Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-282-z Erdnussprotein als entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse)

Stand: Januar 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Erdnussprotein als entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse) (AR 101)
zur Behandlung der Erdnussallergie

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V im Anwendungsgebiet: - Erdnussprotein als entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse) (Erdnussallergie, ≥ 4 Jahre) (Beschluss vom 07.04.2022)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Erdnussprotein als entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse) V01AA08 Palforzia®	Palforzia ist zur Behandlung von Patienten im Alter von 1 bis 17 Jahren mit bestätigter Diagnose einer Erdnussallergie indiziert. Die Anwendung von Palforzia kann bei Patienten, die 18 Jahre und älter sind, fortgeführt werden. Die Anwendung von Palforzia hat in Verbindung mit einer erdnussfreien Ernährung zu erfolgen.
Allergen-Extrakte	
Erdnussprotein als entfettetes Pulver von Arachis ypogaea L., semen (Erdnüsse) V01AA08 Palforzia®	Palforzia ist zur Behandlung von Patienten im Alter von 4 bis 17 Jahren mit bestätigter Diagnose einer Erdnussallergie indiziert. Die Anwendung von Palforzia kann bei Patienten, die 18 Jahre und älter sind, fortgeführt werden. Die Anwendung von Palforzia hat in Verbindung mit einer erdnussfreien Ernährung zu erfolgen. [Stand FI: 08/2022]
Adrenalin-Präparate	
Epinephrin C01CA24 z.B. FASTJEKT® Junior und FASTJEKT®	FASTJEKT Junior/ FASTJEKT ist ein Medikament zur Notfallbehandlung einer schweren allergischen Reaktion (Anaphylaxie) auf z. B. Insektenstiche oder -bisse, **Nahrungsmittel**, Medikamente oder andere Allergene und bei idiopathischer oder durch Anstrengung ausgelöster Anaphylaxie. FASTJEKT Junior/ FASTJEKT Autoinjektoren sind zur unmittelbaren Anwendung bei Patienten, die ein erhöhtes Anaphylaxie-Risiko aufweisen, vorgesehen, einschließlich Patienten, bei denen bereits früher eine anaphylaktische Reaktion aufgetreten ist. FASTJEKT stellt eine Notfallmaßnahme dar und ist nicht als Ersatz für eine anschließende ärztliche Versorgung gedacht. FASTJEKT Junior wird angewendet bei Kindern von 7,5 kg bis 25 kg Körpergewicht/ FASTJEKT wird angewendet bei Erwachsenen und Kindern ab 25 kg Körpergewicht. [Stand FI FASTJEKT® Junior/FASTJEKT: 08/2024]
systemische Anthistaminika	
Dimetiden R06AB03 Fenistil®, Histakut	Zur symptomatischen Akutbehandlung allergischer Erkrankungen, wie z. B. juckende Dermatosen, allergischer Schnupfen, **Nahrungs- und Arzneimittelallergien**, Urtikaria (Nesselsucht), Neurodermitis (endogenes Ekzem), Quincke-Ödem (angioneurotisches Ödem). Bei anaphylaktoiden Reaktionen sowie als Adjuvans bei anaphylaktischem Schock. Zur Prämedikation in Kombination mit einem H2-Rezeptor-Antagonisten zur Vermeidung

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	von durch Histaminfreisetzung ausgelösten klinischen Reaktionen wie z.B. vor Narkosen und vor parenteraler Gabe von Röntgenkontrastmitteln oder Plasmasubstituten [Stand FI Histakut: 02/2018]
systemische Glucocortikoide	
Prednisolon H02AB07 generisch	Okrido® dient zur Behandlung von Erkrankungen, die, je nach klinischem Bild und Schweregrad, eine systemische Therapie mit Glucocorticoiden erfordern: - Allergie und Anaphylaxie: Schwere allergische und anaphylaktische Reaktionen, Asthma bronchiale [Stand FI Okrido: 05/2021]
Prednison H02AB06 generisch	- Anaphylaktischer Schock (nach primärer Epinephrininjektion) Solu-Decortin H wird angewendet bei Erwachsenen, Kindern und Säuglingen [Stand FI Solu-Decortin® H: 02/2022]
Sonstige antiallergische Wirkstoffe	
Cromoglizinsäure A07EB01 Colimune Sachets	Nahrungsmittelallergien, bei denen eine Allergenkarenz nicht möglich ist. Hinweis: Colimune Sachets 100 mg und Colimune Sachets 200 mg sind nicht zur Behandlung akuter Anfälle geeignet [Stand FI: 03/2015]

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-282-z (Erdnussprotein als entfettetes Pulver von Arachis hypogaea L., semen (Erdnüsse))

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	26. November 2024

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Abkürzungsverzeichnis

AIT	Allergen-specific immunotherapy
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCT	Controlled clinical trial
DS	Desensitization
EAACI	European Academy of Allergy and Clinical Immunology
ECRI	ECRI Guidelines Trust
EPIT	Epicutaneous immunotherapy
FA	Food allergy
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IT	Immunotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OFC	Oral food challenge
OIT	Oral Immunotherapy
OR	Odds Ratio
RR	Relatives Risiko
SCIT	Subcutaneous immunotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SLIT	Sublingual immunotherapy
SU	Sustained unresponsiveness
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Personen im Alter von 1 bis 3 Jahren mit bestätigter Diagnose einer Erdnussallergie.

Hinweis zur Synopse: ,,Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt''.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Nahrungsmittelallergie von Erdnüssen* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 30.08.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 416 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurde keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Riggioni C et al., 2024 [5].

Immunotherapy and biologics in the management of IgE-mediated food allergy: Systematic review and meta-analyses of efficacy and safety

Fragestellung

The European Academy of Allergy and Clinical Immunology (EAACI) is updating its Guidelines on the diagnosis and treatment of IgE-mediated FA, last published in 2014 and 2017. The objective of this systematic review with meta-analysis was to inform the development of clinical recommendations on the treatment of IgE-mediated FA with biologics and/or IT.

Methodik

Population:

- all human studies in children, adolescents, and adults with IgE-mediated FA

Intervention:

- IT or biologics, alone or in combination

Komparator:

- Placebo
- standard or care (allergen avoidance)

Endpunkt:

- efficacy (desensitization, SU/remission)

Recherche/Suchzeitraum:

- Medline (via PubMed), Embase, and Cochrane Library up to April 2022

Qualitätsbewertung der Studien:

- Risk of Bias (RoB) tool for RCTs
- Cochrane ACROBAT-NRS tool for CCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 111 studies (32 RCT) on IT for FA
- 41 studies (RCT and CCT) on peanut allergy

Charakteristika der Population/Studien:

Study	Design	Duration (weeks)	Food	*n*	Children	Adults	% males	Age[a]

Trials of immunotherapy								
Anagnostou, 2014a	Phase 2b	26	Peanut	85	85	–	85	12
Anagnostou, 2014	Phase 2b	24	Peanut	99	99	–	71	11
Bird, 2018	Phase 2b	34	Peanut	56	?	?	66	7.5
Chinthrajah, 2019b	Phase 2b	52	Peanut	120	120	–	68	11
Fauquert, 2018	Phase 2b	37	Peanut	30	30	–	30	14.5
Howe, 2019	Phase 2b	24	Peanut	50	50	–	72	10.8
Jones, 2017	Phase 2b	52	Peanut	74	?	?	62	4.1–20.3
Sampson, 2017	Phase 2b	104	Peanut	221	186	–	93	11
Vickery, 2017	Phase 2b	42	Peanut	38	38	–	68	2.3
Blumchen, 2019	Phase 3a	64	Peanut	62	62	–	61	7
Burks, 2015	Phase 3a	172	Peanut	40	40	–	68	16.0
Fleischer, 2013	Phase 3a	68	Peanut	40	?	?	68	15.0
Kim, 2011	Phase 3a	52	Peanut	18	18	–	67	5.2
Kukkonen, 2016	Phase 3a	32	Peanut	60	60	–	58	8.4
O'Hourihane, 2020	Phase 3a	40	Peanut	175	175	–	54	9.1
Varshney, 2011	Phase 3a	52	Peanut	28	28	–	64	5.75
Vickery, 2018	Phase 3a	24	Peanut	496	496	–	57	10
Fleischer, 2019	Phase 3b	52	Peanut	356	356	–	61	7
Jones, 2022	Phase 3b	160	Peanut	146	146	–	68	3.3
NCT02304991	Phase 3b	156	Peanut	50	50	–	56	2.2
Pongracic, 2021	Phase 3b	24	Peanut	393	393	–	58	7.2

Qualität der Studien:

- In the IT studies, six studies had low risk of bias[35,44,49,66,126] and the rest had moderate, unclear, or high risk of bias, the latter being the most common (siehe: Forrest Plots unten).

Studienergebnisse:

- Desensitization: in peanut allergy, OIT showed a RR 11.94 [1.76, 80.84] versus avoidance or placebo

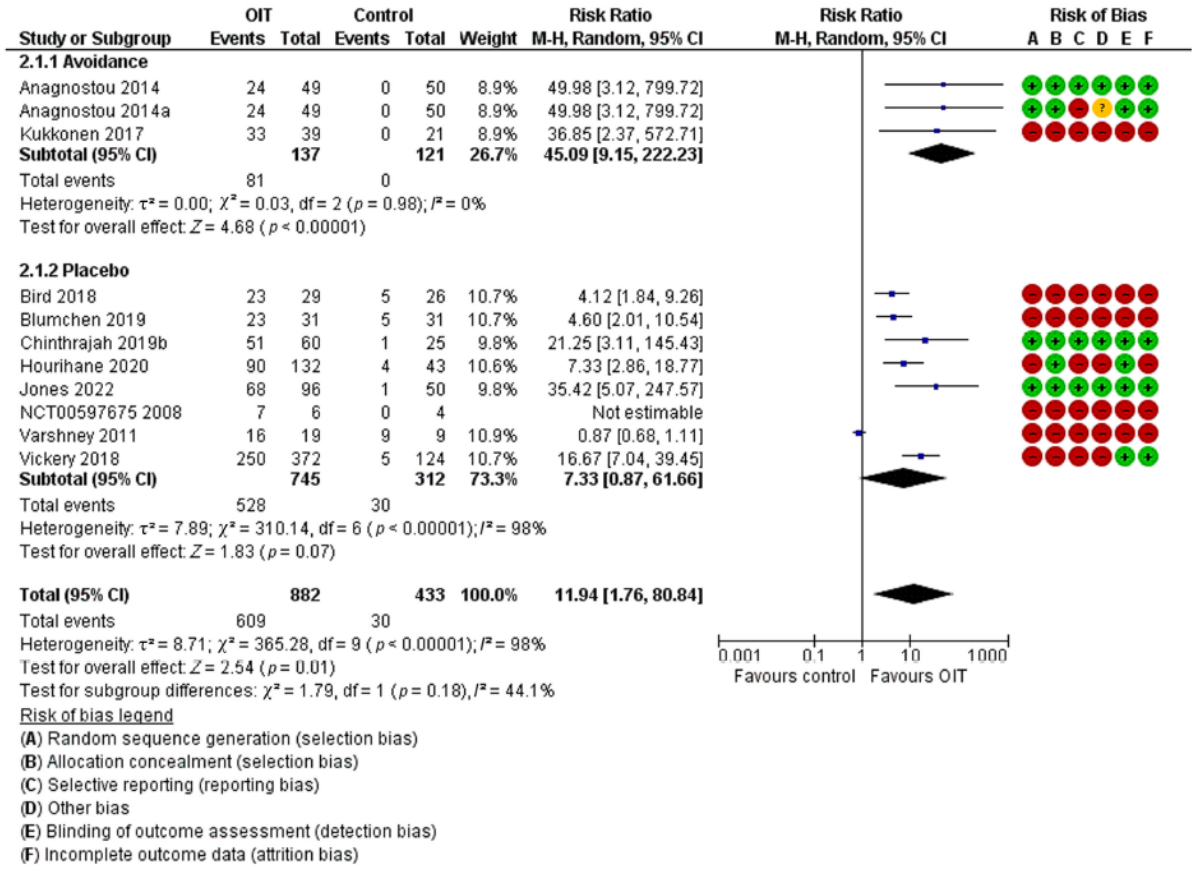


FIGURE 5 Metanalysis of desensitization induced by OIT in peanut allergy.

- For Peanut OIT taking into consideration only low risk of bias studies, the RR for desensitization is 49.98 (CI 7.04–355.2) versus avoidance and 27.36 (CI 6.97–107.38) versus placebo

Figure S12: Sensitivity analysis considering only low risk of bias studies: Peanut OIT in IgE mediated food allergy low risk of bias studies

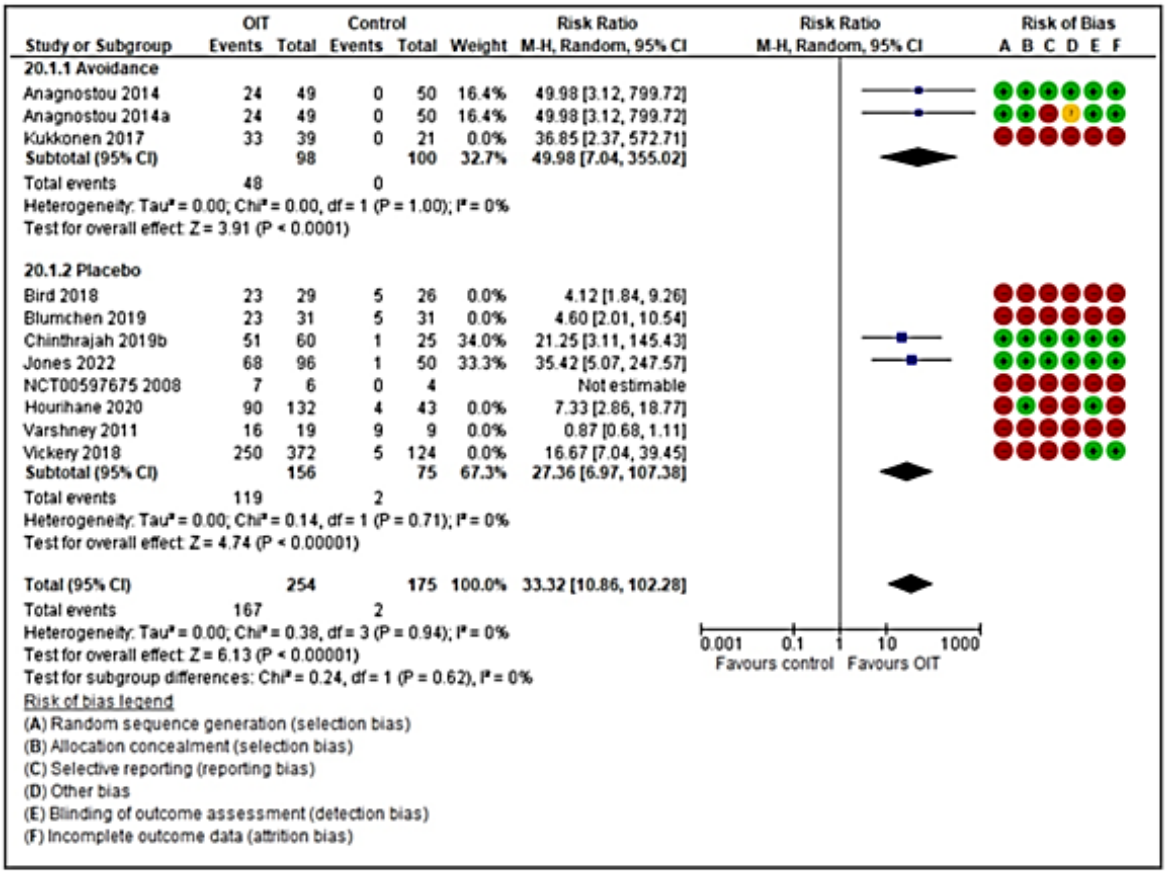


Figure S4: Oral immunotherapy to peanut sub analysis by age groups: Peanut OIT 12 to 17 years

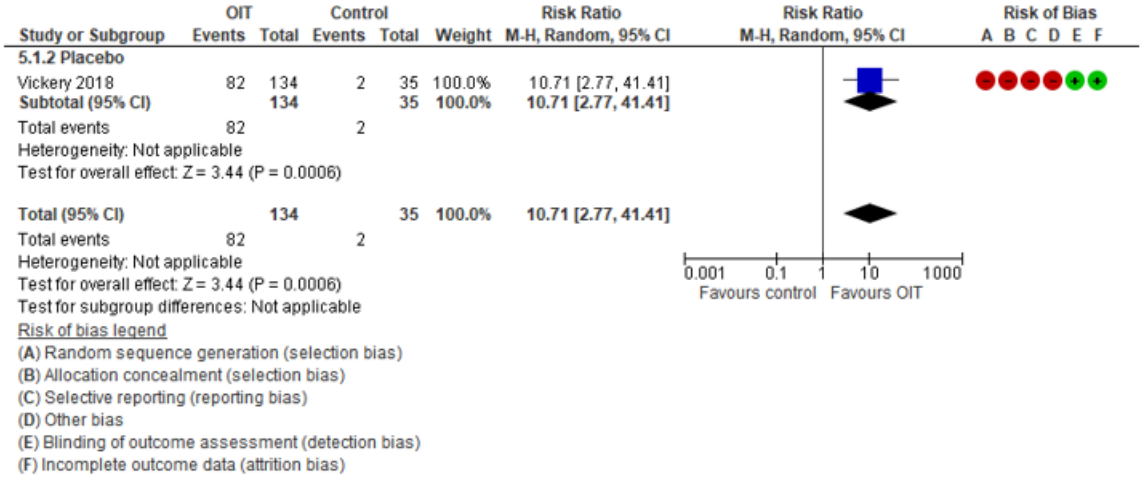
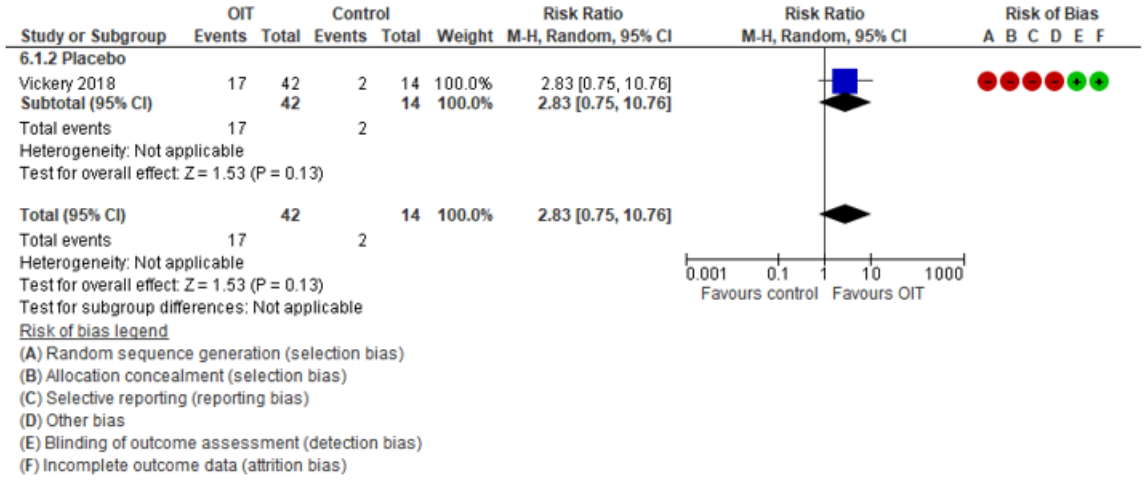


Figure S5: Oral immunotherapy to peanut sub analysis by age groups: **Peanut OIT in Adults**



Anmerkung/Fazit der Autoren

Overall, despite the heterogeneity and high RoB of most studies, omalizumab and IT showed efficacy in terms of desensitization to the culprit food after treatment compared with avoidance or placebo. The protective effect was higher for OIT than other modalities of IT, namely EPIT and SLIT, where evidence was available, and higher for peanut allergy than for cow's milk or egg allergies.

There seem to be differences in efficacy of OIT to the different foods addressed in this SR with peanut OIT seeming more effective than milk or egg OIT; however, there are no head-to-head studies directly comparing these therapies.

Kommentare zum Review

- RCT und CCT eingeschlossen
- Nur eine Studie (RCT) für Altersgruppe (Vickery 2018; siehe Figure S4; S5)
- "Vickery 2018" in Riggioni et al. 2024 entspricht "The Palisade Group 2019" in Lodge et al. 2023
- SR ist Grundlage für Aktualisierung der European Academy of Allergy and Clinical Immunology (EAACI) LL (in Bearbeitung)
- Studiendauer heterogen (6 - 260 Wochen)

Lodge CL et al., 2023 [3].

Efficacy and safety of oral immunotherapy for peanut, cow's milk, and hen's egg allergy: A systematic review of randomized controlled trials

Fragestellung

We aimed to review the current best evidence from RCTs for the effectiveness of peanut, egg, and cow's milk OIT on desensitization and remission and adverse allergic events.

Methodik

Population:

- OFC-proven IgE mediated food allergy to peanut, egg, or milk.

Intervention:

- OIT (roasted peanut flour)

Komparator:

- Placebo
- Food avoidance

Endpunkte:

- Desensitization (DS) is defined as increase in reaction threshold for allergens.
- Sustained Unresponsiveness (SU) is defined as a lack of clinical reactivity maintained for at least 2 weeks despite allergen discontinuation.
- Adverse reactions are any reported adverse reactions in either placebo or treatment groups.

Recherche/Suchzeitraum:

- PubMed, EMBASE and Cochrane databases searched from inception for peer-reviewed English publications (Tables S1–S3). Last search Oct 2022.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 RCTS; 8 davon peanut allergy (n=1414)

Charakteristika der Population/Studien:

- The eight peanut RCTs[11,26–32] included 1414 participants in total with numbers varying between 5629 and 55532 participants. One study was conducted in the UK,[28] one in Germany, [30] three in the USA,[11,27,29] two in multi-country sites[31,32] (Europe and US) and one in Australia (Table 1).[26] Participant age ranged from a mean of 3.127–12.4 years.[28] Age inclusion criteria varied with four studies[28,30,31] including participants up to 16 or 17 years and two[11,29,32] up to 21 years. Four studies[26,27,29,31] excluded children with previous life threatening or severe anaphylaxis and seven studies[11,26–31] excluded children with severe or poorly controlled asthma. Importantly, five of the studies[11,26,29,30,32] provided detailed information on the reasons screened participants were not included in the studies. Of the 1495 people screened in these 5 studies, 205 (14%) were excluded because they were tolerant of peanut on the initial DBPCFC.
- Siehe Anhang

Qualität der Studien:

Author, year	Randomization Process	Deviations from the intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias	Support judgement
Akashi et al. 2017	Some concerns	Low	Low	Low	Low	Some concerns	-Cumulative dose egg tolerated at baseline higher in intervention group (600mg vs 200 mg)
Anagnostou et al. 2014	Low	Low	Low	Low	Low	Low	-
Battista-panjo et al. 2010	Some concerns	Low	Low	Low	Low	Some concerns	There is no information for randomized sequence
Bird et al. 2017	Low	Low	Low	Low	Low	Low	-
Blumchen et al. 2018	Low	Low	Low	Low	Low	Low	-
Caminiti et al. 2015	Some concerns	Low	Low	Low	Low	Some concerns	There is no information for randomized sequence
Chinthrajah et al 2019	Low	Low	Low	Low	Low	Low	-
Dantzner et al 2022	Low	Low	Low	Low	Low	Low	
Della Iacono et al. 2013	Low	Low	Low	Low	Low	Low	-
Escudero et al. 2015	Low	Low	Low	Low	Low	Low	-
Itoh-Nagato et al 2018	Low	Low	Low	Low	Low	Low	-
Hourihane et al 2020	Low	Low	Low	Low	Low	Low	-
Jones et al 2022	Low	Low	Low	Low	Low	Low	
Loke et al 2022	Low	Low	Low	Low	Low	Low	
Maeda et al. 2020	Low	Low	Low	Low	Low	Low	-
Martin-munoz et al. 2019	Low	High	High	Low	Low	High	-Study has high proportion of participants lost to follow-up or refused to continue.
Palisade group 2018	Low	Low	Low	Low	Low	Low	-
Skripak et al. 2008	Some concerns	Low	Low	Low	Low	Some concerns	There is no information for randomized sequence.
Takahashi et al 2017	Some concerns	Low	Low	Low	Low	Some concerns	There is no information for randomized sequence.

Studienergebnisse:

- Meta-analysis of eight OIT trials demonstrated increased DS in the intervention group: RR = 11.32; 95% CI 5.93–21.60, I^2 48.9%

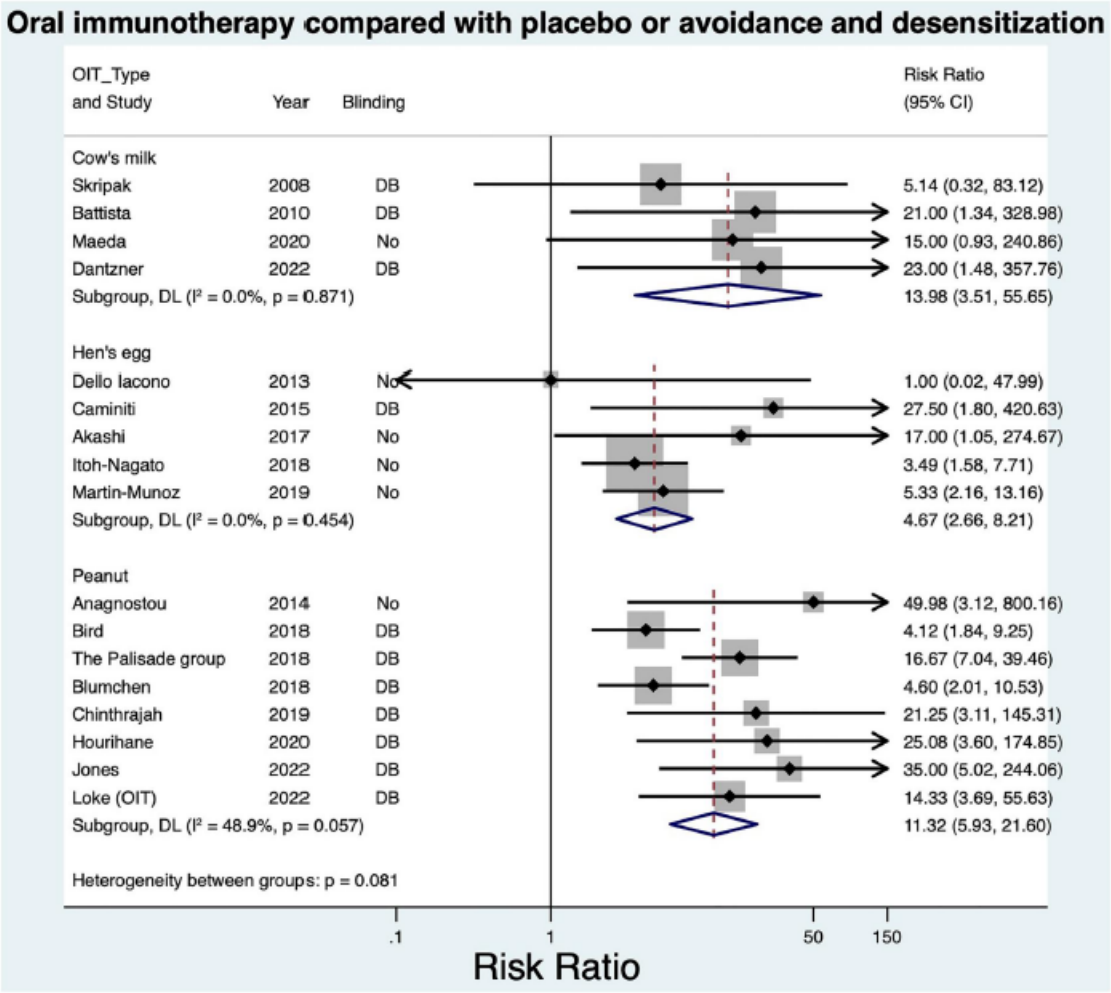


FIGURE 2 Meta-analysis: Oral immunotherapy compared with placebo or avoidance and desensitization.

- Meta-analysis of three OIT trials demonstrated increased SU in the intervention group: RR = 7.74; 95% CI 2.90–20.69, I^2 0%

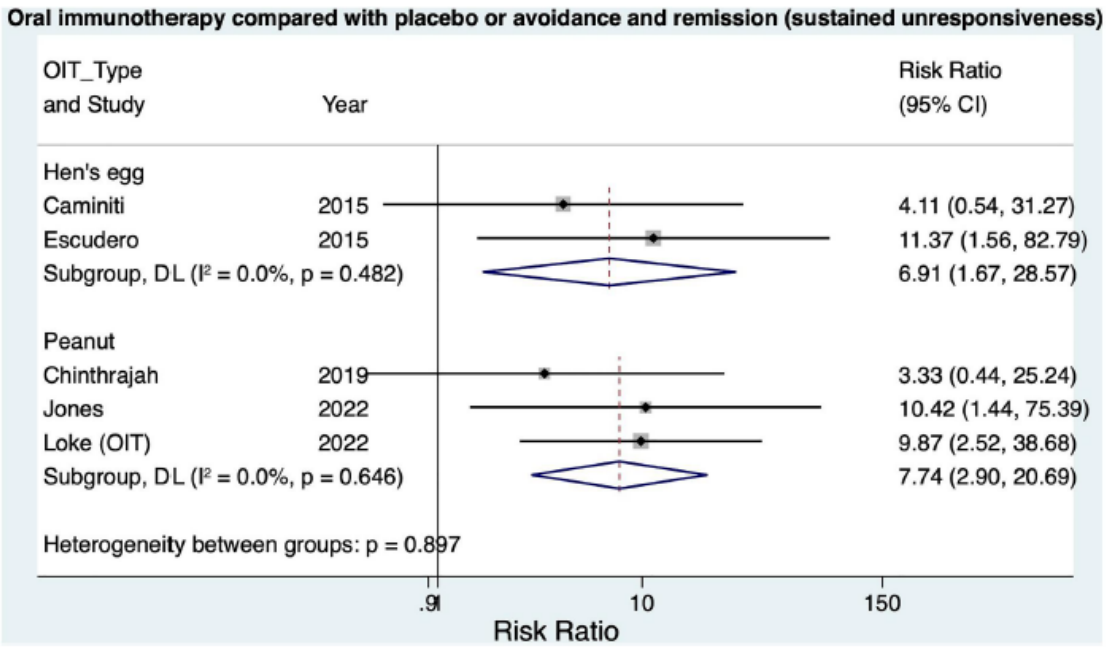


FIGURE 3 Meta-analysis: Oral immunotherapy compared with placebo or avoidance and remission (sustained unresponsiveness (SU)).

- Meta-analysis of any child having an allergic event from the seven double blind placebo-controlled studies found a risk ratio of any allergic reaction for the intervention (compared to placebo) of 1.11; 95% CI 1.03, 1.20; however, heterogeneity was moderate (I^2 = 63.8%).

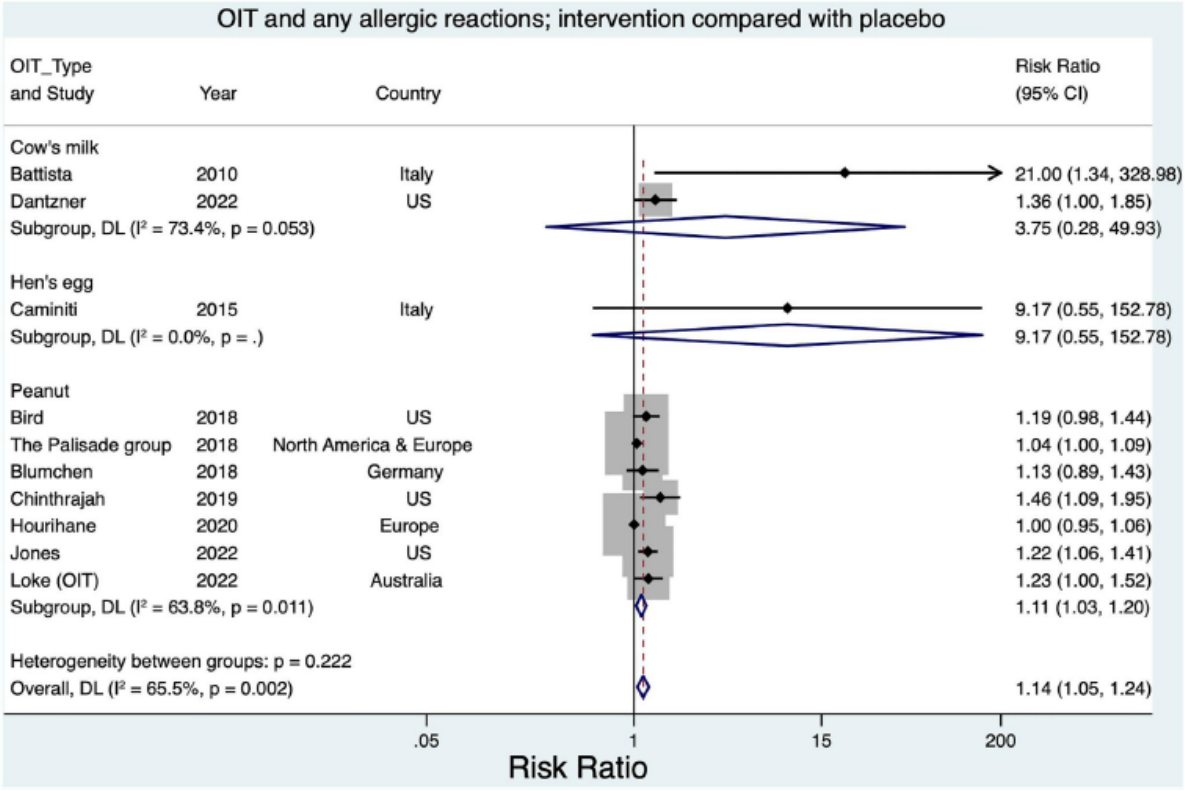


FIGURE 4 Oral immunotherapy and any allergic reactions.

- NNT (adrenaline use) = 1/(2.96–1) ◆ 9/366 = 20.75. Therefore, based on the included studies and regimens, 21 children need to be treated with peanut OIT for one to require at least one dose of adrenaline.

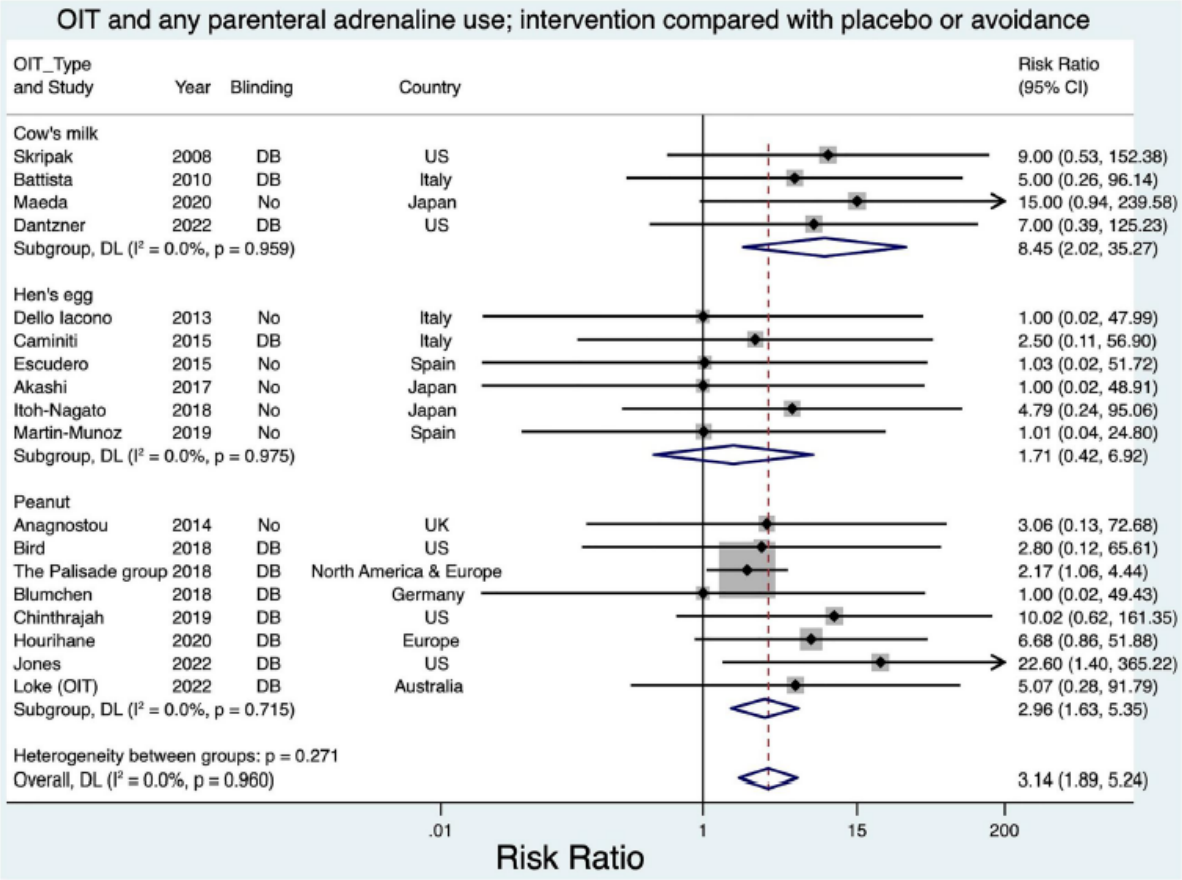


FIGURE 5 Oral immunotherapy and adrenaline use.

Anmerkung/Fazit der Autoren

Reviewing the most robustly designed RCTs, published in English, we found that OIT for peanut, egg, and milk had good efficacy for desensitization and some efficacy for remission. Allergic events were frequent in intervention groups with most being mild to moderate. NNT for adrenaline use was 1 in 20 people for peanut OIT.

Kommentare zum Review

- Nur RCTs eingeschlossen
- Studiendauer heterogen (4-24 Monate)
- Einschlusskriterien für das Alter unterschiedlich (bis 16, 17 und 21 Jahre); nur wenige Erwachsene (18+)
- In 4/8 RCTs wurden Kinder mit vorheriger lebensbedrohlicher oder schwerer Anaphylaxie ausgeschlossen
- "The Palisade Group 2019" in Lodge et al. 2023 entspricht "Vickery 2018" in Riggioni et al. 2024

3.3 Leitlinien

Muraro A et al., 2022 [4].

Global Allergy and Asthma European Network (GA²LEN)

Managing food allergy: GA²LEN guideline 2022

Zielsetzung/Fragestellung

Until recently, people with food allergy were just advised to avoid the food and, for some IgE-mediated allergy, to carry adrenaline at all times in case of anaphylaxis. Today there are additional options available. The guideline sets out the Global Allergy and Asthma European Network's (GA2LEN) recommendations for managing food allergy, based on the latest evidence and expert consensus. Recommendations relate to both IgE and non-IgE mediated food allergy, unless otherwise stated.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

- 2 published systematic reviews on IT and biological therapies [1,2]
- IT SR: CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature), Cochrane Library, Embase (OVID), ISI Web of Science (Thomson Web of Knowledge), MEDLINE (OVID), Scopus from database beginning to 30 April 2021

GoR

Strength and direction	Wording	What does this mean?
Strong recommendation **for** an intervention	"The GA²LEN Task Force **recommends** …"	• We are confident that the benefits outweigh the harms. • Practice: Most people in this situation should be offered the intervention and would likely want it. • Policy: The recommendation can be adopted as a policy in most situations.
Conditional recommendation **for** an intervention	"The GA²LEN Task Force **suggests** …"	• The benefits probably outweigh the harms but we are not fully confident of the size of the effect or the effect may differ in some people. • Practice: Different choices will be appropriate for different people. Clinicians could help each person make decisions consistent with their preferences. • Policy: Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders.
Conditional recommendation against an intervention	"The GA²LEN Task Force **suggests** against …"	• The harms probably outweigh the benefits, but we are not fully confident or the effect may differ in some people • Practice: Different choices will be appropriate for different people. Clinicians could help each person make decisions consistent with their preferences. • Policy: Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders.
Strong recommendation against an intervention	"The GA²LEN Task Force **recommends** against …"	• We are confident that the harms outweigh the benefits. Most people would not want this. • Practice: Most people in this situation should not use this intervention. • Policy: The recommendation can be adopted as a policy in most situations.
No recommendation	"The GA²LEN Task Force makes no recommendation for or against using …"	• There is not sufficient evidence or we are not confident to make a recommendation based on mixed evidence and experience. • Practice: Different choices will be appropriate for different people. Clinicians could help each person make decisions consistent with their preferences. • Policy: Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders.

Table 1. Wording conventions used in recommendations in this guideline.

Sonstige methodische Hinweise

- Infants: aged 0–1 year; Children: aged 1–17 years; Adolescents: aged 12–17 years; Adults: aged 18 years or older

Empfehlungen

Topic	Certainty of evidence
Dietary interventions	
The GA²LEN Task Force makes no recommendation for or against any **prebiotics, probiotics or synbiotics** that have been evaluated so far for managing food allergy, whether used as a supplement or added to infant formula.	Very low
The GA²LEN Task Force makes no recommendation for or against **hydrolyzed plant-based formulas** including rice hydrolysates that have been evaluated so far for managing food allergy in infancy.	Very low
Allergen immunotherapy	
The GA²LEN Task Force makes no recommendation for or against offering: • **oral immunotherapy to adults** with IgE-mediated peanut, cow's milk or hen's egg allergy, • **epicutaneous immunotherapy to adolescents or adults** with IgE-mediated peanut allergy or to people of any age with IgE-mediated cow's milk or hen's egg allergy • **subcutaneous immunotherapy or sublingual immunotherapy** to people of any age with IgE-mediated peanut, cow's milk or hen's egg allergy • immunotherapy by any route for **other food allergies**	Very low
Biological therapies	
The GA²LEN Task Force makes no recommendation for or against offering **etokimab** for treating food allergy.	Very low
The GA²LEN Task Force makes no recommendation for or against offering **omalizumab** for treating food allergy, alone or in combination with immunotherapy.	Very low

Table 3. Areas where guideline makes no recommendation for or against. *Note: The certainty of evidence refers to how confident we are that the available evidence represents the true effect of the intervention. See Box 1 for definitions.*

TABLE S3.4: JUSTIFICATION FOR NOT RECOMMENDING FOR OR AGAINST OTHER IMMUNOTHERAPY

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for adults with IgE-mediated peanut allergy	We make no recommendation for or against OIT in adults with hen's egg allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	There was insufficient evidence available to weigh up benefits versus hams. The intervention could be considered in adults with food allergy where the likely benefit outweighs potential adverse effects.	The burden of the treatment probably is likely to be higher in adults because of the high number of visits to the allergy centre for dosing clashing against working duties. Additionally, adults are likely to have adapted to their peanut allergy such that its impact is minimised.	A pharmaceutical product is licensed in Europe and the United States for children. The same comments as in Table S3.1 related to children apply here.

Recommendation	Certainty of evidence
Dietary interventions	
The GA²LEN Task Force **suggests** that people with a documented food allergy **avoid the offending food** unless their individual circumstances and risks allow for some consumption, as advised by their healthcare professional. We suggest that most breastfeeding mothers whose infants have a food allergy do not need to avoid the offending food themselves, though in rare cases this might be considered.	Low
The GA²LEN Task Force **suggests** that most infants (aged 0–1 years) diagnosed with cow's milk allergy who need a breastmilk alternative use a **documented hypoallergenic extensively hydrolyzed cow's milk formula**, or an **amino-acid based formula** if better tolerated or more appropriate. We suggest against partially hydrolyzed cow's milk formula, mammalian milks and, also for infants under 6 months, against soy-based formula.	Moderate
Allergen immunotherapy	
The GA²LEN Task Force **recommends** offering **peanut oral immunotherapy** under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.	High
The GA²LEN Task Force **suggests** offering **peanut epicutaneous immunotherapy** under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4–11 years with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.	Moderate
The GA²LEN Task Force **suggests** offering **oral immunotherapy** under specialist supervision with standardized evidence-based protocols using food products to selected children (aged 4+ years) with clinically diagnosed persistent severe IgE-mediated **hen's egg or cow's milk allergy** to increase the amount of allergen tolerated while on therapy.	Moderate

Table 2. Guideline recommendations. *Note: The certainty of evidence refers to how confident we are that the available evidence represents the true effect of the intervention. See Box 1 for definitions. Further information including rationale and practical consideration is available in the text.*

TABLE S3.1: JUSTIFICATION OF RECOMMENDATION FOR PEANUT ORAL IMMUNOTHERAPY

The GA2LEN Task Force recommends offering peanut oral immunotherapy under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT in children with peanut allergy	We have high certainty evidence that children with IgE-mediated allergy to peanuts tolerate significantly more peanut while on therapy (RR 6.50, 95%CI 3.31-12.75, N=888) (desensitization).[97] The number needed to treat to achieve 1 child tolerating 300mg or 1000mg peanut protein as a single dose while on therapy was 2. There is low certainty evidence that this benefit persists after therapy discontinues (RR 8.75, 1.24-61.57, n=85). The impact on quality of life is unclear due to very low certainty evidence.	Overall, the benefits of OIT for peanut allergy outweigh the risks in selected children. There was no difference in adverse events between the OIT and control group (RR 1.07, 95% CI 0.99 to 1.16, n=953). Severe reactions were rare and not significantly different between OIT and control groups (RR 1.55, 95%CI 0.69 to 3.48, n=950).[97] However, some studies have excluded extremely allergic individuals so safety in these individuals is unclear A systematic review meta-analysed the different quality of life outcomes used in OIT studies. They found a -0.56 (95%CI -0.92 to -0.20) standardised mean difference between active and control, which means that immunotherapy may improve quality of life.[98] Eosinophilic esophagitis has been reported in relation to OIT, although its prevalence is unknown due to a high rate of transient abdominal symptoms compatible with EoE[99,100] but endoscopic confirmation lacking in most of these individuals.	OIT needs a considerable investment in time from the family. It may also be associated with local adverse effects so some families may prefer to avoid peanut instead. Adherence is important and should be considered especially with adolescents. However, desensitization may be valuable to people with food allergy as it reduces the chance of experiencing a reaction with packaged foodstuffs containing peanut accidentally.[105] Although OIT is associated with adverse events, care givers report that these events are "expected" during the treatment and families are well trained and closely monitored to deal with them better than with the uncertainty of unexpected reactions of full avoidance.[106] However there is likely a need for lifetime therapy given the low rate of sustained unresponsiveness.[97]	A pharmaceutical product has been licensed in Europe and the United States. Many other groups have used non-pharmaceutical formulations.[103,104,107] In some EU countries only licensed products will be allowed . This is based on the consideration that they have been developed according to Good manufacturing practice (GMP) for ensuring consistency of allergen content and biologic potency across the doses and product batches. Treatment is usually given daily, for years, and this represents a significant burden, which may result in lack of adherence and subsequent loss of protection and rise in accidental reactions.[105-109] In the mid/long term, the taste of the treatment may become an issue.[107] Treatment needs to be provided in an appropriate setting by experienced doctors but these centres are not equally distributed,

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
		The baseline reactivity threshold of people included in most trials is very low, ranging from 10mg[101] up to 122mg[102] of peanut protein. It is unclear whether the risk/benefit balance remains the same in people with higher reactivity thresholds Given the logistics around peanut oral immunotherapy and the potential for reactions, we consider that it is indicated in children with severe peanut allergy. This includes those with a substantial risk of severe reactions and those with substantially impaired quality of life. This has to be a shared judgement between the healthcare professional and family. There is some evidence that OIT may reduce the severity of the reactions in addition to increasing the threshold for reaction.[101,103,104]		leading to inequity in access to treatment.[110] Some precautions when administering the treatment are significantly limiting: avoiding exercise/hot shower, infections, intake of NSAIDs, fasting or other cofactors.[111] One US health economics study estimated a high incremental cost effectiveness ratio of $255 431 for an 80 year time horizon based on societal costs, but this has not been replicated.[112]

Allergen Immunotherapy

The immunological pathways underlying IgEmediated food allergy can potentially be targeted with allergen immunotherapy. This involves carefully-controlled exposure using increasing doses of food allergens, which can modify the immune response and increase the threshold at which they react.[26] Immunotherapy may be administered via the oral, epicutaneous, sublingual or subcutaneous routes.

The GA2LEN Task Force recommends offering peanut oral immunotherapy under specialist supervision with standardized evidence-based protocols using peanut products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4+ years) with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

The GA2LEN Task Force suggests offering peanut epicutaneous immunotherapy under specialist supervision using licensed pharmaceutical products if they become available to selected children aged 4–11 years with clinically diagnosed, severe, IgE-mediated, peanut allergy to increase the amount of peanut tolerated while on therapy.

The GA2LEN Task Force suggests offering oral allergen immunotherapy under specialist supervision with standardized evidence-based protocols using food products (or licensed pharmaceutical products, where appropriate), to selected children (aged 4þ years) with clinically diagnosed persistent severe IgE-mediated hen's egg or cow's milk allergy to increase the amount of allergen tolerated while on therapy.

Reason for recommendations

Supplement 3 (Tables S3.1-3.8) contains the evidence and rationale for these recommendations.

Our recommendations about oral immunotherapy (OIT) focus on children with severe, IgE-mediated allergy given the potential time and emotional and physical burden of this therapy, the risk of rare severe reactions and the cost. In this context, we defined severe food allergy as having a substantial risk of severe reactions and/or substantially impaired quality of life.

Our systematic review and meta-analysis found that OIT in children aged 4–17 years probably results in a large increase in threshold for reaction to peanut whilst on therapy. It probably also increases the threshold for hen's egg and cow's milk.14 Sustained unresponsiveness is not achieved in many individuals.14 Severe allergic reactions occurred but were rare (Supplement 3, Tables S3.1, S3.3). Box 4 lists which children to consider for this therapy.

We focus on children aged 4+ years as this is where most evidence exists. Randomized placebo-controlled trial evidence of the efficacy and safety of peanut OIT for the induction

of sustained unresponsiveness in children below 4 years of age has recently been published,27 after our review of the evidence. There are similar data from a recent real-world study.28 However, we make recommendations for allergen immunotherapy from 4 years of age based on the effectiveness evidence, the potential to outgrow the allergy, the logistics and potential harms. Clinicians may consider other age groups depending on individual circumstances.

OIT may be useful for selected adults with IgE-mediated food allergy where potential benefits outweigh risks, but there was no or minimal evidence to support making a recommendation about this.

Epicutaneous immunotherapy in children aged 4–11 years probably results in an increase in the threshold at which they react to peanut whilst on therapy. This intervention is not currently available or licensed, but the task force felt it was important to highlight the positive evidence in trials to date. If it becomes available, professionals and families need to make a shared decision about whether OIT or epicutaneous immunotherapy is best for an individual based on relative effectiveness, safety, and logistics.

There was insufficient evidence to make recommendations about other applications of immunotherapy by route or for different types of foods. There was also insufficient evidence to make a recommendation about adding omalizumab to immunotherapy.

Strength of recommendations

We make a strong recommendation in favor of peanut OIT given the high certainty about the evidence regarding desensitization. The number needed to treat to achieve 1 person tolerating 300 mg or 1000 mg of peanut protein while on therapy was 2 people with food allergy.14

Our recommendations about OIT for hen's egg and cow's milk allergy and for epicutaneous immunotherapy for peanut are positive, but not the strongest possible because we had moderate certainty in the evidence, there are likely variations in individual preferences and we considered the potential burden and cost of treatment.

Practical implications

Allergen immunotherapy should only be used when an individual has proven IgE-mediated, primary food allergy. Given the complexity of allergen immunotherapy and its potential side-effects, clinical staff should be trained and experienced in its use and have the facilities available to deal with any side-effects (Box 4). Treatment should be under the supervision of a specialist with the requisite competencies in food allergy immunotherapy. Only standardized protocols with evidence of effectiveness and safety should be used, under specialist supervision. If food products are used, care should be taken that doses are appropriate and consistent in terms of their allergen content, biological potency and lack of contaminants.

Given these considerations, clinicians and patients may prefer to use licensed medicinal products prepared under Good Manufacturing Practices for pharmaceutical products. Affordability, quality of an alternative, risk-benefit, patient preference and local context should also be taken into consideration.

Clinicians should discuss the potential benefits and harms to help families choose whether immunotherapy is right for them and whether they are capable of adhering to therapy and managing any side effects. Some people may prefer to avoid the offending allergen instead. Careful selection is needed to avoid unnecessary treatment as many children outgrow hen's egg or cow's milk allergies by school age.29,30

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Box 4. Indications and contraindications for allergen immunotherapy for food allergy

Indication:
All the following need to be in place:

- History of IgE-mediated systemic allergic reactions after ingestion and/or positive oral food challenge (especially where allergy may be transient)[9,31]
- Evidence of allergic sensitization (SPT and/or sIgE)[9,31]
- Primary food allergy, as opposed to pollen food allergy syndrome due to cross-reactivity
- Persistent food allergy with low likelihood of spontaneous resolution
- Affected people and care givers (where relevant) have a full understanding of effectiveness, side effects, logistics and the potentially life-long duration of the therapy[32,33]
- Affected people and their care givers should be motivated, adherent and capable of administering emergency treatment (including intramuscular adrenaline) in the case of adverse effects[34]
- Previous severe reactions to the food[35] or impaired quality of life due to burden of food allergy[36,37]
- Willingness of all stakeholders to incorporate the food into diet[38,39]
- Stability of living and family situation

Contraindications:[40,41]
Absolute.

- Inadequate adherence to therapy and/or safety recommendations
- Uncontrolled or severe asthma[42]
- Active malignant neoplasia(s)
- Active systemic autoimmune disorders
- Systemic immunosuppression therapy
- Untreated/uncontrolled active eosinophilic esophagitis and other eosinophilic gastrointestinal disorders
- Initiation during pregnancy

Relative.

- Severe systemic conditions such as cardiovascular diseases
- Systemic autoimmune disorders in remission or organ specific (i.e. thyroiditis)
- Uncontrolled active atopic dermatitis/eczema
- Uncontrolled chronic urticaria
- Therapy with beta-blockers or ACE inhibitors
- Systemic mastocytosis
- Concurrent up-dosing with other immunotherapy
- Chronic gastrointestinal symptoms without a clear diagnosis
- Unable to consume study product (e.g. vomiting, taste problems, allergy to vehicle)
- Psychological problems, suspicion/confirmation of eating disorders

Appropriate staffing, environment and approach:[43]

- Personnel trained and experienced in the use of immunotherapy for food allergy, including a medical doctor and nurse experienced in the diagnosis of food allergy and in recognition and treatment of allergic reactions, including anaphylaxis
- Provision to provide appropriate intervention and observation dependent on the severity of any allergic reaction (may involve transfer to another facility)[34]
- Emergency equipment and medications to manage medical emergencies including severe anaphylaxis and rapid access intensive care if needed
- Standardized, evidence-based protocol; licensed pharmaceutical product where available

TABLE S3.4: JUSTIFICATION FOR NOT RECOMMENDING FOR OR AGAINST OTHER IMMUNOTHERAPY

Intervention	Evidence of effectiveness	Benefits versus harms	Patient/care giver values	Feasibility and cost
OIT for adults with IgE-mediated peanut allergy	We make no recommendation for or against OIT in adults with hen's egg allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	There was insufficient evidence available to weigh up benefits versus hams. The intervention could be considered in adults with food allergy where the likely benefit outweighs potential adverse effects.	The burden of the treatment probably is likely to be higher in adults because of the high number of visits to the allergy centre for dosing clashing against working duties. Additionally, adults are likely to have adapted to their peanut allergy such that its impact is minimised.	A pharmaceutical product is licensed in Europe and the United States for children. The same comments as in Table S3.1 related to children apply here.
EPIT for adolescents and adults with peanut allergy	We make no recommendation for or against EPIT in adolescents and adults with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97] Data from two studies found no significant impact on peanut allergy in a small number of adults.[121,122]	There was insufficient evidence available to weigh up benefits versus hams	No data available.	The EPIT approach necessitates a pharmaceutical preparation. This comes with increased cost potentially reducing access to the approach. A product is not currently available commercially and none has been approved by a regulatory authority. Given the mechanism of delivery, other products (should they become available) may not be comparable.
SCIT for patients of any age with peanut allergy	We make no recommendation for or against SCIT in people with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	Only 2 very small trials assessed the effectiveness of SCIT for peanut allergy.[123,124] Both had a high rate of systemic reactions making SCIT unacceptable for routine use in people with peanut allergy.	No data available, but may be of interest to people with peanut allergy as treatment could be given once per week or month.	Existing studies are almost 30 years old and used aqueous extracts. New forms of subcutaneous immunotherapy may be possible.
SLIT for patients of any age with peanut allergy	We make no recommendation for or against SLIT in patents with peanut allergy because there is insufficient evidence to draw conclusions. The certainty of evidence is very low.[97]	Adverse effects are predominately local. There are much less than for oral immunotherapy and no reactions required adrenaline injection.[97]	No data available	No specific product available outside the research setting.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 08 of 12, August 2024) am 29.08.2024

#	Suchfrage	Treffer
1	[mh ^"Food Hypersensitivity"] OR [mh „Nut and Peanut Hypersensitivity“	1072
2	[mh "Immunoglobulin E"] OR [mh arachis]	1759
3	#2 OR (food* OR peanut* OR arachis OR groundnut* OR nut* OR oleosin* OR immunoglobulin-e* OR IgE*):ti,ab,kw	119687
4	#3 AND (hypersensitiv* OR hyper NEXT sensitiv* OR allerg* OR intoleran*):ti,ab,kw	109263
5	{OR #1, #4}	1072
6	#5 with Cochrane Library publication date from Aug 2019 to present	283

Systematic Reviews in PubMed am 29.08.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage	Treffer
1	"Nut and Peanut Hypersensitivity"[mh]	2254
2	"Immunoglobulin E"[mh] OR arachis[mh]	46021
3	#2 OR peanut*[tiab] OR groundnut*[tiab] OR arachis[tiab] OR nut[tiab] OR nuts[tiab] OR oleosin*[tiab] OR "immunoglobulin-e*"[tiab] OR IgE[tiab]	106593
4	#3 AND (hypersensitiv*[tiab] OR "hyper sensitiv"[tiab:~0] OR allerg*[tiab] OR intoleran*[tiab])	49935
5	#1 OR #4	50251
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR	893

#	Suchfrage	Treffer
	eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])	
7	((#6) AND ("2019/08/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))	350
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])	349

Leitlinien in PubMed am 29.08.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage	Treffer
1	"Food Hypersensitivity"[mj] OR "Nut and Peanut Hypersensitivity"[mh]	20576
2	"Immunoglobulin E"[mh]	46021
3	#2 OR peanut*[tiab] OR groundnut*[tiab] OR arachis[tiab] OR nut[tiab] OR nuts[tiab] OR oleosin*[tiab] OR "immunoglobulin-e*"[tiab] OR IgE[tiab]	106593
4	#3 AND (hypersensitiv*[tiab] OR hyper sensitiv*[tiab] OR allerg*[tiab] OR intoleran*[tiab])	48079
5	#1 OR #4	59362
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*	444
7	(((#6) AND ("2019/08/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND	128

#	Suchfrage	Treffer
	animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))	
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])	128

Iterative Handsuche nach grauer Literatur, abgeschlossen am 30.08.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **De Silva D, Rodriguez Del Rio P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al.** Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy 2022;77(6):1852-1862.

2. **De Silva D, Singh C, Arasi S, Muraro A, Zuberbier T, Ebisawa M, et al.** Systematic review of monotherapy with biologicals for children and adults with IgE-mediated food allergy. Clin Transl Allergy 2022;12(9):e12123.

3. **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;13(7):e12268.

4. **Muraro A, de Silva D, Halken S, Worm M, Khaleva E, Arasi S, et al.** Managing food allergy: GA(2)LEN guideline 2022. World Allergy Organ J 2022;15(9):100687.

5. **Riggioni C, Oton T, Carmona L, Du Toit G, Skypala I, Santos AF.** Immunotherapy and biologics in the management of IgE-mediated food allergy: Systematic review and meta-analyses of efficacy and safety. Allergy 2024;79(8):2097-2127.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Anhang

Abbildung 1: Lodge 2023 Studiencharakteristika

TABLE 1 Overview of included studies.

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Peanut									
Anagnostou 2014 Cambridge UK STOP II DS	NIHR/Wellcome Trust Cambridge clinical research Facility 2-Phase RCT- recruited locally and nationally	*Inclusion:* 1. 7–16 years 2. Immediate hypersensitivity after peanut ingestion 3. Pos SPT peanut ≥3 mm 4. Pos DBPDFC *Exclusion:* 1. Major chronic illness (asthma, eczema, excepted) 2. Household member allergic to peanuts 3.Unwillingness or inability to comply	*Total:* 99 *OIT:* 49 *Control:* 50 Age: 7–16 yrs (median 12.4)	*Method:* Audited on-line system Randomizer, Medical University of Graz, Austria) minimization used based on baseline characteristics with weighting prob 0.8- (sex, age, challenge threshold, sIgE, severity, asthma, other food allergy) *Blinding:* None	*Intervention:* Peanut flour (light roast flour) Golden Peanut Company, Alphretta, GA, USA *Control:* Avoidance *Regimen:* mixed *Duration:* 6 months *Maximum OIT dose:* 0.8 gm peanut protein daily (5 peanuts)	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:* 1.4 gm peanut protein (approx. 10 peanuts) *Tested:* 6 months	**Desensitization** *ITT* OIT: 24/49 (49%) Control: 0/50 (0%) PPA (with censoring and loss to FUP) OIT 24/39 Control 0/46	**Any** Only reported for intervention and not separately for 2 study phases Common, primarily GI Severe OIT 21/49 (22%) wheeze/laryngeal oedema (0.41% of doses) **Adrenaline** OIT 1/49 C Not available **EoE** Not reported	OIT successful for most children for desensitization to clinically meaningful threshold
Bird 2018 United States DS	Peanut allergic children Enrolled from 8 US centres	*Inclusion:* 1. Age 4–26 years 2. History of peanut allergy 3. IgE ≥0.35KUA or SPT ≥3 mm in past 12 months 4. DBPCFC+ at or before 100 mg single dose peanut protein (143 mg cum) (PRACTALL guidelines) *Exclusion:* 1. Hx of CVD 2. Frequent or life threatening anaphylaxis, 3. Eosinophilic gastrointestinal disease, 3. On other intervention 4. Other chronic illness—(except asthma, eczema, rhinitis) 5. Severe or uncontrolled asthma 6. Use of specific medications	*Total:* 56 *OIT:* 29 *Control:* 27 Age: *OIT* 4–21yrs median 7 *Control* 4–14yrs (med 8)	*Method:* 1:1 using central randomization schedule of randomly permuted blocks-independent statistician *Blinding:* DB	*Intervention:* ARA101- defatted lightly roasted peanut flour (capsules) *Control:* Placebo (oat flour) *Regimen:* mixed *Duration:* 5–10 months (average 5.5) *Maximum OIT dose:* 300 mg peanut protein	**Desensitization** *Definition:* Neg DBPCFC single dose of 300 mg (443 mg cumulative) of peanut protein PRACTALL guidelines	**Desensitization** *ITT* OIT: 23/29 (79%) Control: 5/27 (19%)	**Any** OIT 28/29 (26 treated) C 22/26 (10 treated) Primarily GI **Adrenaline** OIT 1/29 C 0/27 EoE 1/29 in OIT gp/ resolved off treatment	

(Continues)

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
The Palisade group 2018 PALISADE Nth Amercia & Europe DS	66 sites in 10 countries in North America and Europe	1. 4–55 years 2. Clinical Hx peanut allergy 3. SIgE ≥0.35 kUA 4. SPT 3 mm > control 5. DBPCFC to up to 100 mg peanut protein (PRACTALL)	*Total:* 555 Then excluded >17 (55 people) So- 496 (3–17years) *OIT:* 372 *Placebo:* 124 *Age* 4–17 yrs	*Method:* random assigned 3:1—central randomization in randomly permuted blocks, interactive online system *Blinding:*DB	*Intervention:* AR101 *Contol:* Placebo *Regimen:* Gradual *Maximum OIT dose:* 300 mg daily *24 week* *maintenance*	Single dose at least 600 mg	**Desensitization** OIT: 250/372 (67%) Placebo 5/124 (4%)	**AEs** **Any** OIT 367/372 98.7% C 118/124 95.2% Severe OIT 8 4.3% C 1 0.8% (9 severe events in 8 participants vs. 1) **Adrenaline** OIT: 52/372 C 8/124 Overall serious or adverse events **EoE** OIT 1/372	No significant effect in patients 18 - 55
Chinthrajah 2019 POISED US DS SU	DBPC Parker Centre for Allergy and Asthma research—Stanford University Adult and pediatric patients aged 7–55 yeas	*Inclusion:* 1.DBPCFC (≤500 mg peanut protein 2.+ve SPT ≥5 mm 3.sIgE >4kU/L Age 7–55yrs *Exclusion:* 1.Severe/uncontrolled asthma 2.Eosinophilic gastrointestinal disease 3.Sensitivity to oats	*Total:* 120 age 11yrs (iqr 8–15) *OIT:* i)60 (OIT then 0 gm) ii)35 (OIT then 300 mg/day) *Control:* 25 Age: OIT 4–21yrs med 11 yrs Control 4–14yrs (med 8)	*Method:* 2 × 2 block design into 3 arms 2.4:1.4:1 *Blinding:* DB	*Intervention:* ARA101- defatted lightly roasted peanut flour (capsules) *Control:* Placebo (oat flour) *Regimen:* ? *Duration:* 24 months then 12 months off OIT *Maximum OIT dose:* 4000 mg peanut protein	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:* 4000 gm(16–18 peanuts) *Tested:* 104 weeks **Sustained Unresponsiveness** *Definition:* Neg DBPCFC *Cumulative dose:* 400 gm(16–18 peanuts) *Tested:* 117, 130, 143, 156 weeks	**Desensitization** ITT Peanut-0 versus Placebo 51/60 (85%) versus 1/25(4%) **Sustained unresponsiveness** ITT Peanut 0 versus placebo 117 21/60(35%) versus 1/25(4%) 130 12/60 (20%) versus 1/25(4%) 143 9/60 (15%) versus 1/25 (4%) 156 8/60(13%) versus 1/25 (4%)	Statistics for first 12 months **Any** OIT Peanut 0–57/60%-95% 53/60 had grade 1 reactions(88%) Resp 34 (57%) Peanut300 32/35 (91%) 30/35 grade 1 (86%) Resp 18(51%) Placebo 16/25(64%) 13/25 (52%) grade. Resp 6 (24%) **Adrenaline** OIT 18/95 C 0/25 **EoE**- 1/120 (OIT) 2% SAE rate in intervention arms	No differences, adults versus children Higher baseline sIgE, Arah1&2 IgE associated with failure Lower basophils at baseline associated with success Increased sIgG4/sIgE assoc with success

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Blumchen 2018 Germany DS	7 German sites- outpatient clinics and tertiary care clinics (consecutive recruitment)	*Inclusion:* 1.Age3-17yrs 2. sIgE>0.35kU/L 3. Challenge proven peanut allergy—Open OFC 4. Parents could understand/follow emergency instructions *Exclusion:* Participation in another trial Any other form immunotherapy Severe disease (eg uncontrolled asthma)	*Total:* 62 *OIT:* 31 *Control:* 31 *Age:* *OIT:* 6.6 (4.8–9.8 IQR) *Control:* 7.9 (4.6—10.7IQR)	*Method:* 1:1 block randomization size 4 (Dat Inf, rand List, version 1.2) Stratified by age (>or<6 yrs) and sIgE (, or > 50 kU/L). Independent statistician *Blinding:* DB	*Intervention:* Light roasted peanut flour (Byrd Mill Company- Ashland, Va) *Control:* Placebo Regimen:mixed Duration: 14 months *Maximum OIT dose:* 125–250 mg peanut protein	**Desensitization** *Definition:* *Open OFC* Neg DBPCFC single dose of 300 mg (443 mg cumulative) of peanut protein PRACTALL Guidelines *Tested:* 16 months	**Desensitization** ITT OIT: 23/31 (74.2%) Control: 5/31 (16.1%)	**Any** OIT 27/311-10 (90%) Control 24/31 (77%) **Adrenaline** No Adrenaline used **EoE** none found AEs more common with intervention doses 83% of intervention versus 45% of placebo	Low-dose OIT is a promising, effective and safe option for peanut allergic children, leading to improvement in QoL, a low BOT, and immunologic changes showing tolerance development
Hourihane 2020 ARTEMIS Europe DS	18 hospitals in Ireland, France, Germany, Italy, Sweden and UK	*Inclusion:* 1.Age 4–17 yrs 2. Clinical Hx peanut allergy 3. SPT≥3 mm and/or sIgE. ≥0.35kU/L 4.+ve DBPCFC 5.Sx at ≤ 300 mg peanut protein (1 peanut) *Exclusion* 1.Severe/life-threatening anaphylaxis within 860 days 2.Severe/uncontrolled asthma 3.Hx of eosinophilic oesophagitis or chronic GI Sx	*Total:* 175 *OIT:* 132 *Control:* 43	*Method* Randomly assigned 3:1 in blocks of 8- proprietary interactive web response system using computerized random number generator *Blinding:* DB	*Intervention* AR101 *Control:* Placebo *Regimen:* Mixed *Duration:* 9 months *Maximum OIT dose:* 300 mg peanut protein	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:* 1000 mg PRACTALL *Tested* 9 months	**Desensitization** ITT OIT: 77/132 (58%) Control: 1/43 (2%)	Any OIT 130/132 C 42/43 OIT: Mild 66 (50%) Mod 63 (48%) Sev 1(1%) Control: Mild 24 (56%) Mod 18 (42%) Sev 0 (0%) Adrenaline OIT 9/132(7%) C 1/43 (2%) No EoE during trial	AR101 led to rapid desensitization with predictable safety profile and improved food allergy related QoL for caregiver and participant

(Continues)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Jones 2022 IMPACT USA DS SU	5 Academic medical centres in USA. (Arkansas, Johns Hopkins, Mount Sinai, Stanford, University of Nth Carolina).	*Inclusion:* 1. Age—12 to 48 months 1.Clinical Hx peanut allergy 2. sIgE ≥5KU$_A$/L, 3.SPT ≥3 mm neg control 4.+ve DBPCFC to cumulative dose ≤500 mg *Exclusion:* 1. severe peanut anaphylaxis 2.Asthma more than mild 3. Uncontrolled asthma 4.Uncontrolled AD 5.Eosinophilic GI disease	*Total: 146* *OIT:* 96 *Control:* 50 *Age:* 12–48 months of age. *Median age* - 39.3 months (IQR 30.8–44.7 months) 68% Male	*Method:* Randomly assigned (2:1) *Blinding:* DB	*OIT*-Lightly roasted, partly defatted peanut flour *Control:* placebo.(oat flour) *Regimen:* mixed *Duration:* 134 weeks. Then 26 weeks avoidance *Maximum OIT dose:* 2000 mg peanut protein/day	**Desensitization (primary outcome)** *Definition:* -ve DBPCFC *Cumulative dose:* 5000 mg peanut protein *Tested* 134 weeks (30.8 months) **SU** *Definition* *Cumulative dose:* 5000 mg peanut protein *Tested* 160 weeks(36.8 months) After 6months (26weeks avoidance)	**Desensitization** ITT OIT: 68/96 (71%, 95% CI 61–80) **Control** 1/50 (2%, 95% CI 0.05–11) Risk difference 69% (95%CI 59%–79%) Risk ratio 35 (95% CI 5.1–248) **Sustained unresponsiveness** ITT OIT: 20/96 (21%, 95% CI 13–30) Control: 1/50 (2%, 95% CI 0.05–11) Risk difference 19% (95% CI 10%–28%) Risk ratio 10.4 (95% CI 1.4–75)	**Any** OIT: 94/96 (98%) Placebo: 40/50 (80%) **Adrenaline:** Peanut OIT: 21/96 (22%) Placebo: 0/50 "Dosing and challenge reactions were expected and not reported unless hypotension, cyanosis, o2 sat <92, confusion, collapse, loc, incontinence or required >2 epinephrine doses" **EoE**—3 in OIT gp (2 resolved off treatment)	Peanut OIT started before age 4 years in children with peanut allergy is associated with increased Peanut desensitization and remission. Window of opportunity Lower baseline IgE associated with greater chance remission
Loke 2022 PPOIT-003 Australia DS SU	3 Australian tertiary hospitals. Women's and Children's Hospital, Adelaide [SA] Royal Children's Hospital Melbourne [VIC] Perth Children's Hospital [WA]	*Inclusion:* 1.Age 1–10 yrs, 2. Weight >7 kg, 3. +ve DBPCFC, 4. +ve SPT (wheal>3 mm) or peanut specific IgE ≥0.35kU/L *Exclusion:* 1. Severe anaphylaxis or during DBPCFC 2. FEV1 <85% pred 3. FEV1/FVC <85% pred 4. chronic persistent asthma 5. cardiac disease 6. Beta blockers or ACE 7 GI disorders 8. Recent surgery 9. Recent probiotics 10. Major illnesses 11. Unable to follow protocol 12. Many others	Randomized: 201 PPOIT (probiotic + peanut OIT)::79 OIT:83 Placebo:39 Age av: Total—5.9 yrs PPOIT 6 OIT 5.8 Placebo 6	*Method:* Randomly assigned permuted blocks of 5(2:2:1) Stratified by site, age >5, SPT>10 mm Blinding: DB	*Probiotic:* *Lactobacillus rhamnosus* ATCC 53103 2×10^{10} CFU *OIT:* Peanut: 12% defatted peanut flour *Control:* Maltodextrin *Regimen:* mixed *Duration:* 78 weeks. Then 12 more months avoidance *Maximum OIT dose:* 2000 mg peanut protein/day	**Desensitization** -ve DBPCFC **Cumulative dose:** 4950 mg peanut protein **SU** (primary outcome) -ve DBPCFCs at treatment completion & 8 weeks after treatment. **Cumulative dose:** 4950 mg peanut protein	**Desensitization** *PPOIT* 61/79 (77%) *OIT:* 61/83 (73%) C: 2/39 (5%) **Risk difference** *PPOIT vs C* 72.1%(95% CI 60.5–83.6) *PPOIT vs OIT* 3.72% (–9.5–17.0) *OIT vs Plac* 68.4% (56.6–80.1) **SU** *PPOIT* 36/79 (46%) *OIT:* 42/83 (52%) *Placebo:* 2/39 (5%) **Risk difference** *PPOIT vs Placebo* 40.4% (95% CI 27.5–53.4) *PPOIT vs OIT* –5.0% (–20.4–10.3) *OIT vs Placebo* 45.5% (32.7–58.3)	**Any** PPOIT 72/79 (91%) OIT 73/83 (88%) Control 28/39 (72%) **Adrenaline** PPOIT: 2/71 (3%) OIT 4/70 (6%) C: 0/39 (0%) **EoE**- 2 cases in OIT group (none in PPOIT or control) Exposure adjusted incidence of AEs PPOIT 10.58, OIT 11.36, control 2.09	Both PPOIT and OIT were effective at inducing desensitization and sustained unresponsiveness. Addition of a Probiotic did not improve efficacyof OIT, but may improve safetyAdverse events,mostly mild, were common inthe activetreatment groups.

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Hen's Egg									
Akashi 2017 Tokyo, Japan DS	Egg allergic patients from Outpatients, National Centre for child Health & Development Threshold dose defined at beginning	*Inclusion:* 1. Egg-specific IgE ≥0.7 U_A/mL 2. DBPCFC pos. to egg 3. Elimination of eggs from the diet 4. Caregiver agreed *Exclusion:* Anaphylaxis (hypotension or dyspnoea on egg challenge)	*Total:* 36 (25 boys; 11 girls) *OIT:* 18 *Control:* 18 Age 3–15 years: mean 5.8	*Method:* Computerized algorithm 1:1 *Blinding:* None	*Intervention:* Hens egg whole (Dried powdered) *Control:* Avoidance *Regimen:* Gradual *Duration:* 6 months *Maximum OIT dose:* 1.7 gm EWP	**Desensitization** *Definition:* Neg DBPCFC (AAAI scoring ≥1) *Cumulative dose* 1.4 gm *Tested:* 6 months	**Desensitization** *PP* OIT: 8/14 (57%) Cont: 0/16 *ITT* OIT 8/18 (44%) Cont 0/18	**Any** OIT 17/18 C not available **Adrenaline**—none given **EoE**- none detected	OIT effective in increasing threshold and inducing desensitization OIT group clearly more tolerant at beginning from OFC
Caminiti 2015 Messina, Italy DS SU	Egg allergic patients from Allergy units of the departments of paediatrics of Messina and Catania university hospitals Inhalant allergy in 9 but no other food allergies	*Inclusion:* 1. Age ≥4 2. Demonstrated IgE-mediated Hens egg: Clinical history; 3. HE specific IgE & SPT 4. Pos DBPCFC (3.7 gm EW protein) *Exclusion* 1.Suspected soy allergy or IgE to soy 2.Sensitized to other foods	*Total:* 31 *OIT:* 17 *Control:* 14 *Age:* 4–11 years (median 6)	*Method* "computer-generated randomization list" *Blinding:* Double	*Intervention:* Hen's egg white (dehydrated) *Control:* Placebo (corn flour) *Regimen:* mixed *Duration:* 10 months (4 months OIT 6 months egg containing diet) Control group avoided HE for 9 months after trial *Maximum OIT dose:* 4 gm EWP	**Desensitization** *Definition:* Neg DBPCFC (EACCI) *Cumulative dose:* 3.7 gm egg white (equiv to 1 boiled egg) *Tested:* 4 months **Sustained Unresponsiveness** *Definition:* Neg DBPCFC Time between OIT & OFC: 3 months	**Desensitization** *ITT* 4 months OIT 16/17 Cont 0/14 **Sustained Unresponsiveness** 13 months *ITT* OIT 5/17 Cont 1/14	**Any** *OIT*: 5/17 C: 0/14 **Adrenaline** **OIT 1/17** **C 0/14** **EoE**- none detected	OIT effective for desensitization
Dello Iacono 2013 Italy DS	Severe egg allergic patients from Paediatric and Allergology Unit of the Fatebenefratelli Hospital in Benevento, Italy Severe egg allergy Reaction eliciting dose used to restrict 0.9 mL raw HE	*Inclusion:* 1. ≥1 anaphylactic reaction to accidental trace exposure to HE within 12 months pre-enrolment 2. Previous HE specific IgE & SPT ≥ 3 mm with raw egg white 3. DBPCFC pos at ≤ 0.9 mL raw HE emulsion *Exclusion* 1.Poorly controlled asthma 2. Parents unreliable 3. Sensitized to other foods	*Total:* 20 *OIT:* 10 *Control:* 10 *Age:* *OIT:* 5–10 (med 6.6) *Cont:*4–11 (med 8.6)	*Method:* Computerized randomisation *Blinding:* None	*Intervention:* Hens egg whole (raw emulsion) *Control:* Avoidance *Regimen:* mixed *Duration:* 6 months *Maximum OIT dose:* 3.3 gm EWP (40 mL hens egg emulsion-1 small egg)	**Desensitization** *Definition:* Neg DBPCFC *Maximum dose:* 40 mL HE emulsion 10–40 mL HE emulsion *Tested:* 6 months	**Desensitization** *ITT* 40 mL 6 months OIT 0/10 Cont 0/10 *ITT* 10-40 mL OIT 9/10 Cont 0/10	**Any** OIT 10/10 No data for avoidance **Adrenaline** OIT 0/10 C 0/10 **EoE** None found	Six months of SOTI with raw HE emulsion resulted in partial tolerance, with regular intake, in a significant percentage of children with severe egg allergy

(Continues)

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Escudero 2015 Spain **SU**	Egg allergic patients consecutively recruited at the Department of Allergy, Hospital Infantil Universitario Nino Jesus in Madrid, Spain.	*Inclusion:* 1.Age 5–17 egg allergic on egg exclusion diet 2. history egg reactions 3. SPT (≥3 mm) and sIgE ≥0.7 kU/L for egg white (EW), ovalbumin (OVA) and/or ovomucoid (OVM), 4. Pos DBPCFC- dehydrated EW powder *Exclusion* 1.Severe anaphylaxis after egg ingestion 2.Egg non-IgE mediated reactions 3.Immune deficiencies 4. CIs to adrenaline 5. Allergy to other components of challenge	*Total:* 61 *OIT:* 30 *Control:* 31 Age: 5–17yrs (med 8) (63% male) *OIT:* 30; 73% male *Cont:*31; 52% male	*Method:* Computerized generated randomization table in 1:1 ratio *Blinding:* None	*Intervention:* Hens egg white (Dehydrated) *Control:* Avoidance *Regimen:* mixed *Duration:* 3 months *Maximum OIT dose:* 2.8 gm EWP	**Desensitization** *Definition:* Neg DBPCFC (only for OIT group) *Cumulative dose:* 2.8 gm *Tested:* 3 months **Sustained Unresponsiveness** *Definition:* Neg DBPCFC *Cumulative dose:* 2.8 gm *Tested:* 4 months Time between OIT & OFC: 1 month	**Desensitization** *ITT* OIT 28/30 (93%) Control—postulated 1/31 (3%) **Sustained Unresponsiveness** *ITT* OIT 11/30 (37%) Control 1/31(3%)	**Any** OIT 21/30 C ? Adrenaline OIT 1/30 C not available **EoE** Not able to test in 2 patients- resolved	Demonstration of SU from a 3 month trial EW-sIgE levels at the end of treatment predicted sustained unresponsiveness.
Martín-Muñoz 2018 Spain SEICAP DS	The Spanish Society of Pediatric Allergy, Asthma and clinical Immunology (SEICAP) multicenter- 9 allergy units in the Spanish Public Health care system	*Inclusion:* 1. Age 6–9 years 2. Pos EW SPT>3 mm 3. EW sIgE >0.35KUA/L 4. Pos. DBPCFC *Exclusion:* 1. Severe or uncontrolled asthma 2. Severe atopic dermatitis 3. Esophagitis symptoms 4. Autoimmune, cardiovascular, or neuropsychiatric diseases 5. Beta blocker treatment 6. Food OIT past 12 months 7. Aeroallergen Immunotherapy in start-up phase	*Total: 101* *OIT:* 76; PI 38 PII 38 *Control:* 25 Age—6–9 years	*Method:* centralized computer algorithm *Blinding:* None	*Intervention:* Hen's egg white (pasteurized) *Control:* avoidance *Regimen:* gradual 2 different: P1-30% weekly and 5% daily updosing P2—30% weekly updosing *Duration:* 12 months *Maximum OIT dose:* 3.3 gm EWP randomized to daily or second daily ? NSAIDs as well	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:*1 raw egg 3.3 gm EWP *Tested:* 12 months	**Desensitization** *ITT* OIT: 64/76 (84%) Control: 4/25 (16%)	**Any** OIT: 66/76 (86.8%) C: 8/25 (%) **Adrenaline** OIT 1/76 C 0/25 **EoE**- None found	PEW OIT is an effective treatment for children with persistent egg allergy. A 30% weekly plus 5% daily increment pattern could be more effective and safer than one with only 30% weekly increments.

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Itoh-Nagato 2018 Japan DS	9 allergy centres in urban areas in Japan	Inclusion: 1.5–15years 2. Hx IgE hen's egg allergy 3. sIgE ≥0.35Ua/ml 4. +ve DBPCFC ≤500 mg dried raw hen's egg white powder Exclusion: 1.Uncontrolled asthma 2. Uncontrolled atopic dermatitis 3.Grade 5 anaphylaxis on DBPCFC	Total:45 OIT: 23 Contol:22 Age: Median(range) OIT: 7(5–12) Control: 8(5–13)	Method Computer based 1:1 allocation Stratified by age, gender, sIgE, TD and grade of Sx at DBPCFC Blinding: None	Intervention: Whole egg lightly cooked Control: avoidance Regimen. Mixed Duration 3 months Maximum OIT: 1 gm EWP—1 whole scrambled egg	**Desensitization** Definition- neg DBPCFC Cumulative dose 1000 mg EWP Tested-3 months	**Desensitization** ITT OIT 20/23 (87%) Control 5/22 (23%)	**Any** ITT 19/23%—83% C 0/22 **Adrenaline** OIT 2/23 (9%) C –0/22 **EoE**; 4 participants receiving OIT developed refractory GI tract symptoms- unable to investigate	
Cow's milk									
Battista Panjo 2010 Italy DS	Department of Pediatrics, Allergy Unit, Messina and Catania University hospitals	Inclusion: 1. Age: 4–10 years 2. Cows milk allergy from clinical history, SPT ≥3 mm, IgE specific antibodies and DBPCFC to cows milk Exclusion: 1.No allergy to soy (SPT, IgE or history) 2. Not sensitized to other foods	Total: 30 OIT: 15 Control: 15 Age: OIT 9 (4–12) Control: 10 (4–13)	Method: not supplied Blinding; DB	Intervention; whole cows milk Control: soy milk Regimen: Gradual Duration: 4 months Maximum; 200 mL whole milk (6.4 gm CM protein)	**Desensitization** Definition: Neg DBPCFC Cumulative dose: milk —200 mL Milk protein (4.6 gm)	**Desensitization** ITT OIT: 10/15 (75%) Control: 0/15 (0%)	**Any** OIT 10/15 C 0/15 **Adrenaline** OIT 2/15 C 0/15 **EoE**- not reported	3 had anaphylaxis at doses of 64 ml,4ml and 2 mL _ all these children were in the most severe group with symptoms elicited by 0.3–1 ml of milk at baseline
Maeda 2021 Japan ORIMA DS	Severe cows milk allergy (tol <=10 mL in OFC) Patients seen at: Dept of Pediatrics, Daisan Hospital, Jikei Univesity school of medicine Dept Pediatrics Showa University Hospital Aug 2011-July 2016 with. Cows milk allergy	*Inclusion:* 1. Age: 3–12 years. 2. Cows milk allergy from clinical history, 3. IgE specific antibodies ≥0.7UA/ml 4. Lived within 30 min of hospital 5. Parents could be present for RUSH OIT 6. Consent given by child and/or parents and DBPCFC to cows milk 7. DBPCFC +ve (At least Sampson's Grade 2 symptoms after up	*Total:* 28 *OIT:* 14 *Control:* 14 *Age:* OIT: 5.5 +/– 2.4 yrs(SD) Control: 5.4 +/–2.3 yrs (SD)	*Method:* Randomization by independent data centre. Dynamic allocation with minimization adjusted for hospital, sex and cow's milk IgE level *Blinding* Not blinded	*Intervention:* Cow's milk *Control:* Elimination *Regimen:* mixed *Duration:* 1 year *Maximum:* 100 mL/day	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:* 100 mL cow's milk	**Desensitization** ITT OIT: 7/14 (50%) Control:0/14 (0%)	**Any** OIT 12/14 C 3/14 **Adrenaline** OIT 7/14 (43%) Avoidance 0/14 **EoE**- not reported	

(Continues)

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
		to cumulative 10 mL Cow's milk) (was 5 mL but changed after May 2013) *Exclusion:* 1.Hx of life threatening anaphylactic shock to cows milk 2. Uncontrolled bronchial asthma 3.Uncontrolled atopic dermatitis 4.Allergic to other foods (soybeans, chocolate, oats) 5. Physician judged ineligible because of complications 6. Difficulty withdrawing oral drugs for OFC							
Skripak 2008 North Carolina USA DS	Paediatric allergy clinics at John Hopkin's University Hospital, Baltimore, Maryland, and Duke University Medical Centre, Durham, NC	*Inclusion:* 1. Children 6–21 years with known history of IgE-mediated milk allergy 2. Pos SPT to milk extract (wheal ≥histamine control) or milk IgE levels >0.35kU/L 3. Pos milk challenge at baseline (cum 2.5 gm milk protein) *Exclusion:* 1. History anaphylaxis requiring hospitalization 2. History of asthma intubation 3. Current severe or persistent asthma	*Total:* 20 *OIT:* 13 *Control:* 7 *Age:* OIT median 9 yrs Control median 11 yrs	*Method:* randomized 2 (OIT) to 1 (placebo)—no information on method *Blinding:* DB	*Intervention:* Powdered milk (non-fat) *Control:* Placebo (maltodextran) *Regimen:* Gradual *Duration:* 3 months *Maximum:* 0.5 gm CM protein (15 mL milk)	**Desensitization** *Definition:* Neg DBPCFC *Cumulative dose:* milk protein 8 gm	**Desensitization** *ITT* OIT: 4/13 (13%) Control: 0/7 (0%)	**Any** OIT: 13/13 not available **Adrenaline** OIT 4/13 C 0/7 **EoE**- not reported	

TABLE 1 (Continued)

First author, year, country	Population/& recruitment location	Inclusion & exclusion criteria	Sample size trial arms & age	Randomisation	Intervention	Outcome definition	Outcomes	Adverse events & adrenaline use	Author conclusion comments
Dantzer 2022 USA DS	John Hopkins Pediatric Allergy clinic, Baltimore	*Inclusion* 1. 3–18 yrs 2.Hx cow's milk reactivity 3. SPT≥3 mm neg control 4. sIgE >5kU/L 5. +ve DBPCFC ≤444 mg baked milk protein 6. Tolerate >3 mg baked milk protein *Exclusion* 1. Hx severe anaphylaxis 2. Severe/poorly controlled asthma 3. Poorly controlled AD 4. Hx of eosinophilic oesophagitis past 3 yrs	*Total:* 28 *OIT:*14 *Control:* 14 *Age:* both groups 9.5 median	Participants allocated 1:1 to Block randomization *Blinding:* DB	*Intervention* Baked milk powder *Control:* tapioca flour (in baked goods) *Regimen:* Mixed *Duration:* 52 weeks *Maximum:* 2000 mg baked milk protein	**Desensitization** *Definition:* -ve DBPCFC *Cumulative dose:* 4044 mg baked milk protein	**Desensitization** ITT *OIT* 11/15(73%) *Placebo* 0/15 (0%) Risk difference 73% Risk ratio 23.0 (95% CI 1.48–358) (0.5 added to each cell) NNT 1.5 (95% CI 1.1–2.2	OIT: AEs for 42% all doses (2222/5277) C: AEs 2% all doses. (94/5132) >95% of AEs in both OIT & placebo groups were rated "mild". Any OIT 15/15 C 11/15 Adrenaline OIT 3/15 C 0/15 EoE: none reported	well tolerated although mild dosing-related AEs were common in the OIT group. BMOIT induced a substantial level of desensitization after 12 months of treatment.

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO