Yu Y, Pu X, Chen J. Oral immunotherapy for Immunoglobulin E-mediated cow's milk allergy in children: A systematic review and meta analysis. Immun Inflamm Dis. 2022;10(10):e704. doi:10.1002/iid3.704
7. Grzeskowiak LE, Tao B, Knight E, Cohen-Woods S, Chataway T. Adverse events associated with peanut oral immunotherapy in children - a systematic review and meta-analysis. Sci Rep. 2020;10(1):659. Published 2020 Jan 20. doi:10.1038/s41598-019-56961-3
8. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019;393(10187):2222-2232. doi:10.1016/S0140-6736(19)30420-9

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM8-3*
Clinical/PICO Question:	Does OIT improve the quality of life of patients? P: Patients with food allergy I: Food allergen administered through Oral route (not sublingual or other routes) C: Placebo or elimination diet (no food allergen) O: Changes in QoL scores, in children and their parents/ adult patients
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**R 8.1: We strongly recommend offering OIT under specialist supervision to children with persistent IgE-mediated peanut allergy to achieve desensitisation (increase the amount of peanut tolerated while on therapy), in centres with expertise and infrastructure in OIT. Informed shared decision making is key in patient's choice to take up OIT.** **R 8.2: We conditionally recommend offering OIT under specialist supervision to children with persistent IgE-mediated hen's egg, cow's milk, tree nut and wheat allergy to achieve desensitisation (increase the amount of allergen tolerated while on therapy), in centres with expertise and infrastructure in OIT.** **R 8.3: We conditionally recommend OIT be offered as a treatment option for adults.**
Rationale:	*Concise summary and explanation of why the recommendations were being made.* Peanut OIT will probably improve the quality of life of patients and/or caregivers. Some improvement is also seen in egg and baked milk OIT, but these were single RCTs' identified in the meta-analyses and low certainty of evidence. The above information supports recommending peanut OIT as a treatment that can improve QoL. However, the paucity of data for hen egg and cow's milk makes it difficult to recommend OIT for these, with a reasonable expectation of improvement in QoL. The CSACI guidelines reported mixed results regarding peanut OIT and its effect on QoL for the patient and parent.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines:** CSACI guidelines 2020[1] (QoL data: Page 34/45): 5 studies, 3 OIT-peanut RCTs' (parent: 1 showed no difference between the groups. Patient: **significant difference OIT vs control** only for Risk of exposure and Emotional impact). **SRs/MAs:** Vassilakou 2023[2] (systematic review): observational and interventional studies were summarised separately, School-aged children and adolescents, until April 2022. Improved QoL in peanut OIT vs placebo (Table 7). de Silva et al 2022[3] – RCTs', peanut (7), milk (8), egg (7), others (3) for OIT. Until Apr 2021. - Peanut (n=336): 2 out of 3 RCTs found improved quality of life in children compared to placebo. 2 found no improvement in parental quality of life compared to placebo. Certainty of evidence: very low - Egg: 1 study (n=45), improvement in QoL in children. Certainty of evidence: very low

	Bognanni et al 2022[4] reported 1 RCT for baked milk OIT: improvement in QoL for children, but no overall difference for parents. **Quality of life of children (follow-up: 12 months)** 1[1] | randomised trials | serious [a] | not serious | not serious | very serious [d] | none | Most of OIT patients experienced an overall improvement in QoL. The only age group in which a between-group comparison could be done was children between 8-12 years of age, surveyed through the FAQOL-CF questionnaire (OIT: 5; Placebo: 5). The results suggest that patients in the OIT arm, were more likely to have a QoL improvement (>0.5 MCID). | ⊕○○○ Very low | IMPO **Quality of life of the caregivers (follow-up: 12 months)** 1[1] | randomised trials | serious [a] | not serious | not serious | very serious [d] | none | The parents of 26 patients (OIT: 12; Placebo: 14) were surveyed through the FAQOL-PF questionnaire. The results highlighted no overall difference between groups, but the parents in the placebo arm appeared more likely to experience an improvement (>0.5 MCID) in the emotional domain. | ⊕○○○ Very low | IMPO Cao et al 2021[5] – searched from 2010 to July 2020. QoL improved in all studies (7, of which 4 were RCTs'). **Other more recent literature or local data:**
Certainty and Magnitude of Effects:	Certainty: Low Magnitude: Low
Risk/Harm vs Benefit Considerations:	
Patient/ caregiver values	**Stakeholder feedback (if available):**
Resource, Cost Considerations:	
Equity **Acceptability** **Feasibility**	**Stakeholder feedback (if available):**
Workgroup Consensus Survey (RAND/UCLA):	**R 8.1: We strongly recommend offering OIT under specialist supervision to children with persistent IgE-mediated peanut allergy to achieve desensitisation (increase the amount of peanut tolerated while on therapy), in centres with expertise and infrastructure in OIT. Informed shared decision making is key in patient's choice to take up OIT.** *Number voted = 19; Number abstained = 0* Lowest score: 2 | Highest score: 9 | Coefficient of Variation: 24% | Median Score: 8 | Interpercentile Range (IPR): 1.0 | Interpercentile Range Adjusted for Symmetry (IPRAS): 6.1 | Overall Consensus: No Disagreement **R 8.2: We conditionally recommend offering OIT under specialist supervision to children with persistent IgE-mediated hen's egg, cow's milk, tree nut and wheat**

allergy to achieve desensitisation (increase the amount of allergen tolerated while on therapy), in centres with expertise and infrastructure in OIT.

Number voted = 19; Number abstained = 0

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
4	9	20%	8	2.0	6.9	No Disagreement

R 8.3: We conditionally recommend OIT be offered as a treatment option for adults.

Number voted = 17; Number abstained = 2

Lowest score	Highest score	Coefficient of Variation	Median Score	Interpercentile Range (IPR)	Interpercentile Range Adjusted for Symmetry (IPRAS)	Overall Consensus
7	9	10%	8	1.0	7.6	No Disagreement

External Review Feedback:	
Public Consultation:	

References:

1. Bégin P, Chan ES, Kim H, Wagner M, Cellier MS, Favron-Godbout C, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol. 2020 Mar 18;16:20.
2. Drakouli AE, Kontele I, Poulimeneas D, et al. Food Allergies and Quality of Life among School-Aged Children and Adolescents: A Systematic Review. Children (Basel). 2023;10(3):433. Published 2023 Feb 23.
3. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al; GA2LEN Food Allergy Guidelines Group. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022 Jun;77(6):1852-1862.
4. Bognanni A, Chu DK, Firmino RT, Arasi S, Waffenschmidt S, Agarwal A, et al; WAO DRACMA Guideline Group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update - XIII - Oral immunotherapy for CMA - Systematic review. World Allergy Organ J. 2022 Sep 8;15(9):100682.
5. Cao S, Borro M, Alonzi S, Sindher S, Nadeau K, Chinthrajah RS. Improvement in Health-Related Quality of Life in Food-Allergic Patients: A Meta-Analysis. J Allergy Clin Immunol Pract. 2021 Oct;9(10):3705-3714.

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Atopic Dermatitis in Food Allergy
Subgroup Members:	Pauline Chan, Elizabeth Tham Huiwen, Nur Farah Addina Lee Binte Zailan
Main Clinical Question(s)	**Systematic Search:** **1.** Rates of food sensitization VS true food allergy in children with AD? **Narrative Search:** **2.** How to diagnose food allergy in children with AD? **3.** How do we reintroduce food allergens in children with AD who are sensitized to food allergens safely? **4.** Is exclusion diet necessary in children with atopic dermatitis?
Population	**Included (All Questions):** Children with atopic dermatitis/eczema (For Question 3: children with atopic dermatitis/eczema and food sensitization) **Excluded (All Questions):** Other allergic disorders
Interventions or Screening/Diagnostic Tools or Management Evaluated:	[All are exposures] Q1: Allergenic food Q2: Investigations Q3: Introducing allergenic food Q4: Exclusion/Elimination Diet
Comparator (if applicable)	N/A
Outcomes	Q1: Rates of food sensitization VS allergy Q2: Diagnosis of food allergy (IgE-mediated and delayed type) Q3: Safety of reintroducing food allergens in children with atopic dermatitis and food sensitization Q4: Treatment/management of atopic dermatitis via exclusion diet
Publication Dates	2000 – 2023
Study Designs	**Inclusion criteria –** Systematic Reviews, Meta-Analysis [Systematic Search]; Reviews, Guidelines, Practice Guidelines [Narrative Search] **Exclusion criteria –** Other study designs

Search Strategy:	**Databases Searched:** PubMed, Embase **Grey Literature Sources?** No **<u>Systematic Search Terms:</u>** **PubMed** (("dermatitis, atopic"[MeSH Terms] OR "Eczema"[MeSH Terms] OR ("atopic dermatiti*"[Title/Abstract] OR "eczema*"[Title/Abstract])) AND ("Food Hypersensitivity"[MeSH Terms] OR (("food"[Title/Abstract] OR "nut"[Title/Abstract] OR "nuts"[Title/Abstract] OR "peanut*"[Title/Abstract] OR "treenut*"[Title/Abstract] OR "seafood*"[Title/Abstract] OR "shellfish*"[Title/Abstract] OR "wheat*"[Title/Abstract] OR "soy"[Title/Abstract] OR "soybean*"[Title/Abstract] OR "seed*"[Title/Abstract] OR "legume*"[Title/Abstract] OR "milk"[Title/Abstract] OR "multiple food*"[Title/Abstract] OR "egg"[Title/Abstract] OR "eggs"[Title/Abstract]) AND ("allerg*"[Title/Abstract] OR "hypersensitivit*"[Title/Abstract] OR "anaphyla*"[Title/Abstract]))) AND ("Sensitivity and Specificity"[MeSH Terms] OR "Prevalence"[MeSH Terms] OR ("sensitivity"[Title/Abstract] OR "specificity"[Title/Abstract] OR "true positive"[Title/Abstract] OR "positive predictive"[Title/Abstract] OR "Prevalence"[Title/Abstract] OR "rate"[Title/Abstract] OR "incidence"[Title/Abstract])) AND ("Systematic Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR ("Systematic Review"[Title/Abstract] OR "Meta-Analysis"[Title/Abstract]))) AND (2000:2023[pdat]) **Embase** ('atopic dermatitis'/exp OR 'eczema'/exp OR 'atopic dermatiti*':ab,ti OR eczema*:ab,ti) AND ('food allergy'/exp OR ((food:ab,ti OR nut*:ab,ti OR peanut*:ab,ti OR treenut*:ab,ti OR milk:ab,ti OR seafood*:ab,ti OR shellfish*:ab,ti OR wheat*:ab,ti OR soy*:ab,ti OR seed*:ab,ti OR legume*:ab,ti OR 'multiple food*':ab,ti OR egg*:ab,ti) AND (allerg*:ab,ti OR hypersensitivit*:ab,ti OR anaphyla*:ab,ti))) AND ('sensitivity and specificity'/exp OR 'prevalence'/exp OR sensitivity:ab,ti OR specificity:ab,ti OR 'true positive':ab,ti OR 'positive predictive':ab,ti OR prevalence:ab,ti OR rate:ab,ti OR incidence:ab,ti) AND ('systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR 'meta analysis':ab,ti) AND [2000-2023]/py **<u>Narrative Search Terms:</u>** **PubMed** (("management"[Title/Abstract] OR "approach"[Title/Abstract]) AND ("atopic dermatitis"[Title/Abstract] OR "eczema"[Title/Abstract]) AND ("food allerg*"[Title/Abstract] OR "food hypersensitiv*"[Title/Abstract])) AND ((guideline[Filter] OR practiceguideline[Filter] OR review[Filter]) AND (2000:2023[pdat])) **Embase** (management:ab,ti OR approach:ab,ti) AND ('atopic dermatitis':ab,ti OR eczema:ab,ti) AND ('food allerg*':ab,ti OR 'food hypersensitiv*':ab,ti) AND ('practice guideline'/exp OR guideline:ti OR guidelines:ti OR [review]/lim) AND [2000-2023]/py

Search Outcomes:	**<u>Systematic Search:</u>** Number of potential studies identified by database searches: 240 Number of additional potential studies identified through other sources: NA Total number of studies screened once duplicates were removed: 169 Number of studies shortlisted for full text review: 10 Number of studies excluded after full text review: 8 Number and type of studies included: 2 [Systematic Reviews] **<u>Narrative Search:</u>** Number of potential studies identified by database searches: 429 Number of additional potential studies identified through other sources: NA Total number of studies screened once duplicates were removed: 292 Number of studies shortlisted for full text review: 28 Number of studies excluded after full text review: 5 Number and type of studies included: 23 [Reviews/Guidelines]

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM9-1*
Clinical/PICO Question:	**Rates of food sensitization VS true food allergy in children with AD?** P: Children with atopic dermatitis/eczema E: Allergenic food O: Sensitization VS Clinical allergy
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**R 9.1: We strongly recommend against the routine use of food allergy tests to screen for food allergy in atopic dermatitis (AD) patients in view of the high rates of food sensitization (i.e. false positive).**
Rationale:	Food allergy needs to be considered in AD of early onset and at least moderate severity. Food sensitization is increased in AD but does not equate to food allergy and hence, if positive, further evaluation with a challenge may be warranted. Early onset and at least moderately severe AD should be referred to allergy for food allergy evaluation. Unnecessary elimination of a food can potentially promote food allergy and prevent development of oral tolerance. Severe AD is defined as any one of the following: • Body surface area (BSA) involved of at least 10% • Significant disruption to daily living (feeding, sleep, activities) • Poor growth from the skin condition
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	Systematic review #1, Christensen et al., 2023[1]: Of 557 articles: Pooled prevalence of FS, FA and CPFA among 225,568 AD individuals was: • FS: 48.4% [43.7–53.2] (n = 12,821 individuals) • FA 32.7% [28.8–36.6] (n = 51,593 individuals) • CPFA 40.7% [34.1–47.5] (n = 2756 individuals) FS test methods: • SPT 40.6% [31.7 – 49.8] • sIgE 53.6% [44.8 – 62.2] • APT 35.7% [16.3 – 58.0] • sIgE and/or SPT 55.9% [47.4 – 64.2] • sIgE and/or SPT and/or APT 43.5% [12.6 – 77.6] The pooled prevalence among n = 1,128,322 reference individuals (no AD) were: • FS 17.9% [12.7–23.7] • FA 9.4% [7.8–11.4] • CPFA 15.5% [7.9–25.2] Children with AD had higher pooled FS (49.8% [44.4–55.1]) and FA (31.4% [26.9–36.1]) prevalence than adults with AD (28.6% [13.4–46.8] and 24.1% [12.1–38.7]). Highest pooled prevalence of FS and FA in AD individuals was found at 0–2 years (54.4% [46.1–62.6] and 39.2% [24.9–54.5]). Examining FS, FA and CPFA prevalence by AD severity, revealed a tendency of AD severity-dependent increase in FS and FA prevalence. Systematic review #2, Tsakok et al., 2016[2]: • Food sensitization and allergy are common in children with AD. Positive allergy test indicates sensitization and does not equate to food allergy. ○ Danish population[3]:

	▪ FA (by challenge): 18 (15%) of 122 children with AD ▪ FS (SPT≥3mm/ sIgE≥Class1): 52% of remainder ○ EAT Study[4] (UK): Higher risk of FS in AD pts VS no AD: ▪ Egg (aOR, 9.48; 95% CI, 3.77-23.83; P < .001) ▪ Milk (aOR, 9.11; 95% CI, 2.27-36.59; P = .002) ▪ Peanut (aOR, 4.09; 95% CI, 1.00-13.16.76; P = .05) ○ Burks et al.[5] (United States): SPT positive 60%, food challenge proven FA 39% ○ Gray et al.[6] (Cape town): amongst mod-severe AD pts, FS 66%, challenge proven FA 44%; egg and peanut most common. • Polysensitization is also more common in AD. • Food allergy is associated with lower age of onset of AD and increasing severity: ○ Burks et al.[5] showed that children with both positive SPT and DBPCFC responses had a significantly lower age of AD onset than patients without positive responses (2 vs 7 months, P=.003). ○ South African study by Gray et al.[6] reported that onset of AD before 6 months was a significant risk factor for FA (P=0.002). Review by Anagnostou, 2021[7]: • Not all infants with eczema are at risk of food allergy. Early onset eczema and severe eczema are risk factors. Martin et al.[8] reported 1 in 5 infants with eczema were allergic to peanut, egg or sesame, compared to only 1 in 25 infants without eczema, and these results were noted to be highly significant (p < 0.001). Infants with early onset eczema were shown to be six times more likely to have an egg allergy and 11 times more likely to have a peanut allergy by 12 months.
Certainty and Magnitude of Effects:	Evidence is high that patients with AD have higher rates of food allergy and sensitization than patients without AD in view that this is consistently seen in various cohort studies.
Risk/Harm vs Benefit Considerations:	Benefit: prevent severe accidental reactions with the knowledge of food allergy the patient has. Con: wait times for paediatric allergy review may be lengthy and hence, may cause delay in the introduction of the food if it is only a food sensitization. Unnecessary and prolonged elimination may potentially cause loss of tolerance.
Patient/ caregiver values	**Stakeholder feedback (if available):**
Resource, Cost Considerations:	There may be limited slots for specialist review and waiting times may lengthen. There may also be increased costs for specialist review and performance of tests for food allergy diagnosis such as SPTs, sIgEs and oral food challenges. Centres will also need specialized OFC facilities which may not be present in all settings.
Equity **Acceptability** **Feasibility**	Access to specialist care in Singapore is relatively equitable. There are government subsidies to cover subsidized specialist consultations in the public healthcare sector. This is generally acceptable and feasible for most patients in Singapore. A small minority may face difficulties travelling to specialist clinics due to time, logistical and cost constraints. **Stakeholder feedback (if available):**

<table>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 9.1: We strongly recommend against the routine use of food allergy tests to screen for food allergy in atopic dermatitis (AD) patients in view of the high rates of food sensitization (i.e. false positive).
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest Score</th><th>Highest Score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>31%</td><td>9</td><td>0.6</td><td>7.9</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

1. Christensen MO, Barakji YA, Loft N, et al. Prevalence of and association between atopic dermatitis and food sensitivity, food allergy and challenge-proven food allergy: A systematic review and meta-analysis. *Journal of the European Academy of Dermatology and Venereology* 2023; 37: 984-1003.
2. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *Journal of Allergy and Clinical Immunology* 2016; 137: 1071-1078.
3. Eller E, Kjaer HF, Høst A, et al. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy* 2009; 64: 1023-1029.
4. Flohr C, Perkin M, Logan K, et al. Atopic Dermatitis and Disease Severity Are the Main Risk Factors for Food Sensitization in Exclusively Breastfed Infants. *Journal of Investigative Dermatology* 2014; 134: 345-350.
5. Burks AW, James JM, Hiegel A, et al. Atopic dermatitis and food hypersensitivity reactions. *The Journal of Pediatrics* 1998; 132: 132-136.
6. Gray CL, Levin ME, Zar HJ, et al. Food allergy in South African children with atopic dermatitis. *Pediatric Allergy and Immunology* 2014; 25: 572-579.
7. Anagnostou A. Addressing Common Misconceptions in Food Allergy: A Review. *Children* 8.
8. Martin PE, Eckert JK, Koplin JJ, et al. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clinical & Experimental Allergy* 2015; 45: 255-264.

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM9-2*
Clinical/PICO Question:	**How to diagnose food allergy in children with AD?** P: Children with atopic dermatitis/eczema E: Investigations O: Diagnosis of food allergy – IgE mediated and delayed type
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**R 9.2: We strongly recommend food allergy evaluation by an allergy specialist in young patients (less than 2 years old) with severe and refractory AD despite optimisation of, and adherence to, conventional therapy and where there are concerns of food reactions.** **GPP 9.5: We recommend against the use of patch tests to diagnose food allergy in AD patients.**
Rationale:	SPT and sIgEs are tests that can help with making a diagnosis of food allergy but a confirmatory test is doing a double-blind placebo-controlled food challenge. However, a double blinded placebo-controlled food challenge is not practical for routine clinical practice and hence, a food challenge by trained personnel would be a reasonable alternative. SPT and sIgEs need to be done appropriately and interpreted with caution in order to avoid unnecessary elimination of foods that can cause poor growth and nutritional deficiencies. There is insufficient evidence to use patch tests in routine clinical practice due to the lack of standardization of concentrations and preparation of food for reliable outcomes. No role for intradermal test due to the risk of adverse reactions – have not included in the guidelines unless group feels that it is required.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	Review by Taieb, 2005[9]: • Niggemann et al.[10]: Of 77 children with positive food challenges, 39 had early immediate type reactions, 12 had delayed reactions (AD exacerbation), 17 had combined early and delayed reactions. • Essential to clear eczema with intensive treatment beforehand to assess food challenges correctly. • Allergy testing as second line management. • "Gold standard" = double-blinded, placebo-controlled food challenge but single blinded food challenges are still helpful. • Labial food challenge (LFC) might be an alternative to classic food challenge, particularly when testing egg and peanut allergy. A drop of commercial food extracts or crushed food resuspended in saline is applied to the lower lip. The result can be read after 15 minutes. Grading of the LFC is as follows: (i) swelling of the lip, (ii) erythema of the buccal area of the lip, (iii) contiguous urticaria, (iv) oedema of the cheek, rhinitis and watery eyes, and (v) systemic reaction. Easy to do but low sensitivity. • Allergy testing not relevant in mild disease readily controlled with topical steroids, but about a third of moderate-severe AD may have an underlying food allergy. Review by Anagnostou, 2021[7]:

	• Not all infants with eczema are at risk of food allergy. Early onset eczema and severe eczema are risk factors.
	• Martin et al.[8] reported 1 in 5 infants with eczema were allergic to peanut, egg or sesame, compared to only 1 in 25 infants without eczema, and these results were noted to be highly significant ($p < 0.001$). Infants with early onset eczema were shown to be six times more likely to have an egg allergy and 11 times more likely to have a peanut allergy by 12 months.
	• Moderate and severe eczema mostly identify infants at risk for food allergy development. In the LEAP screening study[11], an analysis of 834 infants revealed that sensitization to skin testing for peanut (defined as SPT 1–4 mm versus 0 mm) was associated with **egg allergy and severe eczema**. The investigators reported that severe eczema, egg allergy or both may be used as screening criteria to identify high-risk infants.
	
	Guidelines from Germany by Werfel et al., 2009[12]:
	• Provocation tests can lead to 3 different types of reactions:
	  • IgE-mediated
	  • Isolated eczematous delayed reaction (flare of eczema after hours or 1-2 days)
	  • Combination of both
	• Triggering of AD by pollen-associated food is especially relevant for adolescent and adult patients.
	• The placebo-controlled, double-blind challenge is the gold standard in diagnosis of food allergy as specific IgE, prick tests and history often do not correlate with clinical findings.
	• No single confirming parameter exists in the diagnosis of food allergy in atopic dermatitis, although a stepwise approach taking into account individual factors is a sensible approach:
	  1. History but limited by caregivers' observations that are often times not specific enough
	  2. When food allergy is suspected, skin tests and sIgEs (sent together with total IgE can be done)
	  3. Skin tests include: prick test and atopy patch test (latter not recommended routinely, only for the following instances: 1. Clarification of a food allergy in AD without identification of an IgE-mediated sensitization; 2. Severe or persistent atopic dermatitis with unknown trigger factors; 3. Multiple IgE-mediated sensitizations without proven clinical relevance in patients with atopic dermatitis
	  4. Symptom-food diary over a period of 2 – 4 weeks
	• If association with food and eczema reaction is unclear despite above, then oligoallergenic basic diet can be adopted: EHF in infants, young children:
	  1. Grain: white rice
	  2. Meat: lamb, turkey
	  3. Vegetables: cauliflower, broccoli, cucumber
	  4. Oil: refined vegetable oil, non-dairy margarine
	  5. Beverages: mineral water, black tea
	  6. Spices: Salt, sugar
	• If after 4 weeks at most, no improvement, then a food allergy for the patient's symptoms is IMPROBABLE.
	• If there is an improvement, then this should be followed by open provocation testing especially if negative is helpful, however limitations: psychological factors, lack of

	objectivity and the expected delayed reactions in AD. Consider double-blind placebo-controlled challenges if the above occurs. • AD control should be stable prior to challenge, if not intensify topical treatment before proceeding and then keeping at a stable dose thereafter. • Observation following challenge at least 48 hours, skin should be objectively assessed 24h after the challenge. • Introduce a new food every 4-7 days, suggested by guidelines in this order: 1. Cow's milk 2. Hen's egg 3. Wheat 4. Further vegetables 5. Fruits 6. Further grain products 7. Further meat varieties 8. Others: nuts, celery, spices • Mother's exclusively breastfeeding their child who suspects that her child has a food allergy transmitted through her breastmilk will first need to confirm it by re-introducing the food then eliminating. If an elimination diet is justified, a dietician should be involved to avoid nutritional deficiencies in mother and child. Guideline is outdated as it mentions introducing peanut and tree-nuts after first year of life. Review by Eigenmann et al., 2020[13]: • Risk factors for FA development: earlier the onset in first year of life, more severe AD. • While about 40% with moderate-severe AD have food allergies, only a subset has AD flares from those foods, others have immediate anaphylactic reactions. Diagnostic evaluations should consider both issues. • While young children with AD, especially severe AD, frequently are sensitized to a variety of food allergens (positive skin prick tests or elevated allergen-specific serum IgE), only 30%-40% reflect clinical reactivity as demonstrated by DBPCFC. Egg, milk, and peanut allergy were the most common food allergens responsible for reactions in these children, but egg and to a lesser degree milk were most commonly implicated in exacerbating AD since peanut reactions were typically anaphylactic in nature. • A subgroup of patients with AD identified as allergic to cow's milk, hen's egg, wheat, and/or possibly also soy, may benefit from an avoidance diet as it may significantly, but most often not completely, reduce the severity of the AD. • Infants who have early evidence of sensitization to peanut are at increased risk of developing FA and should have early introduction of peanut and potentially other foods such as hen's egg (if tolerated). • Atopic infants with eczema who are already consuming and tolerating a food in their diet in the first few years of life should not have SPT or sIgE testing performed to that food which they are eating. • The unproven perception that ingestion of these foods will lead to worsening of eczema as a justification for the removal of these foods from the infant's diet has the **potential consequence of promoting FA and preventing the development of oral tolerance.** • Steps in addressing FA in AD patients: 1. Medical management of AD (skin care) should be optimized. 2. History of which foods worsen AD should be taken – differentiate from irritant dermatitis.

	3. If allergy tests (SPT or serum sIgE tests) are indicated, they should be restricted to the very few foods which have been identified as triggers of AD flares, e.g. egg, milk, wheat, and very rarely soy by allergy specialists. Negative predictive values of these tests are sufficient to exclude FA. 4. After maximal skin care (hydration and topical corticosteroids), a short avoidance diet (2-3 weeks in general) under continuous skin care may help assess the relevance of positive tests. Address the pros and cons of an avoidance diet with the family if it is deemed required. For avoidance diet, to determine if complete or partial elimination is required (e.g. avoid pure eggs but can take baked egg goods). Review by Papapostolou et al., 2022[14]: • Sensitization rates for food allergens in AD patients vary from 30 to 80%, but **the actual clinically relevant food allergy proportions are lower,** especially in less-severe phenotypes of AD. • **More severe** phenotypes of AD are associated with more frequent diagnosis of food allergy, ranging between 33% to 39%, with occasional studies reporting higher rates up to 80%, while food allergy prevalence in the general population is estimated about 0.1–6%. Atopic dermatitis is a major risk factor for food sensitization and IgE-mediated food allergy. • The Danish Allergy Research cohort (DARC)[3]: FS = 53%, confirmed FA 15%. • Rates of food sensitization are high in patients with AD, but frequency of IgE-mediated food allergy confirmed by oral food challenges varies, with more severe AD linked more frequently with food allergy. → food allergy considered only in moderate to severe cases. • There are high asymptomatic food allergen sensitization rates in patients with AD. AD is predominantly a TH2-cell-mediated disease, with IgE being more a "bystander" than an actual driver in the disease. Hence, management of food sensitization and allergy in AD patients can be challenging. • NIAID recommendations[15, 16] RE: peanut allergy: 1. In infants with severe AD and/or egg allergy, measurement of peanut IgE level and/or SPT should be conducted before introduction into the diet 2. infants with mild-to-moderate AD should not be tested for peanut sensitization, and peanut should be introduced in diet approximately at six months of age 3. infants without AD should be free in introduction of peanut and other foods according to the wish of the family • Negative predictive value of SPTs to foods in patients with AD is 90–95%, while the positive predictive value is less than 50% → useful to EXCLUDE food allergy. • Patch testing is **NOT** suggested for routine diagnosis of food allergy in AD patients. sIgE and CRDs may be useful in differentiating between tolerance and allergy in patients with severe AD - Frischmeyer-Guerrerio et al.[17] found that patients with severe AD had significantly higher values of IgE and CRDs (decision trees for egg, milk and peanut were shown in their paper). Review by Cartledge & Chan, 2018[18] from EAACI group: • EAACI position paper[19] on late eczematous reactions to food in AD recommends further investigations in the following circumstances: 1. AD and a history of an immediate reaction against one or more foods; 2. Persistent, moderate-to-severe AD, no history of immediate-reactions to food, no suspected eczematous reactions to food;

	3. Food is suspected by patients or parents as trigger factor of persistent AE (without obvious immediate reactions). • NICE Guidelines[20]: moderate or severe AD below age 12 years with suspected food allergy should be referred for specialist investigation and management of the AD and allergy, particularly if it is associated with gut dysmotility or failure to thrive. • Investigations: SPT and sIgE • Negative results may be a reflection of an underlying non-IgE mediated pathology and do not exclude food-triggered AD. On the other hand, low positive results may indicate sensitization, which is not necessarily associated with clinical food allergy. Therefore, unnecessary elimination diets based on equivocal results of allergy tests alone should be avoided. Strongly positive results in the absence of immediate symptoms need to be carefully managed. • Algorithm:

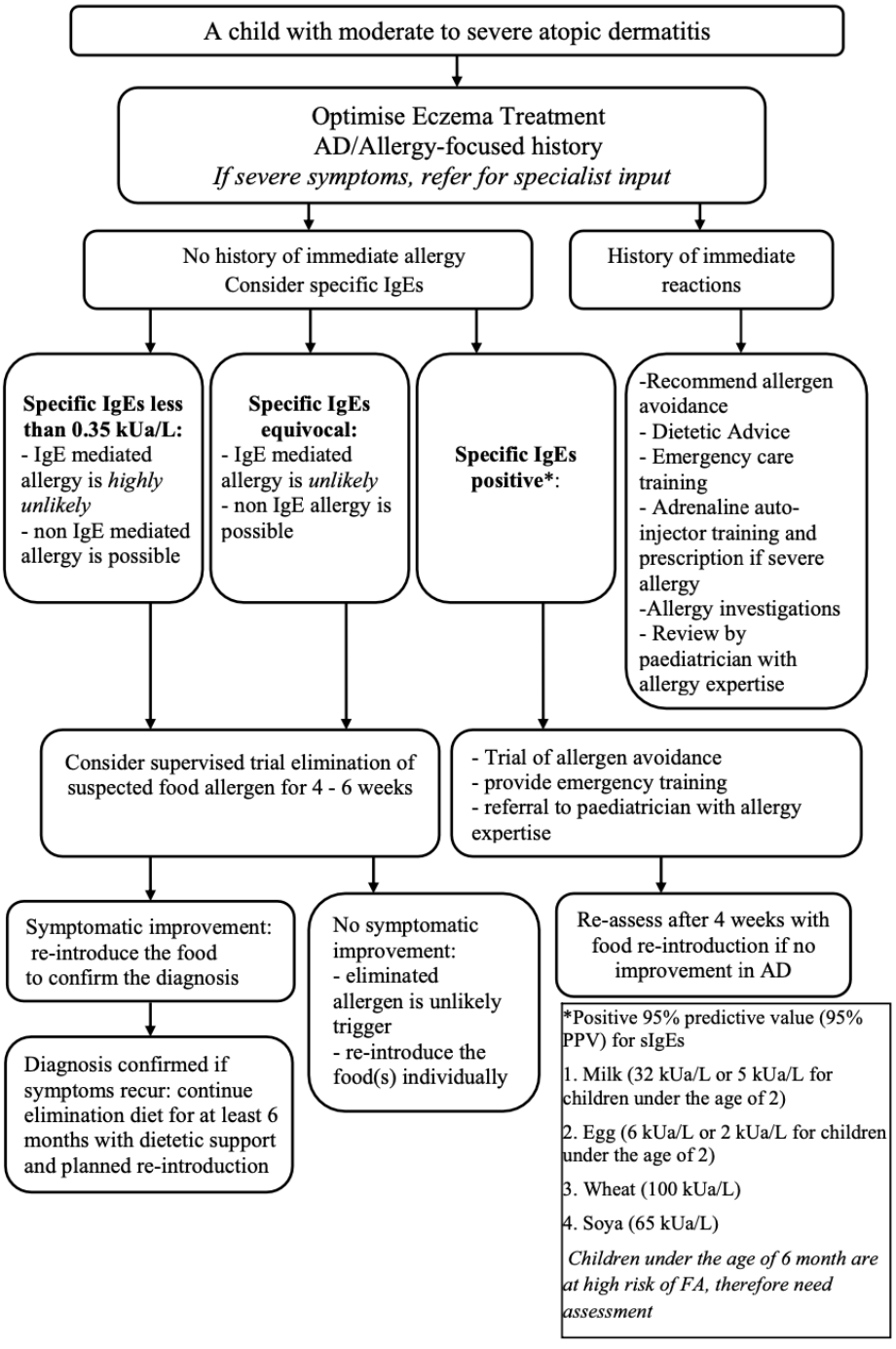

Table 3. Non-standardized test which are *not* recommended for diagnosis of food allergy.

• Lymphocyte stimulation
• Facial thermography
• Gastric juice analysis
• Endoscopic allergen provocation
• Hair analysis
• Applied kinesiology
• Provocation neutralization
• Allergen-specific IgG_4
• Cytotoxicity assays
• Electrodermal test
• Mediator release assay

	Review by Jesenák & Bánovcin, 2006[21]: • Patch testing read at 48 and 72 hours can be useful to determine delayed type food allergies (particularly milk, egg, wheat and soy) and may help with prevention of unnecessary elimination diets or DBPCFC in patients with positive SPT as well. Limitation is that there is no standardized dilution, authors recommend using fresh food. Sensitivities and specificities and evidence for APT not reported in this paper as well – not convinced that it can be used in routine clinical practice. Review by Silverberg et al., 2016[22]: • American Academy of Dermatology for the management of AD have recommended testing for food allergies in children younger than 5 years who have intractable AD or known food-induced reactions.[23] • Against food elimination based on tests alone. Risk of elimination diets: nutritional deficiencies and poor growth. Review by Leung et al., 2004[24]: • Studies indicate that food-specific serum IgE concentrations may be useful for diagnosing symptomatic allergy to certain foods, such as egg, milk, peanut, and fish, and could eliminate the need to perform controlled food challenges in some patients. *(Yunginger et al., 2000[25]; Sampson, 2001[26]; Rance et al., 2002[27])* • However, the amount of food causing a reaction and the severity of the reaction are not predicted by prick skin testing or concentration of food-specific serum IgE. *(Sicherer et al., 2000[28])* • If the patient has a history suggestive of food allergy but there is no evidence of food-specific IgE antibodies, it may be necessary to perform an oral food challenge to rule out food sensitivity that is not IgE mediated. *(Niggemann et al., 2001[29])* • In children who have undergone double-blind, placebo-controlled food challenge, milk, egg, peanut, soy, wheat, and fish account for nearly 90% of the foods that exacerbate atopic dermatitis. *(Lever et al., 1998[30])* • Avoidance of foods implicated by controlled food challenge has been shown to result in clinical improvement. *(Woodmansee & Christiansen, 2001[31]; Niggemann et al., 2001[29])* • Extensive elimination diets, which in some cases can be nutritionally deficient, are rarely required, because, even with multiple positive skin test results, most patients will react to 3 or fewer foods on blinded challenge. Review by Sampson, 2003[32]: • While parents can sometimes attribute worsening of eczematous symptoms to the ingestion of certain foods, most often the history is not particularly informative, especially in cases of severe AD. A number of factors can lead to worsening of the eczematous rash, e.g. Staphylococcus infection, irritants, heat and humidity etc., so it is often difficult to identify the ingestion of a food allergen as the cause of an eczematous flare. In a series of nearly 500 children with moderate to severe AD, only 35–40% of parental historical accounts of food allergy could be verified by DBPCFCs. (no ref provided for this statement) • Egg allergy is the most frequent cause of food-induced eczematous symptoms, affecting two thirds of children with food allergy and AD in our series. (*Sampson, 1997[33]*) • SPTs are the most informative when they are negative because the negative predictive value of the tests is very high (>95%) while the positive predictive value is <40% (*Sampson & McCaskill, 1985[34]; Bock et al., 1978[35]; Sampson & Albergo,*

	1984[36]). Thus, a positive test in isolation cannot be considered proof of clinically relevant food hypersensitivity, but a negative test virtually rules out IgE-mediated food allergy to the food in question.
	• Intradermal allergy skin tests with food extracts should not be used because they give an unacceptably high false-positive rate and a greater risk for adverse reactions to testing. (*Bock et al., 1978*[35])
	• Although slightly less sensitive than prick skin tests, in vitro tests for specific IgE antibodies (RAST) may be more practical than prick skin tests for the screening of food allergies in most office settings and can be used while the patient is taking antihistamines and does not depend on having an area of eczematous-free skin for testing. Like skin tests, a negative result is fairly reliable in ruling out an IgE-mediated reaction to a particular food, but a positive result has low specificity. (*no reference provided for this statement)*
	• Quantitative measurements of food-specific IgE appear to be more useful in predicting clinical reactivity. As shown in Table 3, "decision points" have been established that provide >95% confidence that a patient has symptomatic food allergy. (*Sampson, 2001*[26]*; Sampson & Ho, 1997*[37]*)* An oral challenge would be needed to confirm reactivity for children with levels falling below the 95% predictive decision point.
	
	Review by Newland et al., 2013[38]:
	• Studies (a DBPCRCT, RCT, retrospective reviews of OFCs) have shown that food may trigger eczema flares.[30, 34, 39-44]
	• A late phase IgE response may be implication in eczematous reactions to food[45] with homing of food-responsive T cells to the skin[46].
	• Allergy testing should be considered in:
	  ○ all infants with severe eczema under the age of 6 months
	  ○ infants with moderate to severe eczema who do not respond to standard topical therapy (soap substitutes, emollient, mild to moderate topical steroids with or without wet wrapping)
	  ○ infants with a suggestive clinical history of food induced immediate or delayed reactions to certain foods.
	• The positive predictive value of food-specific IgE in eczematous reactions is 33%.[47]
	• Hen's eggs, cow's milk, soy, wheat and peanuts account for the most allergenic foods in children with atopic eczema.[47, 48] We therefore recommend serological IgE testing for these 5 foods in infants with severe atopic eczema as the first step in evaluation of food allergy.
	• A number of studies have confirmed that negative SPT responses have excellent negative predictive values (>90%) for excluding the presence of an IgE-mediated food allergy and is superior to that of serological testing. Thus, in the presence of a positive serology test without a clear history of allergy, a negative SPT could be used to exclude an IgE-mediated food allergy.[49]
	• Atopy patch testing does not lead to a significant reduction of the need for OFCs when food-induced eczema is suspected[50], and thus is not recommended in the diagnostic algorithm.
	• Food specific IgG and IgG4 antibodies have never shown a correlation with DBPCFC outcomes and are not useful in the investigation of a food allergy.[51]
	
	Japanese Food Allergy Guidelines by Ebisawa et al., 2020[52]:
	• Key points in history taking are causative foods and their intakes, age at symptom onset, reproducibility, the last time when symptoms occurred, details of the

	induced symptoms, time from food ingestion to onset of symptoms, other causative conditions (exercise, medication, etc.), past test results, and present ingestion of the causative foods. • The presence of specific IgE antibodies can be confirmed through specific serum IgE antibody test, SPT, basophil histamine release test, etc. Although the diagnostic values of these tests have been evaluated in many studies, their results vary depending on the selection of the general population and the diagnostic methods used. • A SPT is recommended to determine the causes of food allergy. • Avoid intradermal tests using food antigens, because they are more likely to yield false positive results and cause anaphylactic reactions than the SPT. • Reportedly, an atopy patch test, in which a food antigen is applied on the skin, is useful for predicting non-immediate reactions in the diagnosis of atopic dermatitis. However, no consensus has been reached on this finding. • An OFC is the most reliable for identifying the causative foods of a food allergy. Review by Rustad et al., 2022[53]: • Positive sIgE and epicutaneous testing have high false positive rates in patients with AD. In patients with AD, SPT to foods have a negative predictive value of 90–95%, yet a positive predictive value of less than 50%; these tests may be more useful in ruling out rather than diagnosing FA.[32, 54, 55] Therefore, testing relying on the presence of food sIgE is impractical without a suggestive immediate reaction history, and would not predict eczematous responses to the tested food. • Patients with AD who are tolerating a food without any symptoms of an IgE-mediated reaction should not be subjected to unnecessary allergy testing and avoidance. Review by Greenhawt, 2010[56]: • In patients with AD, nearly 80% will have positive food (or pollen) sIgE, often against multiple foods, although very few are clinically relevant.[41, 48, 57] Therefore, caution must be taken before considering a positive test in the setting of AD. Although negative skin tests confer upward of a 95% negative predictive value (NPV) for an allergy, positive tests have a positive predictive value (PPV) of only 60%.[58-60] • One should start by taking a thorough history, which includes specific delineation of which suspected food exposures actually are attributed to directly causing a flare within hours after ingestion, the extent that particular food is consumed in the present diet, and the extent that elimination of that food has helped, as well as the extent of skin treatment that has been used to help treat the AD. The history, despite a low PPV, is still a helpful guide to understand the family's concerns, treatments already tried, and to rule in likely food allergens. It is recommended to skin/serum test only to relevant exposures supported by the history, because of high false positive rates and low PPVs of these tests. The use of screening panels that include items unlikely to be contributing factors should be discouraged. Review by Campbell, 2012[61]: • Clinicians are frequently confronted with infants and children covered in poorly controlled AD and asked to determine the extent to which a food allergy may be contributing to the disease. In this setting, it is imperative to ensure that the parents and child (if age appropriate) understand that moderate-to-severe AD is a chronic,

	relapsing and remitting disorder, which will not be cured by any form of dietary manipulation. • However, AD can be significantly improved with an individualised management plan, which may include dietary manipulation in some children. The age of the child, severity of the AD and the history of past IgE-mediated and delayed reactions to foods (urticaria, angioedema, cough, wheeze) will determine how likely it is that foods may be exacerbating the AD. • Delayed eczematous reactions to foods are harder to identify from history and are likely to be significantly less frequent than co-existing IgE-mediated food allergy.[62, 63] • SPT sensitivity does not equal clinical reactivity, and most food challenges detect immediate, not delayed, eczematous reactions to the offending foods. Overall, a positive SPT in the presence of past known ingestion without immediate reaction has a very poor positive predictive value for identifying food allergens triggering AD. • Children who have IgE sensitisation (positive SPT or in vitro specific IgE) and a history of tolerating the food without immediate reaction should not have the food excluded from the diet until an observed challenge clearly confirms a delayed eczematous reaction. **Table 1** Approach to the child with atopic dermatitis and suspected food allergy Possible scenarios / SPT/RAST / Food strategy / Additional management / Reintroduction Eaten the food/s previously with immediate IgE reaction / Yes / Avoid food / As per ASCIA for food allergen avoidance / Not until tolerance established Eaten the food/s previously with observed delayed reaction / No / Remove from diet for short period of time (3–4 weeks) if AD moderate-severe / Eczema diary – daily skin score† OFC if significant improvement Only continue exclusion following positive OFC / Reintroduce if no improvement after 3 weeks Reintroduce food with caution if removed for long period of time Eaten the food/s previously – No observed immediate or delayed reaction / No / Do not remove from diet Eaten the foods previously – No observed immediate or delayed reaction SPT/*in vitro* specific IgE positive / / / OFC / Reintroduce food with caution if removed for long period of time Never eaten the food / No – unless high index of suspicion of food allergy or very severe disease / Slow introduction of foods / OFC If SPT/*In vitro* specific IgE performed and positive – as below Never eaten the food SPT/*in vitro* specific IgE positive / Confirm positive test / OFC unless SPT or *in vitro* specific IgE >95% PPV for IgE-mediated reaction[24,25] †Parents record daily parental/child assessment of AD on a scale of 1–10, new foods introduced or foods removed are recorded. ASCIA, Australian Society for Allergy and Clinical Immunology; OFC, observed food challenge; RAST, radioallergosorbent tests; SPT, skin prick test.
Certainty and Magnitude of Effects:	There are no RCTs done in this area and most of the evidence are from cohort studies and expert consensus. Certainty of evidence that food sensitization is higher in AD is high due to consistent cohort studies demonstrating this. There is also a "dose-related" effect with more severe AD having higher rates of FS (and FA). Well established that SPT and sIgEs are helpful in the diagnosis of IgE-mediated food allergy, especially with respect to the exclusion of food allergy considering the high negative predictive value. There is however, limited information on the cut offs for corresponding PPVs but generally low positive titres are associated with lower PPVs and hence, are non-specific. With the above principles, experts have recommended avoiding screening tests that include foods that a patient is unlikely to be allergic to, so as to avoid unnecessary anxiety and elimination of foods. GPP 9.5: Not graded (GPP). Inadequate evidence for patch tests. Diagnosis of delayed type reactions have to be made clinically based on expert opinion.

<table>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td>Unnecessary administration of tests and incorrect interpretation of results can potentially cause anxiety to caregivers and lead to unnecessary elimination of foods which can lead to risk of loss of tolerance, nutritional deficiencies and poor growth.</td></tr>
<tr><td>Patient/ caregiver values</td><td>Patients usually value accurate information which would affect provision of their care, and evidence-based advice which would prove or disprove the existence of a food allergy.
The potential for dietary expansion and removal of food restrictions if unnecessary would significantly enhance their quality of life – a valuable outcome for patients.

Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>There may be limited slots for specialist review and waiting times may lengthen.
There may also be increased costs for specialist review and performance of tests for food allergy diagnosis such as SPTs, sIgEs and oral food challenges.
Centres will also need specialized OFC facilities which may not be present in all settings.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Access to specialist care in Singapore is relatively equitable.
There are government subsidies to cover subsidized specialist consultations in the public healthcare sector.
This is generally acceptable and feasible for most patients in Singapore. A small minority may face difficulties travelling to specialist clinics due to time, logistical and cost constraints.

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 9.2: We strongly recommend food allergy evaluation by an allergy specialist in young patients (less than 2 years old) with severe and refractory AD despite optimisation of, and adherence to, conventional therapy and where there are concerns of food reactions.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest Score</th><th>Highest Score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>29%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table>
GPP 9.5: We recommend against the use of patch tests to diagnose food allergy in AD patients.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest Score</th><th>Highest Score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>22%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
</table>

Public Consultation:	

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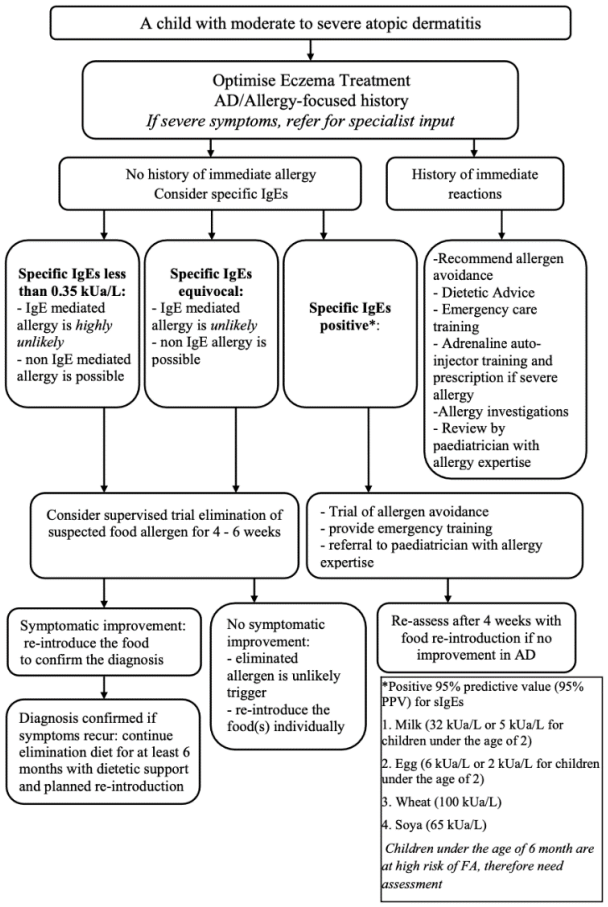
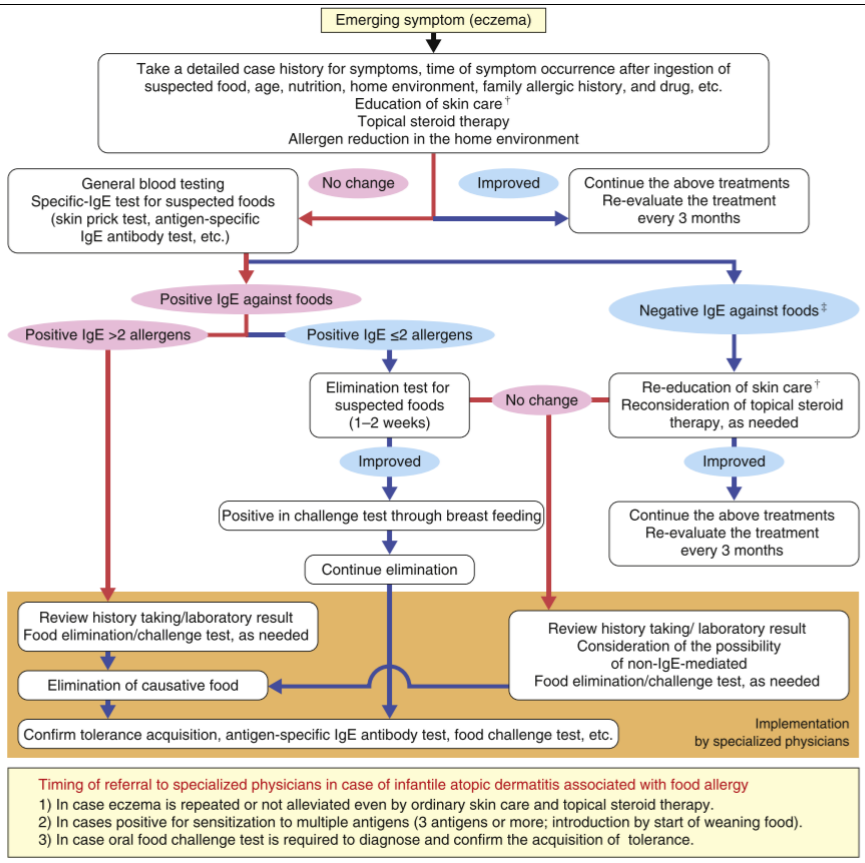
Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM9-3*
Clinical/PICO Question:	**How do we reintroduce food allergens in children with AD who are sensitized to food allergens safely?** P: Children with atopic dermatitis/eczema with food sensitization E: Introduction of Allergenic Food O: Safe introduction of allergenic food
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no)*	**GPP 9.3: We recommend referral to an allergy specialist for young infants with severe AD, whose timely introduction of solids and allergenic foods may be delayed due to parental concerns.** Remarks: Timely introduction of food allergens may be beneficial for food allergy prevention. **R 9.4: We strongly recommend against long-term untargeted elimination of foods in AD patients, as it is detrimental to a patient's health and quality of life.** If a diagnostic elimination diet is required, it should be limited to only 2-4 weeks while ensuring that AD management is optimized. If there is no significant improvement in the child's eczema despite the elimination diet, the eliminated foods are unlikely to be a trigger and should be reintroduced into the diet one by one.
Rationale:	Children with moderate severe AD may be sensitized to foods but do not have a true clinical food allergy. A careful evaluation through a detailed history, optimization of skin care, targeted food elimination guided by allergy diagnostic testing in a tertiary setting, and reintroduction of food allergens after a trial period of elimination are required to avoid unnecessary prolonged dietary restrictions.
Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	• In children with moderate to severe AD, reintroduction of food allergens should begin with a detailed history of symptoms and their relation to ingestion of suspected foods. • Other important details in the history would include the child's current diet, whether they are avoiding or consuming suspected foods, the current skin care regimen for management of their eczema, any concomitant environmental allergen triggers and avoidance measures put in place to address these. [Sampson, 2003[1]; Ebisawa et al., 2020[2]] • Skin care should be fully optimized to ensure eczema is well controlled, through the appropriate use of topical steroids, calcineurin inhibitors, moisturizers, and/or second line therapeutics such as phototherapy, immunosuppressants or biologics.[3] • Referral to allergy specialists should be done in patients where: a) Eczema is not controlled despite adequate compliance to standard skin care regimens and topical steroid therapy b) Clinical history is suggestive of clinical reactions temporally related to food allergen exposure c) Avoidance of multiple foods due to perceived food reactions d) Weaning guidance is required otherwise introduction of allergenic foods might be delayed[4,5]

	• Diagnostic allergy testing that may be performed in the tertiary setting to guide introduction of allergenic foods may include SPTs, sIgEs and component resolved diagnostics, as well as oral food challenges • In children with positive test results without a history of immediate food reactions and poorly controlled eczema despite adequate topical therapy, a trial of short-term elimination of specific relevant food triggers for no longer than 3-4 weeks may be instituted, alongside institution of aggressive eczema skin care. Re-evaluation should be performed after this period to document whether there has been significant clinical improvement. [Campbell, 2012[6]] • Following the period of elimination, re-challenge to the food allergens should then be performed one by one, beginning with foods least likely to be responsible for reactions, while ensuring ongoing good skin care. Oral food challenges may be performed in the tertiary setting for higher risk foods. Multiple dietary restrictions are rarely necessary. • If re-challenge to the food allergen induces a clear reaction, then the implicated food should be eliminated from the diet. • Re-evaluation of the food allergy status should still be done periodically, such as on a 6-monthly interval, to evaluate whether the child may have outgrown the food allergy with time. Algorithm from Cartledge & Chan, 2018[7]:  Algorithm from Ebisawa et al., 2020[2]

	 **Fig. 3.** Flow chart for diagnosis of food allergy (Infantile atopic dermatitis associated with food allergy). †Instruction for skin care. Fundamentals of skin care are skin cleansing a moisturizing. The details are discussed in the "Guidelines for the Management of Atopic Dermatitis 2012." ‡Positive for specific IgE antibody. As infants aged <6 months may ha negative value for blood antigen specific IgE antibody, the prick test is useful.
Certainty and Magnitude of Effects:	GPP 9.3: Not rated (GPP) R9.4: Certainty and Magnitude: Low
Risk/Harm vs Benefit Considerations:	• Unnecessary extensive and prolonged dietary restrictions are detrimental to the child's growth and nutrition, as well as have a significant impact on the family's quality of life. • Referral to tertiary centres may come with additional wait times and higher costs of allergy testing, but will allow accurate diagnosis of food allergy and safe reintroduction of higher risk foods • Adequate counselling and optimization of eczema care in the primary setting may mitigate the need for referral should eczema be able to be controlled
Patient/ caregiver values	Patients usually value accurate information which would affect provision of their care, and evidence-based advice which would prove or disprove the existence of a food allergy. The potential for dietary expansion and removal of food restrictions if unnecessary would significantly enhance their quality of life – a valuable outcome for patients. **Stakeholder feedback (if available):**
Resource, Cost Considerations:	There may be limited slots for specialist review and waiting times may lengthen. There may also be increased costs for specialist review and performance of tests for food allergy diagnosis such as SPTs, sIgEs and oral food challenges. Centres will also need specialized OFC facilities which may not be present in all settings.
Equity	Access to specialist care in Singapore is relatively equitable.

<table>
<tr><td>Acceptability

Feasibility</td><td>There are government subsidies to cover subsidized specialist consultations in the public healthcare sector.
This is generally acceptable and feasible for most patients in Singapore. A small minority may face difficulties travelling to specialist clinics due to time, logistical and cost constraints.

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 9.3: We recommend referral to an allergy specialist for young infants with severe AD, whose timely introduction of solids and allergenic foods may be delayed due to parental concerns.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest Score</th><th>Highest Score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>24%</td><td>9</td><td>0.6</td><td>7.9</td><td>No Disagreement</td></tr>
</table>
R 9.4: We strongly recommend against long-term untargeted elimination of foods in AD patients, as it is detrimental to a patient’s health and quality of life.
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest Score</th><th>Highest Score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>1</td><td>9</td><td>22%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table></td></tr>
<tr><td>External Review Feedback:</td><td></td></tr>
<tr><td>Public Consultation:</td><td></td></tr>
</table>

References:

1. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. Clinics in Dermatology 2003; 21: 183-192.
2. Ebisawa M, Ito K, Fujisawa T, et al. Japanese guidelines for food allergy 2020. Allergology International 2020; 69: 370-386.
3. De Benedetto A, Boguniewicz M, Ong PY, et al. Atopic Dermatitis (Eczema) Guidelines 2023: Highlights. The Journal of Allergy and Clinical Immunology: In Practice 2024; 12: 2955-2965.
4. College of Paediatrics & Child Health. Section on Paediatric Allergy and Immunology - Consensus Statement on Primary Prevention of Allergy in At-Risk Infants [Main Guidelines]. AMS Guidelines and Statements. Singapore: College of Paediatrics & Child Health, College of Obstetricians & Gynaecologists, Academy of Medicine, 2019.
5. College of Paediatrics & Child Health. Section on Paediatric Allergy and Immunology - Addendum for Consensus Statement on Primary Prevention of Allergy in At-Risk Infants. AMS Guidelines and Statements. Singapore: College of Paediatrics & Child Health, College of Obstetricians & Gynaecologists, Academy of Medicine, 2024.
6. Campbell DE. Role of food allergy in childhood atopic dermatitis. Journal of Paediatrics and Child Health 2012; 48: 1058-1064.

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Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM9-4*
Clinical/PICO Question:	**Is exclusion diet necessary in children with atopic dermatitis?** P: Children with atopic dermatitis E: Diet exclusion/elimination O: Optimal nutritional management of atopic dermatitis
Linked Recommendation Statements: *(Type = R or GPP)* *(Chapter no. statement no.)*	**R 9.4: We strongly recommend against long-term untargeted elimination of foods in AD patients, as it is detrimental to a patient's health and quality of life.** If a diagnostic elimination diet is required, it should be limited to only 2-4 weeks while ensuring that AD management is optimized. If there is no significant improvement in the child's eczema despite the elimination diet, the eliminated foods are unlikely to be a trigger and should be reintroduced into the diet one by one.
Rationale:	Elimination diets have a significant nutritional and psychosocial impact on patients and their families. A diagnostic elimination diet targeting only the most common food allergens (milk, egg, wheat and soy) from the diet for a short time-limited period of 4-6 weeks should be attempted. A lack of improvement in the child's eczema despite the elimination diet would mean that the eliminated foods are not triggers for the eczema and should be reintroduced into the diet one by one. If the child's eczema improves during diagnostic elimination, then each food allergen should be reintroduced one by one with an interval of 4-7 days between each food. A corresponding worsening of eczema with introduction of that particular allergen helps confirm the diagnosis.

Evidence Summaries	• Dietary elimination of a food significantly impacts a child's nutrition and quality of life and must be discussed and considered in shared decision-making. Good skin care management must first be instituted, and evaluation for food triggers be considered for patients who do not fully respond despite compliance. [Eigenmann et al., 2020[1]]
	• The negative consequences of an elimination diet include:
	  ○ Inducing clinical allergy, including anaphylaxis, in whom dietary elimination of a previously consumed food was initiated without first establishing the presence of a true clinical allergy. This is due to loss of a tolerant state following a period of no oral exposure.
	  ○ Risk of nutritional deficiencies
	  ○ Significant impact on quality of life and may cause anxiety
	• In non-IgE mediated allergy, a diagnostic elimination diet may be attempted if there is a strong suspicion of delayed allergy. [Chang et al., 2016[2]].
	• Examples of this include:
	  ○ Eczema exacerbations upon consumption of a suspected food allergen in the absence of an IgE-mediated type of reaction
	  ○ Persistent moderate to severe eczema while continuing a full non-restrictive diet, despite first ensuring compliance to intensive eczema skin care
	• This involves elimination of the most common food allergens (milk, egg, wheat and soy) from the diet for a short time-limited period of 4-6 weeks.
	• If there is no improvement in the child's eczema despite the elimination diet, the eliminated foods are unlikely to be a trigger and should be reintroduced into the diet one by one. [Papapostolou et al., 2022[3]; Newland et al., 2013[4]]
	• If the child's eczema improves during the diagnostic elimination period, food allergens should still be reintroduced one by one with an interval of 4 -7 days

<table>
<tr><td></td><td>between each food, to confirm the diagnosis in case the improvement in symptoms might have been due to a confounding factor or placebo effect. [Cartledge & Chan, 2018[5]]
• Elimination diets should be performed with input from nutrition experts such as dietitians, especially in young children at risk of growth and nutritional deficiencies. [Rustad et al., 2022[6]]
• There is no evidence to support the use of long-term elimination of multiple foods without evaluation of food allergy status and its impact on eczema, and this should not be performed.</td></tr>
<tr><td>Certainty and Magnitude of Effects:</td><td>Certainty and Magnitude: Low
Evidence base for this section is mainly from expert commentaries, opinion pieces and food allergy management guidelines.
The data is thus presented narratively.</td></tr>
<tr><td>Risk/Harm vs Benefit Considerations:</td><td>Unnecessary dietary restrictions negatively impact child nutrition and quality of life. A detailed evaluation of food allergen triggers, true clinical allergy status and aggressive skin care for eczema is essential to ensure good control of eczema and to allow continued consumption of non-trigger foods for nutritional optimization.</td></tr>
<tr><td>Patient/ caregiver values</td><td>Dietary restrictions confer a detrimental impact on the child and family's quality of life, affecting food choices, dining out and increasing anxiety. It would be in the patient/caregivers' best interests to ensure proper evaluation of true food allergy in order to liberalize diets under allergist guidance.

Stakeholder feedback (if available):</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>Instituting effective eczema skin care in the primary care setting will improve eczema control in the majority of patients, without requiring extensive dietary restrictions.
If primary care physicians do not recommend blanket dietary avoidance, there will then be no need for allergist referrals except in the minority in whom eczema is still not adequately controlled despite good skin care.
This will then reduce the burden on tertiary care dermatology and allergy services, reduce healthcare costs and avoid impairment of families' quality of life.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Access to good primary care services are available in Singapore, although knowledge about effective eczema control can vary between providers.
The cost of treating eczema effectively is not high, unless second and third-line treatment options are required, which will require referral to tertiary care.
Parents may request immediate referral to tertiary care if they feel this will hasten access to specialist advice and quicker recovery. This will however drive up healthcare costs and lengthen waiting times in tertiary care.

Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>R 9.4: We strongly recommend against long-term untargeted elimination of foods in AD patients, as it is detrimental to a patient's health and quality of life.
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</table></td></tr>
</table>

External Review Feedback:	
Public Consultation:	

References:

1. Eigenmann PA, Beyer K, Lack G, et al. Are avoidance diets still warranted in children with atopic dermatitis? Pediatric Allergy and Immunology 2020; 31: 19-26.
2. Chang A, Robison R, Cai M, et al. Natural History of Food-Triggered Atopic Dermatitis and Development of Immediate Reactions in Children. The Journal of Allergy and Clinical Immunology: In Practice 2016; 4: 229-236.e221.
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4. Newland K, Warren L and Gold M. Food allergy testing in infantile eczema: A clinical approach and algorithm. Australasian Journal of Dermatology 2013; 54: 79-84.
5. Cartledge N and Chan S. Atopic Dermatitis and Food Allergy: A Paediatric Approach. Curr Pediatr Rev 2018; 14: 171-179.
6. Rustad AM, Nickles MA, Bilimoria SN, et al. The Role of Diet Modification in Atopic Dermatitis: Navigating the Complexity. Am J Clin Dermatol 2022; 23: 27-36. 20211023.

Clinical Practice Guidelines on Diagnosis and Management of Food Allergy

Evidence Matrix

Subgroup/Chapter Cover Page

Subgroup/Chapter Name:	Unproven and Disproved Tests and Treatments
Subgroup Members:	Lee Bee Wah, Anne Goh, Hugo van Bever
Main Clinical Question(s):	Which diagnostic tests and treatment modalities should not be used for the management of food allergy?
Population (age limit, inclusion criteria, excluded groups, special groups):	Children and adults with suspected food allergy
Interventions or Screening/Diagnostic Tools or Management Evaluated:	For Diagnosis: ALCAT – Antigen Leucocyte antibody test Applied Kinesiology Food specific IgG antibodies Intradermal skin tests Neutralization Provocation tests Bioresonance For Treatment Rotational Diet Bioresonance
Comparator (if applicable):	Standard testing and therapy
Outcomes (specify critical/primary vs secondary):	Unproven/disproven allergy testing and therapies listed here should not be used for diagnosis of food allergy
Publication Dates:	(2000) – 2023 There was no limit for earlier publications as some of these topics do not have recent publications.
Study Designs (specify inclusion/exclusion criteria):	Only English language articles considered
Search Strategy:	**Databases Searched:** PubMed, Embase, CINAHL **Grey Literature Sources?** No **Search Terms:** 'unproven allergy test' 'disproven allergy test'

	'unproven allergy treatment' 'disproven allergy treatment' 'unproven food allergy tests' <u>For each Diagnosis: AND 'Food allergy'</u> ALCAT Antigen Leucocyte antibody test Applied Kinesiology Food specific IgG antibodies Intradermal skin tests Neutralization Provocation tests Bioresonance Atopy patch test <u>For each Treatment AND 'Food Allergy'</u> Rotational Diet Bioresonance Neutralization Provocation tests
Search Outcomes:	**Number of studies:** Number of potential studies/reviews identified by database searches: Pubmed = 173 CINHAL = 14 EMBASE = 107 Number of additional potential studies identified through other sources: Nil Total number of studies screened once duplicates were removed: Not counted Number of studies shortlisted for full text review: 28 + 6 consensus/position papers Number of studies excluded after full text review: 18 Number and type of studies included: 9

Subgroup/Chapter Evidence Matrix

Evidence Matrix No.	*EM10-1*
Clinical/PICO Question:	Which diagnostic tests and treatment modalities should not be used for the management of food allergy?
Linked Recommendation Statements: *(Type = R or GPP) (Chapter no. statement no.)*	**GPP 10.1: Unproven/disproved tests should not be used in the diagnosis of food allergy. The tests include:** • **ALCAT - Antigen leucocyte antibody test** • **Food specific IgG antibodies** • **Intradermal skin tests** • **Atopy patch test** • **Neutralization provocation tests** • **Applied kinesiology** • **Bioresonance** • **Hair analysis** **GPP 10.2: Unproven/disproved modalities should not be used in the treatment of food allergy. These modalities include:** • **Neutralization Provocation tests** • **Bioresonance** • **Rotational Diet**
Rationale:	There is no scientific rationale or evidence base for the use of unproven/disproven tests listed. It can be dangerous (misdiagnosis and mistreatment) and an economically wasteful.

Evidence Summaries (include GRADE SoF Tables and EtD Frameworks if available): *(* see examples below; or this section can be a narrative summary.)*	**Other guidelines and consensus statements:** 1. **IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper.** Ansotegui IJ et al. WAOJ 2020.[1] Summary table of the unproven tests are listed below.

Test	Description	Scientific evidence	References
Specific IgG antibodies	Food specific IgG or IgG4 panels are available as diagnostic tool for food allergy (NOTE: healthy subjects can produce specific IgG and IgG4 to commonly eaten foods without being allergic).	The titer of specific IgG-antibodies does not correlate with oral food challenges. In children with proven milk allergy (positive oral challenge) no increase in specific IgG was detected. There is no evidence that IgG subclasses are a reliable diagnostic tool. Seventy-three patients were challenged in a double-blind manner to the IgG4 positive food, with no adverse reactions reported.	233-235
Cytotoxic test	This is an *in vitro* test in which food allergens (up to 180) are put into contact with whole blood. Any change in leukocytes' shape indicates a positive reaction.	In controlled conditions the reproducibility and diagnostic efficiency were largely insufficient.	236,237
Hair analysis	Nutritional deficiencies, detectable in hair (e.g., zinc, magnesium) are due to food allergy/intolerance.	Nine allergic patients to fish (positive challenge) and 9 healthy controls underwent the test. The test did not recognize allergic patients, and additional allergies were found without clinical significance. Hair samples of two teenagers were tested in 13 different laboratories, which reported different results.	238,239
Iridology	Anatomical/morphological changes in the iris may suggest systemic diseases.	A systematic review on iridology concluded that this test as a diagnostic tool is not supported by scientific evidence.	240
Kinesiology	The patient holds a vial with a specific food in one hand, while the examiner tests the muscular strength of the opposite arm by applying a light pressure. Food allergy/intolerance is indicated by a decreased muscular contraction when the offending substance is held.	According to two controlled studies the scientific evidence suggests that this diagnostic modality is not validated, and kinesiology as a diagnostic tool is no better than random guessing.	241,242
Electrodermal testing	The patient is placed in a circuit where a galvanometer measures skin conductance. Vials with food extract are sequentially inserted into the circuit. A positive response consists of a drop in conductance.	According to two double-blind placebo-controlled studies this method failed to distinguish between allergic and non-allergic patients, and between positive and negative tests. Poor reproducibility was always reported.	243,244

Table 19. Unproven diagnostic approaches

Volume 13, No. 2, February 2020

2. **Position Paper. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task force Report**. Stapel SO et al. Allergy 2008.[2]

In conclusion, food-specific IgG4 does not indicate (imminent) food allergy or intolerance, but rather a physiological response of the immune system after exposition to food components. Therefore, testing of IgG4 to foods is considered as irrelevant for the laboratory work-up of food allergy or intolerance and should not be performed in case of food-related complaints.

3. **Critical Issues in Food Allergy: A National Academies Consensus Report.** Sicherer AH et al. Pediatrics 2017:140:e20170194.[3]

The report concluded that a number of diagnostic modalities were not recommended for routine use, including food allergy patch testing (atopy patch test), measurement of total IgE, and the basophil activation test. Other tests were not recommended and were considered "unproven and non-standardized" for diagnosing food allergy. These tests include allergen-specific IgA, IgG, or IgG4; provocation neutralization; immune complexes; human leukocyte antigen screening; lymphocyte stimulation; facial thermography; gastric juice analysis; endoscopic allergen provocation; hair analysis; applied kinesiology; cytotoxic assays; electrodermal testing; mediator release assays; bioresonance; and iridology. (No references were provided for these statements)

4. **EAACI Guidelines on the Diagnosis of IgE-mediated Food Allergy.** Santos AF et al. Allergy 2023.[4]

Recommendation 5: In patients with suspected IgEmediated food allergy, the isolated use of IgG and IgG subclass tests and the other tests listed on Table S2 is recommended against in the diagnosis of IgE mediated food allergy (very low certainty of evidence, expert opinion).

Reason for recommendation: There are numerous tests purported to be of use in the diagnosis of IgE-mediated allergy; however, they lack evidence and rigorous validation to support their use (Table E2). Strength of recommendation: Despite the absence of specific studies addressing the diagnostic utility of these alternative tests (Table E2), the expert panel considered that there is no rationale and there are ethical issues around conducting such studies. Given the
risks involved in the use of these tests (see below), a strong recommendation against these tests was made.

Table E2. Examples of non-recommended tests for the diagnosis of IgE-mediated allergy.

Test type	**Background**	**Rationale for recommending against these tests.**
IgG and IgG subclass testing	IgG4 is made in response to tolerance and presence of these antibodies have relevance to frequency of ingestion and tolerance to foods. IgG, and IgG4 values have no role, when used in isolation, for the diagnosis of IgE mediated food allergy. The presence of these antibodies does not indicate disease.	Currently use should be limited to the research setting. There is no evidence to support the use of IgG in isolation for the diagnosis of IgE-mediated allergy and its widespread use carries the same risks as detailed above.
Antigen Leukocyte Cellular Antibody Testing	The ALCAT tests claims to identify immune response to various food antigens by analysing white blood cell changes as visualised under microscopy.	There is no/insufficient evidence to recommend these tests for the diagnosis of IgE-mediated allergy. The use of these testing modalities may carry significant risks including allergen exposure (false negative results) and unnecessary dietary restriction (false positive results). Unwarranted dietary avoidance may be associated with dietary compromise. The use of these tests may increase cost (to patients and/or health system) and reduced QOL. Dietary expansion may also be limited or delayed due to non-relevant diagnoses being made which may lead to a delay in dietary exposure to relevant allergens*.
Electrodermal testing	Electrodermal testing (typically using the VEGA machine) aims to diagnose food allergies by measuring the body's electrical resistance at acupuncture points. Possible allergens or toxins, or prospective treatments, are placed within a device called a honeycomb that is said to test the effects of that substance on the body. More recent devices use a computer that supposedly simulates the presence of test substances.	
Hair analysis	This test applies electromagnetic resonance to a hair sample for the diagnosis of food allergy.	
Applied Kinesiology	Applied Kinesiology claims to identify specific allergic sensitizations by measuring the patient's muscle strength with manual muscle testing in the	

	presence of a suspected allergen. Practitioners assert that pathologic conditions in individual organ systems are reflected in corresponding muscle groups (*viscerosomatic relationships*) maintained through energy fields communicating throughout the body.	
Iridology	Iridology claims to diagnose food allergy through the study of the patterns and colours on the iris.	
Gene analysis e.g. detecting polymorphisms	There is currently no genetic marker validated for the use to diagnose IgE mediated food allergy However, an increasing number of genes have been associated with the development of IgE mediated food allergy; these include, mutations and variant in the Filaggrin (*FLG*) gene, the association of *HLA-DR* and *–DQ* regions with food allergy, CNVs impacting *CTNNA3* and *RBFOX1*, DNA methylation that partially mediates SNP association at the *HLA-DR* and *–DQ* loci as well as other genes. There are also studies that have implicated differences in gut microbiota composition in food allergy.	

SRs/MAs:

Nil

(Other more recent literature or local data): Outlines of Studies Found

Study	Contributed to R/GPP	Study Type	Region/ Country	Total participants	Age group	Method	Outcome
Benson TE et al (J Allergy Clin Immunol 1976)[5]	In vitro cytotoxic testing	Double blind study	USA	9 patients 5 non-atopic patients 10 food antigens	Adults – age not specified	In vitro cytotoxicity test	No reproducibility of tests and no correlation with clinical symptoms
Teuber SS, Porch-Curren C. Curr Opin Allergy Clin Immunol 2003; 3(3): 217-221.[6]	In vitro cytotoxic testing	Review of literature	Germany				No supporting studies and lack scientific rational

	Niggeman n B, Grüber C.. Allergy 2004; 59(8): 806-808.[7]	In vitro cytotoxic testing	Review of literature	Germany	Review of 4 studies showing poor reproducibilit y of test			No reproducibility and not recommended
	Beyer K, Teuber SS. Curr Opin Allergy Clin Immunol 2005; 5(3): 261-266.[8]	In vitro cytotoxic testing	Review of literature	Germany	No new studies to support test			Not recommended
	Garrow JS .Brit Med J 1988;296: 1573-4.[9]	Applied Kinesiology and food allergy	Blinded study with allergen in bottles	UK	20 consecutive patients 11 allergens tested	Adults – age not specified		Our experience indicates that the kinesiology response is not reproducible under conditions of blind testing and therefore cannot be a reliable indicator of food allergy
	Ludtke R, Kunz B, See ber N, Ring J. Complem ent Ther Med 2001;9:14 1-145.[10]	Applied Kinesiology in diagnosing wasp venom allergy (not food allergy)	DBPC	Germany	7 patients with wasp venom allergy	adults	Clinical trial – DBPC. All examiner s used the anterior deltoid as indicator muscle.	No difference between placebo bottle and venom bottle group. The results suggest that the use of Health Kinesiology as a diagnostic tool is not more useful than random guessing.
	Kirsten Beyer, Suzanne S Teuber. Curr Opin Allergy Clin Immunol 2005;5:26 1-266.[8]	Applied Kinesiology and food allergy	Review on unproven tests, including Applied Kinesiolo gy					
	John M Kelso. J Allergy Clin Immunol Pract 2018;6:36 2-5.[11]	Applied Kinesiology and food allergy	Review on unproven tests, including Applied Kinesiolo gy					
	Klinkoski B, Leboeuf C. J Manipulati ve Physiol Ther 1990;13:1 0-194.[12]	Applied Kinesiology and food allergy	A review was undertak en of the type and scientific quality of 50 papers which had been					

			published between 1981 and 1987					
	Kvehaugen AS et al. BMC Gastroenterology 2018;18.[13]	IgG to food	Cross-sectional study	Norway	97 patients	Adults with IBD and morbid obesity with BMI ≥40kg/m^2 or BMI ≥35kg/m^2 with obesity complications	IgG antibodies against 44 common foods measured with an enzyme immunoassay from R Biopharm AG(RIDA SCREEN) form Germany	The measured food antibodies did not discriminate between those with and without perceived food intolerances adjusted for intake of the offending foods
	Savilahti EM et al. JACI 2010;125(6):1315-1321.e9.[14]	IgG to CM	118 CMA children from a birth cohort who were still allergic at 8 yrs (persisting CMA) compared to children who recovered from CMA by 3 yrs	USA	23 children with CMA (11 with persisting CMA and 12 with early recovery of CMA) 6 non-atopic controls	Children mean age 8.6yrs (range 8.1 -9.3 yrs)	Peptide microarray based immunoassay against casein and β-lactoglobulin for IgE and IgG was done	High IgG4 was found in children with early recovery from the CMA and is a marker of the development of tolerance
	Fox RA et al. J Allergy Clin Immunol. 1999; 103:907-11.[15]	Provocation neutralisation tests	Double blind, randomised study	Canada	132 patients experiencing anaphylaxis or disruptive symptoms	Age 9-78yrs	Intradermal testing with 13 foods, 9 chemicals and 4 placebo normal saline	70% of patients reported symptoms with normal saline. 67% of those who reacted to saline also reported reactions to allergens. Reactions by symptoms to foods, chemicals or saline showed a random pattern and should not be used as a basis for clinical intervention
	Sheldon L. Spector. Chest 1984;86(1):132-133.[16]	Provocation neutralisation tests	Position statement	USA	NA	NA	Review of studies	Recommend that it is not acceptable practice
	John M. Kelso. J Allergy Clin	Provocation neutralisation tests	Review article	USA	NA	NA	Review of studies	Recommend that it should not be used for diagnosis or

	Immunol Pract 2023;6(2): 362-365.[11]							therapeutic purposes
	Suzanne S. Teuber, Christina Porch. Curr Opin Allergy Clin Immunol 2003;3:217-221.[6]	Provocation neutralisation tests	Review article	USA	NA	NA	Review of studies	Not recommended and should be considered a disproved technique
	Suzanne S Teuber, Philip J Vogt. Am Allergy Asthma Immunol 1999;82:61-65.[17]	Provocation neutralisation tests	Case report	USA	Case report of a 68 yr old woman with mastocytosis treated with provocation neutralization technique who developed anaphylaxis from the treatment	NA	NA	Should not be used in patient with mastocytosis as at risk of anaphylaxis
	Jewett et al DL. New Engl J Med 1990;323: 429-33.[18]	Food Provocation test and neutralization for treatment by intradermal, and subcutaneous injections for diagnosis of food sensitivity	Double blind	USA	18 patients 2 physicians20 sessions (2 patients tested twice)	18-60 years old		For provocation testing and neutralization of such reactions: The frequency of positive responses to injected extracts appears to be the result of suggestion and chance.
	Lewith GT et al. BMJ 2001; 322:131-4.[19]	Electro-dermal testing		UK	15 patients with sensitization to cats and 15 controls without sensitization to cats 3 operators	18-65 years old	Double blind randomised block Each participant was tested with 6 items by each of 3 operators of the Vegatest electrodermal testing device in 3 separate sessions (a total of 54 tests per participant). For each participant the 54 items	Electrodermal testing cannot be used to diagnose environmental allergies.

								comprised 18 samples each of house dust mite, cat dander, and distilled water, though these were randomly allocated among the operators in each session. A research nurse sat with the participant and operator in all sessions to ensure blinding and adherence to the protocol and to record the outcome of each test.	
	Kenyon J, ed. Schiltach, Germany: Vega Grieshaber, 1981.[20]	Electrodermal testing	58 page manual describing the test also known as Vegatest						NA
	Herrmmann E et al Eur J Integrative Med 2011. European Journal of Integrative Medicine 3 (2011) e237–e244.[21]	MORA Bioresonance for treatment of allergies	Retrospective review of cases, neurological pain, infection, allergies **No Control Group**	Germany	for allergies-pollen allergy, asthma, food intolerance n= 169 (with zapper) and 407 (without)				For patients suffering from diseases in the frame of the internal-orthopaedic-neurological spectrum, as well as particular in the fields of allergies, pain and infections the MORA therapy has a high practical-therapeutic effectiveness
	Schoni MH et al Int Arch Allergy	Bioresonance for treatment of AD in children	double-blind parallel group	Switzerland	32 children 1.5-16.8 years				Considering the high costs and false promises caused by the

	Immunol 1997. doi: 10.1159/000237460.[22]		study in children admitted for long-lasting atopic eczema					promotors of this kind of therapy, it is concluded that Bioresonance has no place in the treatment of children with atopic dermatitis
	Sozmen SC et al. Pediatr Allergy Immunol 2015.[23]	Atopy Patch testing in children with food allergy	Cross-sectional Compare SPT vs patch testing in evaluation of cow milk and egg allergy. using OFC as the gold std dx	Italy	243 children	mean age 51 months		Sensitivity of **skin prick test** for both milk and egg was 92%, specificity 91%, positive predictive value 35%, and negative predictive value of 93%. Sensitivity, specificity, positive predictive value, and negative predictive value of **atopy patch test** for both milk and egg were 21%, 73%, 20%, and 74% **Conclusions**: Our study suggests that there is insufficient evidence for the routine use of atopy patch test for the evaluation of egg and cow's milk allergy.
	Chris A. Liacouras, Glen T. Furuta, Ikuo Hirano, Dan Atkins et al. J Allergy Clin Immunol 2011;128(1):3-20.[24]	Atopy patch test	Guideline recommendation	USA	Review of articles	NA	NA	Committee recommend that further studies are needed to evaluate role of atopy pact tests in guiding food avoidance
	James JMBA. Food allergy: current diagnostic methods and interpretation of results. In: Kemp	Intradermal testing	Textbook chapter. Does not recommend intradermal testing for food allergy	USA	NA	NA	NA	Not recommended

	SFLR, ed. Diagnostic Testing of Allergic Disease. New York: Marcel Dekker Inc.; 2000:199–215.[25]							
	Sampson HA. J Allergy Clin Immunol. 1999;103(6):981–989.[26]	Intradermal testing	Review article not recommending IDT as does not improve sensitivity and potential fatality	USA	NA	NA	NA	Not recommended
	Sethi TJ, et al. Lancet. 1987;1(8524):92–94.[27]	Hair Analysis	Cross sectional. 9 fish allergic and 9 non allergic volunteer controls	UK	18	adults	Blood tests and Hair analysis from each subject	The results gave clear evidence of diagnostic failure, lack of reproducibility, and a remarkably high number of reports suggesting that unsuspected allergies were present in our group of volunteers
	Barrett S. J Am Med Assoc. 1985;254(8):1041–1045.[28]	Hair Analysis	Comparative study between 13 laboratories	USA	2 healthy	adolescents	Hair analysis to 13 labs for mineral analysis	Non-reproducible results between laboratories.
	Rinkel H. J Pediatr 1948; 32:266–274.[29]	Rotational diet	Description of rotary diet with 3 case reports For eczema, rhinitis and headache	USA	3 case reports			No controls. Observational report only.

Certainty and Magnitude of Effects:	Not rated (GPP)
Risk/Harm vs Benefit Considerations:	There are no benefits to these tests and therapies.

<table>
<tr><td></td><td></td></tr>
<tr><td>Patient/ caregiver values</td><td>Stakeholder feedback (if available):
Patient stakeholders requested a special mention of NAET be listed as a specific intervention under applied kinesiology that is not a proven form of allergy diagnosis or treatment.</td></tr>
<tr><td>Resource, Cost Considerations:</td><td>These tests consume considerable resources and expenses to the patient, which is economically wasteful.</td></tr>
<tr><td>Equity

Acceptability

Feasibility</td><td>Stakeholder feedback (if available):</td></tr>
<tr><td>Workgroup Consensus Survey (RAND/UCLA):</td><td>GPP 10.1: Unproven/disproved tests should not be used in the diagnosis of food allergy. The tests include:
• ALCAT - Antigen leucocyte antibody test
• Food specific IgG antibodies
• Intradermal skin tests
• Atopy patch test
• Neutralization provocation tests
• Applied kinesiology
• Bioresonance
• Hair analysis
Number voted = 18; Number abstained = 1
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>3</td><td>9</td><td>17%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table>
GPP 10.2 Unproven/disproved modalities should not be used in the treatment of food allergy. These modalities include:
• Neutralization Provocation tests
• Bioresonance
• Rotational Diet
Number voted = 19; Number abstained = 0
<table>
<tr><th>Lowest score</th><th>Highest score</th><th>Coefficient of Variation</th><th>Median Score</th><th>Interpercentile Range (IPR)</th><th>Interpercentile Range Adjusted for Symmetry (IPRAS)</th><th>Overall Consensus</th></tr>
<tr><td>3</td><td>9</td><td>16%</td><td>9</td><td>0.0</td><td>8.4</td><td>No Disagreement</td></tr>
</table></td></tr>
</table>

External Review Feedback:	
Public Consultation:	Patient stakeholders requested a special mention of NAET be listed as a specific intervention under applied kinesiology that is not a proven form of allergy diagnosis or treatment.

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