Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Erdnussprotein

Stand: Februar 2020

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

Erdnussprotein [orale Immuntherapie bei 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 Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht zutreffend.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Nicht zutreffend.
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 *(Arachis hypogaea)* PALFORZIA®	
Es sind keine Arzneimittel zugelassen.	

Quellen: AMIS-Datenbank, Leitlinien

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: Erdnussprotein

Auftrag von:	Abt. AM
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Datum:	13. Januar 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AAI	Adrenaline autoinjector
AIT	Allergen immunotherapy
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
FA	Food allergy
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IgE	Immunoglobulin E
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OIT	Oral immunotherapy
OR	Odds Ratio
RR	Relatives Risiko
sIgE	specific IgE
SIGN	Scottish Intercollegiate Guidelines Network
SPT	Skin prick test
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung der Erdnussallergie

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Erdnussallergie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.12.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 150 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 4 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Chu DK et al., 2019 [1].

Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety.

Fragestellung

The principal aim of this study was to systematically review and meta-analyse the health benefits and harms of oral immunotherapy compared with allergen avoidance or placebo (no oral immunotherapy) for the treatment of peanut allergy.

Methodik

Population:

- Patients with peanut allergy

Intervention:

- Oral immunotherapy

Komparator:

- Placebo or allergen avoidance

Endpunkte:

- Siehe Ergebnisse

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane Controlled Register of Trials, Latin American & Caribbean Health Sciences Literature, China National Knowledge Infrastructure, WHO's Clinical Trials Registry Platform (ICTRP), US Food and Drug Administration (FDA), and European Medicines Agency databases from inception to Dec 6, 2018

Qualitätsbewertung der Studien:

- We used the Cochrane risk of bias tool for randomized trial with modified responses as "Definitely yes", "Probably yes", "Probably no", or "Definitely no",to examine risk of bias per outcome.
- We evaluated the certainty (quality) of evidence using the GRADE approach.

Ergebnisse

Anzahl eingeschlossener Studien:

- 12

Charakteristika der Population:

	Country	Setting		Intervention and comparator assignments						Restrictions		Participants		
		Entry OFC	Median follow-up, years	OIT group	Proprietary	No OIT group	Starting dose (mg)	Target dose (mg)	Time to achieve maintenance (weeks), median	Strictly avoid peanut?	Other restrictions	Sample size, n	Median age, years	Women, n (%)
Varshney et al (2011)[23]	USA	No	1·00	OIT	No	Placebo	0·1	4000	50	Yes	No dose if fever, infection, or otherwise feeling ill; dose on full stomach	28	5·75	10 (36%)
STOP II (2014)[24]	UK	Yes	0·50	OIT	Yes	Avoidance	2	800	26	No mention	Dose with food; no exercise for 2 h after dose	99	12·4	29 (29%)
PPOIT (2015)[25–27]	Australia	No	5·80	OIT and probiotic	Yes	Placebo	0·1	2000	36	Yes	-	62	5·95	25 (40%)
Narisety et al (2015)[28]	USA	Yes	1·33	OIT	No	Sublingual immunotherapy	0·1	2000	16	Yes	No exercise for 2 h after dose; call for individualised instructions during fever, and either full dose or skip dose	21	11·1	10 (48%)
ARC001 (2017)[29]	USA	Yes	0·42	OIT	Yes	Placebo	0·5	300	22	Yes	No exercising, or taking hot showers or baths within 4 h; dose reduction during menstrual period	55	7·5	19 (35%)
PMIT (NCT00597675; 2017)	USA	No	1·00	OIT	No	Placebo	2	4000	..	No mention	..	10	5·4	3 (30%)
PnOIT3 (NCT00815035; 2017)	USA	No	0·85	OIT	No	Placebo	..	4000	..	No mention	..	16	5	10 (63%)
PNOIT (NCT01324401; 2018)	USA	No	1·08	OIT	No	Avoidance	..	4000	44	No mention	..	30	9	12 (40%)
Blumchen et al (2018)[30]	Germany	Yes	1·33	OIT	No	Placebo	0·5	125–250	56	Yes	No exercise activity for 2 h	62	6·8	24 (39%)
PALISADE (2018)[33,34]	North America and Europe	Yes	1·00	OIT	Yes	Placebo	0·5	300	26	Yes	No exercise, or showering or bathing within 3 h; dose reduction during menstrual period; no dose within 2 h of bedtime; no dose without food; must dose daily	551	11·3	236 (43%)
PITA (2018)[35]	France	Yes	0·46	OIT	No	Placebo	2	400	24	Yes	No sports for 2 h after dose nor any condition of stress likely to be induced either by effort or sun exposure	30	14·75	8 (27%)
TAKE-AWAY (2018)[31,32]	Norway	Yes	1·07	OIT	No	Avoidance	1	5000	56	Yes	No exercise within 2 h after dose; monitor during menses; no dose if ongoing infections, asthma exacerbations, excessive tiredness, or vaccinations	77	9·5	33 (43%)

OFC=oral food challenge. OIT=oral immunotherapy.

Table 1: **Characteristics of included oral immunotherapy studies**

Qualität der Studien:

- Overall, the risk of bias for all outcomes across the included trials was low.

Studienergebnisse:

	Sample size	Risk ratio* (95% CI)	Anticipated absolute effects (95% CI) per 1000 individuals			Grades of evidence	Main findings†‡§
			No OIT	OIT	Risk difference		
Anaphylaxis	9 RCTs; 891 participants	3·12 (1·76–5·55)	71¶	222 (125–394)	151 (54–323)	High	Peanut OIT results in large increase in anaphylaxis; NNT_H 7 (3–19); IRR 2·72 (1·57–4·72)
Epinephrine use‡	9 RCTs; 984 participants	2·21 (1·27–3·83)	37	82 (47 to 142)	45 (10–105)	High	Peanut OIT results in large increase in epinephrine use; NNT_H 22 (10–100); IRR 2·87 (1·70–4·85)
Serious adverse events	12 RCTs; 1041 participants	1·92 (1·00–3·66)	62‖	119 (62–227)	57 (0–165)	Moderate**	Peanut OIT probably increases serious adverse events (death, life threatening, disability, or requiring urgent medical intervention or hospitalisation to prevent these events); NNT_H 18 (6–5376)
Vomiting, representative of gastrointestinal reactions††	6 RCTs; 755 participants	1·79 (1·35–2·38)	186	334 (252–444)	147 (65 to 257 more)	High	Peanut OIT results in large increase in vomiting frequency; NNT_H 6 (4–14); IRR 2·11 (1·54–2·89)
Angioedema, representative of mucocutaneous reactions‡‡	5 RCTs; 694 participants	2·25 (1·13–4·47)	39	88 (44–174)	49 (5 to 135 more)	High§§	Peanut OIT increases angioedema; NNT_H 20 (7–200); IRR 2·51 (1·79–3·51)
Nasal congestion or blockage, representative of respiratory reactions§§	6 RCTs; 724 participants	1·36 (1·02–1·81)	178	241 (181–321)	64 (4 to 144 more)	Moderate¶¶	Peanut OIT probably increases nasal congestion or blockage (rhinitis); NNT_H 16 (7–250); IRR 1·48 (1·04–2·10)
Surrogate for exposure to peanut outside of clinic without a reaction: passing a supervised food challenge in-clinic	9 RCTs; 917 participants	12·42 (6·82–22·61)	32	397 (218–723)	365 (186 to 691 more)	High‖‖	Peanut OIT results in large increase in completing a supervised oral food challenge without an allergic reaction, but this does not translate into less reactions outside of clinic; for every gram increase in total cumulative challenge dose, the chance of passing decreases by 26%; NNT 3 (1–5)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). IRR=incidence rate ratio. MID=minimally important difference. NNT=number needed to treat. NNT_H=number needed to treat to harm. OIT=oral immunotherapy. RCT=randomised controlled trial. *Similar findings for all outcomes were found when accounting for if patients could have more than one event using IRR analysis. †Three events of eosinophilic esophagitis occurred across five trials, all in the oral immunotherapy group, precluding an accurate estimate of the relative and absolute effect between groups on the risk of eosinophilic esophagitis. ‡Likelihood of improving quality of life by the MID by parent report (risk ratio [RR] to achieve MID 1·14 [0·66–1·99], risk difference [RD] 0·01 [–0·16 to 0·17]), self-report (RR to achieve MID 1·20 [0·80–1·81]; RD 0·09 [–0·10 to 0·27]), or combined (RR 1·21 [0·87–1·69], RD 0·03 [–0·12 to 0·18]); weighted mean quality of life scores between oral immunotherapy and no oral immunotherapy groups by either parent report (weighted mean difference in change from baseline –0·23 [–0·62 to 0·16]) or child self-report (standardised mean difference in change from baseline 0·23 [–0·15 to 0·61]). §Similar findings were obtained when analysed by incidence rate. ¶Vander and colleagues[18] leak observational study estimates, which are similar to those of Cherkouai and colleagues.[19] ||Similar findings for reactions severe enough to cause study discontinuation. **Rated down for imprecision because of wide CIs. ††Similar findings for abdominal pain, mouth itching, and any allergic or adverse reaction. ‡‡Similar findings for urticaria. §§We did not rate down for imprecision despite the lower limit of the risk difference approaching no effect because of the large number of events and sufficient information size in trial sequential analysis. ¶¶Similar findings for asthma attack or wheeze. ||||A substantial proportion of trials and their contributing information were either unblinded or terminated early for benefit specifically with this oral food challenge outcome; although the true effect estimate might be smaller than the presented estimate, sensitivity analyses that adjusted for risk of bias and early termination yielded similar results to the main analysis; we did not rate down the evidence given the very strong association.

Table 2: **Summary of findings in studies comparing oral immunotherapy with no oral immunotherapy (avoidance or placebo) for peanut allergy**

Anmerkung/Fazit der Autoren

This systematic review and meta-analysis, representing the most comprehensive and rigorous to date, to our knowledge, provides high and moderate certainty evidence that current approaches to oral immunotherapy effectively achieve a modest degree of desensitisation but, clinically, they promote net more allergic and anaphylactic reactions instead of preventing them as intended. These data support the need for improved food allergy treatment approaches with an enhanced safety profile and trials focused on patient-important outcomes. Considering the current view of peanut allergy oral immunotherapy as a model for other food allergies combined with the rising global prevalence of food allergy, these findings are significant and important to the ongoing development of food allergy therapeutics and improved patient outcomes.

Kommentare zum Review

Es liegt keine Zulassung für eine orale Immuntherapie im Anwendungsgebiet vor.

3.4 Leitlinien

Pajno GB et al., 2018 [3].

European Academy of Allergy & Clinical Immunology

EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy

Leitlinienorganisation/Fragestellung

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE-mediated Food Allergy. It is part of the EAACI Guidelines on Allergen Immunotherapy. This Guideline aims to provide evidence-based recommendations for the use of AIT in patients with diagnosed IgE-mediated FA.

This Guideline aims to assist qualified clinicians in the optimal use of AIT in the management of patients with IgE-mediated FA, and highlight gaps for further research.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz (siehe [2]);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Cochrane Library, MEDLINE, EMBASE, ISI Web of Science, TRIP and CINAHL from inception to 31 March 2016

LoE / GoR

BOX 4 Assigning levels of evidence and recommendations (adapted from Oxford Centre for Evidence-based Medicine)[22]

Levels of evidence

Level I: Systematic reviews, meta-analysis, randomized controlled trials

Level II: Two groups, non-randomized studies (e.g. cohort, case-control)

Level III: One group non-randomized (e.g. before and after, pretest, and post-test)

Level IV: Descriptive studies that include analysis of outcomes (single-subject design, case series)

Level V: Case reports and expert opinion that include narrative literature, reviews, and consensus statements

Grades of recommendation

Grade A: Consistent level I studies

Grade B: Consistent level II or III studies or extrapolations from level I studies

Grade C: Level IV studies or extrapolations from level II or III studies

Grade D: Level V evidence or troublingly inconsistent or inconclusive studies at any level

Strength of recommendations

Strong: Evidence from studies at low risk of bias

Moderate: Evidence from studies at moderate risk of bias

Weak: Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong, "is recommended"; moderate, "can be recommended"; weak, "may be recommended in specific circumstances"; negative, "cannot be recommended."

Approach adapted from Oxford Centre for Evidence-based Medicine—Levels of Evidence and Grades of Recommendations.[22] The adaptation involved providing an assessment of the risk of bias, based on the Cochrane risk of bias tool, of the underpinning evidence and highlighting other potentially relevant contextual information.

Sonstige methodische Hinweise

- Es liegt keine Zulassung für eine orale Immuntherapie im Anwendungsgebiet vor.

Empfehlungen

BOX 9C Recommendations on efficacy of OIT in children with persistent peanut allergy

Recommendations[a]	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
OIT is recommended as a treatment option to increase the threshold of reaction while on treatment in children with peanut allergy from around 4-5 years of age	I	A	Strong recommendation based on consistent evidence from SR and meta-analysis[18] with low risk of bias RCTs[45-47]	Risk of adverse reactions to be considered. Age recommendation is based on expert opinion	Nurmatov et al[18]; Narisety et al[45]; Tang et al[46]; Varshney et al[47]
A recommendation cannot currently be made for OIT as a treatment option to achieve post-discontinuation effectiveness in children with peanut allergy	I	B	Strong recommendation based on two RCTs at low risk of bias[23,45]	Inconsistent study results. Further studies needed	Vickery et al[23]; Narisety et al[45]

[a]OIT for food allergy should only be undertaken in highly specialized clinical centers with expertise and facilities to safely deliver this therapy.

BOX 10 Recommendations on efficacy of OIT in adults with persistent food allergy

Food	Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
Peanut	No recommendation can be made about OIT as a treatment option in adults with peanut allergy	II	B	Weak as only one CCT including mixed populations.[51] No recommendation due to lack of evidence.		Syed et al[51]

BOX 11 Recommendations on safety of FA-AIT

Recommendations	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
It is recommended to carefully monitor patients for local and systemic allergic reactions in FA-AIT particularly during the up-dosing phase of FA-OIT	I	A	Strong recommendation based on SR and meta-analysis[18] including RCTs at low risk of bias[9,42]		Nurmatov et al[18]; Pajno et al[9]; Caminiti et al[42]
It is recommended to monitor patients for symptoms of new-onset eosinophilic esophagitis which may appear in the course of FA-OIT	I	B	Moderate recommendation based on SR[33] including one RCT and case reports		Lucendo et al[33]
A careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is recommended before starting AIT	V	D	Moderate recommendation based on the risks identified by experts in RCTs at low[7] and unclear risk of bias[40]		Longo et al[7]; Skripak et al[44]
A careful evaluation of levels of sIgE, SPT, and concomitant asthma control is recommended before starting FA-AIT as high levels of sIgE and skin reactivity, and asthma have been found as risk factors for adverse events.	IV	C	Weak as based on expert review of consistent observational data[57-61]	Individual predictors of severe reactions still need to be identified	Vazquez-Ortiz et al[57]; Vazquez-Ortiz et al[58]; Martínez-Botas et al[59]; Varshney et al[60]; Narisety et al[61]

Referenzen aus Leitlinien

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Stiefel G et al., 2017 [4].

British Society for Allergy & Clinical Immunology

BSACI guideline for the diagnosis and management of peanut and tree nut allergy

Leitlinienorganisation/Fragestellung

This guideline informs the management of peanut and tree nut allergy. Adherence to this guideline does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar; Beteiligung von Patientinnen und Patienten nicht beschrieben
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche beschrieben; systematische Auswahl und Bewertung der Evidenz nicht beschrieben;
- Formale Konsensusprozesse nicht beschrieben; externes Begutachtungsverfahren unklar;
- Empfehlungen der Leitlinie sind nicht eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist nicht explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität beschrieben.

Recherche/Suchzeitraum:

MEDLINE and EMBASE from 2011 to 2014; additional references were hand-searched and provided by committee members, experts and reviewers from 2014 to 2017. Where evidence was lacking, a consensus was reached amongst experts on the committee.

LoE:

Level of evidence	Definition
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GoR:

Grade of recommendation	Type of Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population,
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
E (is not contained in SIGN)	Recommended best practice based on the clinical experience of the guideline development group

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zu relevanten Behandlungsoptionen wird die LL jedoch ergänzend dargestellt.

Empfehlungen

The term 'nut allergy' refers to both peanut and tree nut allergy, unless otherwise specified

- Patients should be provided with a comprehensive management plan including avoidance advice, patient-specific emergency medication and an emergency treatment plan, and training in administration of emergency medication. Regular retraining is required. (B)
- As part of the comprehensive management plans for children, all staff within the school and early years setting require appropriate training in managing an allergic reaction. (D)
- Nut allergy can lead to significant psychological burden as well as social and dietary restrictions that may affect quality of life. (C)
- Peanut oral immunotherapy can induce desensitization in peanut-allergic children. (A)

Backgroundinfos aus Leitlinien:

Management

A comprehensive management plan is essential and should include advice on avoidance of nuts, individual nut recognition, treatment of allergic reactions and provision of, and training in the use of emergency medications including adrenaline self-injectors. Detection and management of allergic comorbidities, particularly active management of asthma, are especially important, because of the association between poor asthma control and severe allergic reactions.

Additionally, in nut-allergic children the management plan needs to be delivered to the wider family (e.g. grandparents if appropriate, nursery, preschool and school). It is also essential to include and establish links with healthcare professionals who provide education of staff in schools and early years settings. Reactions to accidental exposures are frequent, but with good management, further reactions can be reduced in both frequency and severity.

Dietary management

All patients and their families/carers require clear information on nut avoidance. Dietitians can play a key role in educating patients and families on how to avoid nuts and how to give advice on an individual basis. This should also be supported by the relevant written information.

Medical management

Provision of emergency medication

Oral antihistamines. All patients should be supplied with oral antihistamines. Long-acting antihistamines with rapid onset of action, e.g. cetirizine are preferred. These should be used at the onset of any mild/moderate reaction, not requiring adrenaline.

AAI provision and training. The decision to provide an AAI should follow a risk assessment. The allergist should lead on advice and should consider and discuss views of the family/patient. Clear indications to provide injectable adrenaline include any previous episodes of anaphylaxis to a nut. Published BSACI guidelines advise on the provision of AAI [128]. Patients with PFS normally do not require an AAI, unless there have been severe reactions or another indication for an AAI is present. UK data suggest that children who are not at risk are being prescribed AAI [129]. All at-risk patients will require adrenaline to treat an episode of anaphylaxis. However, most patients will only need one injection of adrenaline [128, 130]. The decision to recommend one or more AAIs must be individualized with each patient and also requires a thorough risk assessment [128]. The provision of AAI training does significantly improve the ability to use an AAI effectively but over time, this ability diminishes [131–133]. In addition, specific training is required prior to switching between brands of any AAI device [134]. Even though AAI provision has greatly increased over recent years [129], patients often do not carry prescribed AAIs with them, when outside the home environment [5, 50, 135]; encouraging patients to carry AAI at all times is an essential part of training. The provision of written emergency action plans is essential [130, 136–138].

Immunotherapy

Clinical trials of peanut oral immunotherapy (OIT) have shown promising results [149–152]. Various routes of allergen administration are being explored, including the oral (OIT), sublingual (SLIT) and epicutaneous (EPIT) route. Although SLIT and EPIT appear to have a favourable safety profile, SLIT appears ineffective, and the effect of desensitization with EPIT is unknown [153]. Further evaluation of the use of immune modulators (anti-IgE and probiotics) in peanut OIT is required [150, 154].

The acquisition of long-term tolerance (where participants are able to consume peanut ad lib, without any need for ongoing therapy) vs. sustained unresponsiveness (ability to tolerate substantial gaps in nut ingestion) vs. transient desensitization

(an increase of the threshold of reactivity to peanut, which requires regular consumption in order to be maintained), following the administration of peanut immunotherapy, is under investigation [155].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2019) am 29.11.2019

#	Suchfrage
1	[mh "peanut hypersensitivity"]
2	[mh arachis/AE]
3	#1 OR #2
4	peanut*:ti,ab,kw
5	arachis hypogaea:ti,ab,kw
6	a hypogaea:ti,ab,kw
7	(ara NEXT h):ti,ab,kw
8	#4 OR #5 OR #6 OR #7
9	allerg*:ti,ab,kw
10	hypersensivit*:ti,ab,kw
11	reaction*:ti,ab,kw
12	hyperallerg*:ti,ab,kw
13	acute sensitiv*:ti,ab,kw
14	anaphyla*:ti,ab,kw
15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
16	#8 AND #15
17	#3 OR #16
18	#17 with Cochrane Library publication date from Nov 2014 to Nov 2019

Systematic Reviews in Medline (PubMed) am 29.11.2019

#	Suchfrage
1	peanut hypersensitivity[mh]
2	arachis/AE[mh]
3	#1 OR #2
4	peanut*[tiab]
5	arachis hypogaea[tiab]
6	a hypogaea[tiab]
7	ara h*[tiab]
8	#4 OR #5 OR #6 OR #7
9	allerg*[tiab]
10	hypersensivit*[tiab]
11	reaction*[tiab]
12	hyperallerg*[tiab]
13	acute sensitiv*[tiab]
14	anaphyla*[tiab]
15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
16	#8 AND #15

17	#3 OR #16
18	(#17) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
19	(#19) AND ("2014/11/01"[PDAT] : "3000"[PDAT])
20	(#20) NOT "The Cochrane database of systematic reviews"[Journal]
21	(#21) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 29.11.2019

#	**Suchfrage**
1	food hypersensitivity[mh]
2	fabaceae/AE[mh]
3	#1 OR #2
4	peanut*[tiab]
5	arachis hypogaea[tiab]
6	a hypogaea[tiab]
7	ara h*[tiab]
8	#4 OR #5 OR #6 OR #7
9	allerg*[tiab]
10	hypersensivit*[tiab]

11	reaction*[tiab]
12	hyperallerg*[tiab]
13	acute sensitiv*[tiab]
14	anaphyla*[tiab]
15	#9 OR #10 OR #11 OR #12 OR #13 OR #14
16	#8 AND #15
17	#3 OR #16
18	(#17) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
19	(#18) AND ("2014/11/01"[PDAT] : "3000"[PDAT])
20	(#19) NOT ((comment[ptyp]) OR letter[ptyp])
21	(#20) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
22	(#21) NOT retracted publication[ptyp]

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