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An Exploration of the Introduction of Oral Immunotherapy in a Paediatric Population with IgE-Mediated Egg Allergy: a Review of the Literature

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Abstract

Background and objectives: IgE-mediated egg allergy is commonly found in the paediatric population. Traditionally, management of egg allergy was through egg avoidance. The Irish College of General Practitioners and other paediatric societies across the globe recommend reintroducing egg into the diet to improve tolerance and quality of life. Oral immunotherapy (OIT) has been emerging as a potential method to induce desensitisation and even long-term tolerance in children with egg allergy, with many trials reporting significant differences after its implementation. The aim of this study is to combine and appraise the literature on OIT methods that have been trialed to improve tolerance in paediatric populations with IgE egg allergy and their outcomes.

Methodology: A search strategy based on the objectives of this review was used to conduct electronic searches on PubMed and Wiley Online Library. After the application of filters, 152 articles were obtained and after application of the inclusion and exclusion criteria, ten articles satisfying the criteria of this review were identified.

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Results: Six studies reported achievement of desensitisation or tolerance in more than 50% of the intervention group after OIT. Several reported immunological changes in the intervention group including decreased IgE levels, increased IgG4, and decreased SPT sizes. Allergic reactions were seen across studies, however, two studies reported a reduction in reactions over time. The patient's baseline IgE levels and egg tolerance, as well as the duration of the protocol, use of antihistamines, and participant compliance emerged as factors affecting the outcomes of these studies.

Conclusion: Although different OIT methods were utilised by each of these studies, most indicated that OIT has a role in improving the dose of egg tolerated by allergic patients. Future research needs to elicit whether the allergic reactions during OIT protocols are an acceptable risk and identify predictive markers for success with OIT.

Keywords

Egg allergy; IgE antibodies; OIT; Immune tolerance; Ovalbumin

Abbreviations

OIT: Oral Immunotherapy; EW: Egg White; IgE: Immunoglobulin E; sIgE: Specific IgE; OFC: Oral Food Challenge; OVO: Ovomucoid; OVA: Ovalbumin; SPT: Skin Prick Test; DBPCFC: Double-Blind Placebo-Controlled Food Challenge; BE: Baked Egg; HyDE: Hydrolysed Egg; LFQ: Long-term Follow-up Questionnaire

Introduction

Egg allergy is among the most common food allergies worldwide in children and occurs in around 3% of Irish children [1]. IgE-mediated egg allergies are type I hypersensitivity reactions involving the production of IgE antibodies to egg protein allergens. Albumin, ovalbumin, ovotransferrin, ovomucoid, and lysozyme are the five major egg protein allergens [2]. The symptoms may include angioedema, urticaria, and vomiting. Severe symptoms involve respiratory or cardiovascular compromise, known as anaphylaxis, and can be life threatening [1].

Around 80% of egg allergies resolve in childhood, however evidence is increasingly showing slower rates of resolution [3,4]. Traditionally, strict egg avoidance was the management strategy. This however comes with a series of challenges including adequate patient education and high vigilance regarding food intake on the patient's part. The COFAR study on 512 infants with likely milk or egg allergy showed that despite receiving care in food allergy clinics, the annualised reaction rate was 0.81 per year for all foods [5]. Furthermore, persistent food allergies have shown to have negative effects on quality of life and psychosocial welfare [6]. Taking these factors into account, oral immunotherapy methods implemented in childhood have the potential to help avoid years of suffering. OIT, also known as oral desensitisation, generally entails increasing doses of egg protein in IgE mediated egg allergy patients during the escalation and build up phases, after which the maximum tolerated dose is maintained [7,8]. (Figure 1) shows a typical OIT protocol.

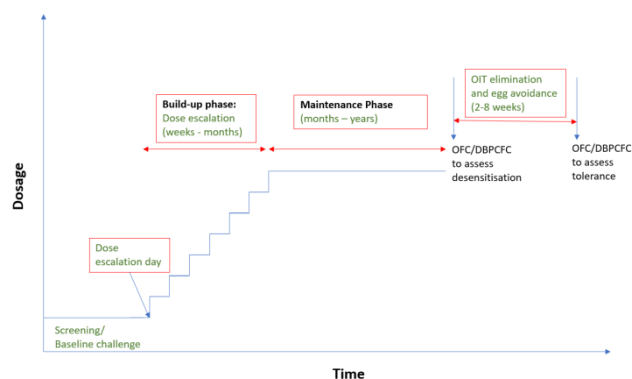


Figure 1: Typical OIT protocol.

It could help patients introduce egg into their diet and in high risk patients, increase the egg dosage they can tolerate to prevent adverse reactions with accidental intake [8]. OIT may initially induce desensitisation, whereby immune effector cells become less/non-reactive with increased doses of an allergen. Desensitisation may be lost if the allergen is not consumed regularly. The long-term goal is to induce tolerance or sustained unresponsiveness, whereby TH2 cells are downregulated and non-reactivity to the allergen will remain after OIT, even without daily egg consumption [9].

Studies have used different egg protein products for OIT ranging from less allergenic forms like baked egg, to more allergenic like raw egg white [10-13]. When tolerance is induced, serum-allergen sIgE levels reduce, while IgG4 (non-inflammatory antibody) levels rise [14].

Factors such as high baseline sIgE have been associated with a greater frequency and severity of adverse reactions during OIT [12,15]. Moreover, children already tolerating baked egg are more likely to become tolerant after OIT [4, 11]. Greater achievement of desensitisation/tolerance has also been reported with longer protocols [13,16]. Variation in compliance with the protocol also possibly influences outcomes [11]. Currently, the Irish College of General Practitioners guidelines recommend promoting tolerance to foods the child is allergic to, by reintroducing and avoiding unnecessary exclusions of the food in the diet [1]. Numerous methods have been trialed but currently there is no standardised method being used to improve tolerance to egg in paediatric populations.

Aim

This review aims to combine and appraise the literature on OIT methods that have been trialed to improve tolerance in paediatric populations with IgE egg allergy and their outcomes.

Objectives

The objectives of this review are to:

- Outline the current oral immunotherapy methods being trialed to improve tolerance to egg in children with IgE-mediated egg allergy.
- Analyse the outcomes of oral immunotherapy methods.

- Analyse factors that affect the outcomes of these methods.

Methodology

Literature search strategy

An electronic search was conducted on EBSCO host to identify 2 databases containing literature addressing the title and objectives of this review. The 2 databases identified to carry out further intensive searches were: PubMed and Wiley Online Library.

The following search strategy was utilised for PubMed:

- IgE egg allergy*[Title/Abstract] OR IgE mediated egg allergy*[Title/Abstract] OR Egg Hypersensitivity*[Title/Abstract] OR Immunoglobulin E egg allergy*[Title/Abstract] OR Immunoglobulin E egg mediated allergy*[Title/Abstract]
- "Oral immunotherapy*" [Title/Abstract] OR "food immunotherapy*" [Title/Abstract] OR "Desensitization" [Title/Abstract] OR "Desensitization" [Title/Abstract] OR "oral therapy*" [Title/Abstract]
- "Tolerance" [All Fields] OR "Immune Tolerance" [MeSH Terms] OR "Sustained Unresponsiveness" [All Fields] OR "Desensitization" [All Fields] OR "Desensitisation" [All Fields]

The following search strategy was utilised for Wiley Online Library:

- "IgE egg allergy* OR IgE mediated egg allergy* OR Egg Hypersensitivity* OR Immunoglobulin E egg allergy* OR Immunoglobulin E egg mediated allergy*" anywhere and
- "Oral immunotherapy* OR food immunotherapy* OR Desensitization OR Desensitisation OR oral therapy*" anywhere
- "Tolerance OR "Immune Tolerance" OR "Sustained Unresponsiveness" OR Desensitization OR Desensitisation" anywhere
- "Children OR Adolescent*" anywhere

Filters that were applied to the literature searches were, texts written in the English language, full text availability and studies that were original randomised clinical trials and clinical trials.

Additional filters applied to Wiley only: Paediatric Allergy and Immunology journal, "Child or Adolescent", Date of publication: 2011–2021.

The PubMed search yielded 59 results. After filters of "full text only" and only "clinical trials and randomised clinical trials" were added, 19 results were yielded. Attempts were made to broaden the results by removing filters regarding the study type and publication dates, however this again resulted in 19 results. The terms "children" and "adolescents" was not included in the search strategy to increase the results obtained, as with these terms and the above filters, only 16 results were derived. Since most IgE egg allergies present in childhood and resolve by adulthood, removal of this search term was unlikely to impact the results obtained/omit studies important to this review.

Although the "Children OR Adolescent*" search was not used in PubMed, this search field was added on Wiley because without it, 2,347 results were yielded. After adding filters of a "year range between 2011-2021" and "journals", 994 results were yielded. Adding additional filters including restricting search fields 1 or 2 to title only yielded 0 results. Limiting search fields 1 and 2 to abstract only also

resulted in 0 results. Hence, the decision was made to narrow down the search results by adding the filter of “articles from Paediatric Allergy and Immunology journal only”, a journal with one of the highest impact factors for paediatric allergy.

The word “outcomes” was not added in the searches but was a byproduct in most articles found. The term “desensitization” was added in search field 2 as the terms oral immunotherapy and oral desensitisation were used interchangeably in many studies but involved the same underlying principles. The term was also included in search field 3, as desensitisation was often a primary outcome of many studies that also evaluated tolerance as a secondary outcome.

Inclusion and exclusion criteria

Articles published within the last 10 years were included in this review to evaluate a range of OIT methods and analyse whether these methods and their outcomes have changed across the years. (Table 1) contains the criteria used.

Inclusion criteria	Exclusion criteria
Articles in English.	Articles in languages other than English.
Articles published between 2011-2021.	Articles published prior to 2011.
Articles with full text availability.	Articles without full text availability and content that was not subscribed to by University College Cork.
Original research articles only, including clinical trials, randomised control trials and quantitative studies.	Systematic reviews, meta-analysis, case reports, book chapters and editorials.
Study sample: Children formally diagnosed with IgE-mediated egg allergies or children who tested positive for specific IgE to egg.	Non-IgE mediated egg allergies, IgE allergies to foods other than egg.
Study sample with children and adolescents (age < 18 years) diagnosed with IgE-mediated egg allergy.	Study samples with participants over the age of 18 or children without IgE-mediated egg allergy.
Studies evaluating the use of oral immunotherapy.	Studies examining therapies other than oral immunotherapy.
Studies whose outcomes directly related to children's tolerance to egg after OIT or studies that at least did a long term follow up evaluation of participants post the OIT protocol.	Studies whose outcomes were not related to tolerance to egg.

Table 1: Inclusion and Exclusion Criteria.

Study selection process

The initial search on PubMed yielded 59 results, which was subsequently reduced to 19 after the addition of filters. The search on Wiley yielded 2,131 results which were reduced to 139 after filters were applied. Once duplicate articles were removed, 152 articles remained which were screened based on their titles, leading to the exclusion of 138 articles. The abstract and full text of the remaining 14 articles was read to assess which ones best fit the inclusion and exclusion criteria of this review. Finally, 10 articles were selected to be included in this review. The reasons for exclusion are summarized in (Table 2) and the study selection process is summarized in (Figure 2).

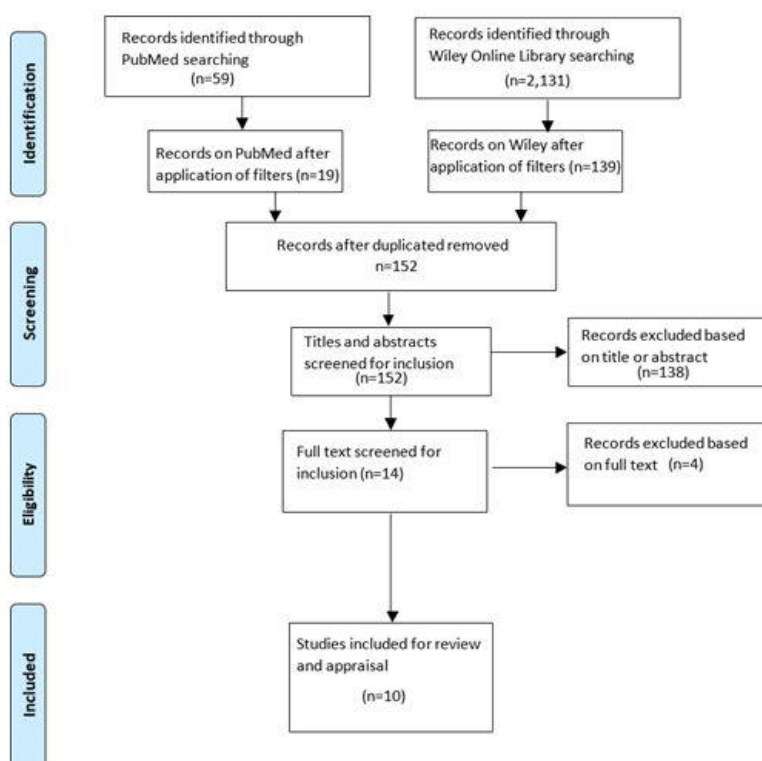


Figure 2: Selection process flowchart.

Reason for exclusion from review	Number of articles excluded
Study published prior to 2011.	1
Continuation of a study that was selected for inclusion in the review.	1
Studies that solely focus on measuring immunological profiles before or after OIT.	3
Studies that focused only on safety of OIT.	4

Titles that did not mention oral immunotherapy or oral desensitisation.	7
Articles that also assessed other allergies and were not specific to egg allergy alone.	47
Not original research articles.	78
Retrospective chart review.	1
Total	142

Table 2: Reasons for exclusion of articles from this review.

Data extraction and management

Data regarding author name, study location, study objectives, methods, sample size and characteristics, key findings and strengths and limitations was extracted for each of the 10 selected articles. The reference manager software Zotero was utilised to manage references.

Article validity and quality

The CASP critical appraisal checklist for the relevant article types was used to assess their quality and validity. Two questions in the randomised control trial CASP checklist regarding application of 'methods to my local population' and 'those in my care' were not applicable to this review and hence were not included.

Results

Eight articles were randomised control trials and two were prospective cohort studies. Their sample sizes varied from 20 - 72 children. A summary of the results is presented in (Table 3). The results after critical appraisal are shown in (Table 4 and 5).

Current oral immunotherapy methods being trialed

Different egg products were used in each study. Five studies used powdered egg [13,16-18,22]. One used egg proteins [12]. Three used pasteurised egg [11,17,20]. One used hydrolysed egg and another used raw egg [19,21]. The shortest protocol lasted 5 days, and the longest, 4 years [16,20].

Dose escalation followed by a maintenance phase was commonly implemented [11-13,16,22]. Four studies conducted dose escalations without a maintenance dose [17-21]. Giavi et al, was the only study without dose escalation, with a daily maintenance dose of 9 ± 1 g HyDE throughout the protocol [22].

The final dose administered differed across OIT protocols. Jones et al's maintenance phase was 2g EW powder [16]. The target maintenance dose in Kim et al's study was 2500mg and 1g in Palosuo et al's study [11,13]. The cumulative dose for Meglio et al's study was 25ml, 8ml for García Rodríguez et al,

10g for Fuentes et al, 2808 mg for Escudero et al, and 4g for Caminiti and Akashi et al [12,17,18, 20,22].

Outcomes of oral immunotherapy methods

Some studies aimed to induce tolerance while others aimed to desensitise patients. Seven assessed desensitisation and tolerance [11,12,16-18,20,21]. Three assessed desensitisation only [13,19,22]. In 6 studies desensitisation/tolerance was achieved in more than 50% of the OIT group [11-13,17,20-22]. Seven studies noted an increase in IgG4 in the OIT group [11,13,17-20,22]. The SPT size decreased after OIT as compared to baseline in 5 studies [12,17,18,20,21].

Decreased IgE was noted post protocol by 4 studies [12, 13, 20, 21]. Giavi et al additionally found lower levels of CD63+ ($P = 0.07$) and CD203c+ ($-10.96 (\pm 22.56)$ vs $9.94 (\pm 21.31)$, $P = 0.04$) cells post OIT as compared to post placebo [22].

Allergic reactions during protocol occurred in 9 studies [11-13,17-22]. Meglio et al found that at follow up, all children were symptom free [21]. Kim et al and Jones et al reported reductions in dosing symptoms after year 1 and 2 of their studies respectively [11,16].

Factors that affect the outcomes of these methods

Patient factors

Kim et al suggested that patients who were already tolerant to baked egg were more likely to achieve SU (43.5% vs 17.9%) [11]. Another study showed an inverse correlation between patient's sensitisation to all 4 egg allergens and their tolerated doses at 8 months of OIT ($r = -0.477$; $P < .001$) [13]. Escudero et al found that those who had adverse reactions during follow up had higher baseline IgE levels (8.6 (0.7–162) vs 4.7 (0.7–15.5) OVM-sIgE levels (kU/L), $P < 0.05$) and Palosuo et al noted that most desensitised at 8 months, had lower baseline IgE levels (95% of desensitised subjects had IgE levels below 57 kU/L for egg white) [12,13]. Compliance to protocols varied, with Escudero reporting 57% of patients disliking the egg product used [12].

Akashi et al reported that 1 patient refused product intake [19]. Kim et al noticed increased compliance in the OIT group as compared to the BE group (95.1% and 95.4% vs 89.8%) [11].

Protocol factors

Jones et al concluded that SU was enhanced with a longer protocol [16]. Palosuo et al also reported greater numbers achieving desensitisation at 18 months as compared to 8 months (72% vs 44%) [13]. Meglio et al administered cetirizine with each egg dose and Palosuo et al administered antihistamines before every dose until maintenance phase [13,21]. Spontaneous tolerance during the protocol was not accounted for by Caminiti and Jones et al [16,18]. Spontaneous tolerance was achieved by 21.8% of Fuentes- Aparicio's control group [17]. There were varying definitions of desensitisation and tolerance across all studies.

Author, (Year), Location, Title	Objectives	Study population, sample size, selection criteria	Study design, methods	Key findings	Strengths and limitations
Jones et al. (2016) United States “Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy” (16)	Primary: To evaluate the efficacy and safety of egg oral immunotherapy (eOIT) in participants treated for up to 4 years. Secondary: To assess safety during additional years of continued use of eOIT.	N=55 <u>Inclusion:</u> -Children aged 5-18. -History of egg allergy. -Serum egg-specific IgE >5kU/L in children ≥ 6 years of age, or 12kU/L in children who were 5 years old. <u>Exclusion criteria:</u> -Children likely to outgrow the egg allergy during OIT. -Children with IgE levels lower than that indicated above. -History of anaphylaxis.	Randomised Control Trial -Forty participants randomly assigned to eOIT with EW powder and 15 to placebo. -Dosing halted at 10 months in placebo group. eOIT group continued dosing for 4 years and stopped after SU achieved. -Maintenance phase = 2g egg white powder daily. -OFCs to assess desensitisation. -If OFC 1 passed, OIT halted for 4-6 weeks. Second OFC and 10g open egg feeding conducted to assess SU. -Those achieving SU instructed to follow ad libitum egg intake. -Wilcoxon rank sum tests, Fisher Exact tests using SAS software	-SU defined as passing 2 nd OFC and open egg feeding. -At year 2, 27.5% of eOIT patients achieved SU, and 50% at year 4. -Mild symptoms with dosing in 54.5%. Reduction in dosing symptoms after year 2. -At LFQs eOIT patients achieving SU reported consuming higher quantities and frequencies of egg. -sIgG4 increased (P = .001) and SPT decreased (P = .0002) in eOIT patients achieving SU. -Egg IgE levels at baseline lower in those achieving SU (P = .07).	<u>Strengths:</u> -Long assessment period. -Multicenter study. <u>Limitations</u> -No food challenges in placebo group after treatment, hence long-term efficacy reported was not controlled. -Not controlled for spontaneous resolution of allergy. -LFQs based on recall. -Underpowered end of study analysis due to participant withdrawal in the 4 years.
Giavi et al. (2016) Athens, Davos, Padua. “Oral immunotherapy with low allergenic hydrolysed egg in egg allergic children” (22)	Evaluate the safety and efficacy of Hydrolysed egg (HydE) product OIT for desensitisation in children with egg allergy.	N=29 commenced, n=25 completed study. Participants recruited from 3 study sites. <u>Inclusion:</u> -Age: 1-5.5 years old. -Diagnosis of IgE mediated egg allergy.	Prospective Cohort Study -Fifteen patients randomly assigned to the HydE OIT group, 4 withdrew. Fourteen assigned to placebo. -Daily administration of a sachet of 9 ± 1g placebo or HydE for 6 months. -Fisher's exact test, t-test and ANCOVA model or Wilcoxon rank sum test conducted using SAS software.	-Increase in IgG4 to EW, egg yolk and OVA (P = 0.07, P = 0.01 and P = 0.04) in the HydE group compared to placebo. -Nine adverse effects. -No significant difference in the maximum cumulative dose tolerated between groups (P = 0.35). -Lower percentage of CD63+ and CD203c+ cells seen in HydE group compared to placebo group (P = 0.07 and P = 0.04).	<u>Strengths:</u> -Placebo group. -HydE is safer for OIT. -Basophil activation tested. <u>Limitations:</u> -Adverse effects in placebo group. -No explanation on the determination of whether adverse reaction was related or unrelated to the product. -Small study sample.

Meglio et al. (2012) Rome, Italy "Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg" (21)	Desensitise children with moderate-severe IgE egg allergies to hen's eggs by gradual increased daily dosage of raw hen's eggs over 6 months to induce tolerance to the highest dose possible or allow consumption of 25ml of the product.	N=20 <u>Inclusion:</u> -Children aged >4years. -Classified as having IgE hen's egg (HE)allergy. <u>Exclusion:</u> -Receiving other oral immunotherapy. -Unstable asthma.	Randomised Control Trial -Ten children allocated to oral desensitisation (DG) and 10 to control group (CG). -CG: HE free diet. -EW and yolk diluted with water. -Doses doubled at 8 day intervals until 80th day. Then doubled every 16 days to reach 25ml HE by 6 months. -Cetirizine administration per day. -Those achieving 25ml/day advised to continue raw HE intake. -Wilcoxon rank sum test analysis.	-SPT decreased in DG only in 6 months ($p<0.01$). -In DG 80% able to tolerate 25ml/day ($p<0.01$). -Two months post protocol these children were symptom free. -Significant difference in sIgE OVO in DG ($p=0.02$). -In CG after 6 months, all but 2 had a positive DBPCFC. -Adherence to the protocol = 98.7%.	<u>Strengths:</u> -Graduated protocol, with calculations for each dose that equally distribute the risk of adverse effects throughout protocol. -Suggests an ability to predict failure/success of desensitization protocols based on REAST. <u>Limitations:</u> -No DBPCFC at the end of the protocol for the DG, only for CG. -Small sample size.
Kim et al. (2020) New York, Maryland, Arkansas, Colorado, North Carolina, U.S "Induction of sustained unresponsiveness after egg oral immunotherapy compared to baked egg therapy in children with egg allergy" (11)	Evaluate the safety and efficacy of BE consumption with egg OIT in patients who are tolerant to baked egg but allergic to unbaked egg	N=50, recruited from 5 U.S sites. <u>Inclusion:</u> -Age group: 3-16years. -IgE level ≥ 5 kUA/L to EW. -Negative DBPCFC to BE. -Positive DBPCFC to unbaked egg and dose limiting symptoms to ≤ 1444 mg EW protein. <u>Exclusion:</u> -Severe anaphylaxis history. -Eosinophilic gastrointestinal disease in the last 2 years. -Poorly controlled asthma.	Randomised - BE tolerant participants: 27 assigned BE, 23 assigned OIT. -Thirty nine BE reactive, added as a comparison group, given OIT. -SU defined as passing DBPCFC with cumulative dose of 7444 mg 8-10 weeks post termination of BE or OIT. -OIT: Dried EW powder. -BE dose: 2000mg EW protein for 2 years. -Daily home administration, escalation in clinic every 2 weeks. -Target maintenance dose for OIT group: 2500 mg. Control Trial Those passing DBPCFC at 2 years stopped BE/OIT for 8-10 weeks. -Barnard exact unconditional test and Wilcoxon rank sum test.	-SU achievement higher ($P=0.009$) in BE tolerant OIT group than BE group. -Success at SU DBPCFC higher in BE tolerant than BE reactive OIT group ($P = .031$). -OIT groups had higher sIgG4 than BE group ($P < .0001$). -In all groups after the 1st year, a lower percentage of dosage symptoms were seen. -At year 3 follow up: 73.7% in BE tolerant OIT group, 23.5% in BE group consumed unbaked egg in diet. (OIT-R vs BE: $P = .003$). -Higher compliance in OIT groups. -Discontinuation from the study due to symptoms from dosing observed in 3.7% participants in BE group, 8.7% participants in BE tolerant OIT group, 15.4% participants in BE reactive group.	<u>Strengths:</u> -Multicenter study. -Different egg tolerance phenotypes and forms of egg compared. -Long term followup. -Showed BE treatment has smaller effects than was previously hypothesised. <u>Limitations:</u> -Assumed BE reactive based on 1DBPCFC. -Small sample size. -Extra information about dosing given to OIT group. -No placebo group. -Lack of racial diversity in sample.
García Rodríguez et al. (2011)	Using an oral rush desensitisation method to assess its efficacy, safety,	N=23 patients aged 5-17 years (mean age	Prospective Cohort Study -Pasteurised raw EW. -Day 1: 5 doses of EW given to the patient at	-In total 20/23 patients achieved tolerance to full cooked egg, 14/20 achieved it in the 5 days of protocol. -Patient with highest IgE levels terminated protocol.	<u>Strengths:</u> -After age 5 there is lower rate of tolerance acquisition. -Anaphylaxis

Ciudad Real, Spain "Oral rush desensitization to egg: efficacy and safety" (20)	and immunological effects in egg allergic patients.	8.1 years), 6 girls, 17 boys. Inclusion: -Children aged 5 or over who visited the Allergy Department of Ciudad Real General Hospital. -Diagnosed with IgE mediated egg allergy. -Informed consent. Exclusion: -Children with intercurrent disease. -Children with unstable respiratory function.	1 hour intervals. -Day 5: 8 ml followed by 2hr interval and then 2 doses of half cooked egg 30 mins apart. -Desensitisation defined as tolerating 8ml raw egg and 1 whole cooked egg. -Patients tolerating a full cooked egg instructed to continue daily ingestion for 3 months. -Then interval of exposure was broadened to 48 hrs and at 6 months to 72 hrs. -SPSS software. Descriptive statistics, Wilcoxon test, t-test or Mann-Whitney test.	-SPT and mean sIgE in those taking >5 days to achieve tolerance was larger than those taking 5 days ($P=0.037$, $P=0.009$). -Allergic reactions in 78.3%. -sIgG levels significantly high at 3 weeks. -Significant decrease in sIgE by the 6 month follow up.	patients included. -8ml raw EW tolerance should be enough to protect patients from egg in normal diet. -Quick achievement of tolerance. -Good safety margin. <u>Limitations:</u> -Small sample size. -No control group. -Dosage in hospital potentially contributed to success rate.
Fuentes- Aparicio et al. (2013) Madrid, Spain "Specific oral tolerance induction in paediatric patients with persistent egg allergy" (17)	-Using an oral desensitisation protocol with powdered pasteurised egg to induce clinical tolerance in children with persistent egg allergy. -When total tolerance is not induced, the aim is to raise the tolerance threshold to avoid potential adverse effects from accidental egg consumption.	N=72 Inclusion: -Children aged 4-15. -Male and female. -Persistent egg allergy. -Egg allergy confirmed by OFC.	Randomised control trial -40 children randomised into specific oral tolerance induction (SOTI) group and 32 into the egg elimination diet (control group). -Protocol: 13 weeks duration. -Powdered pasteurised egg mixed into milkshakes or juice. -Began with 1mg and there were weekly increases in the dose until tolerance to 10g (equivalent to 1 full egg) was achieved. -Doses increased weekly at clinic and the last tolerated dose was continued at home daily for that week. -One month after the	-Tolerance achieved by 37/40 (92.5%) of children in SOTI group, compared to only 21.8% of the control group developing spontaneous tolerance ($p<0.0001$). -During protocol, 21/40 (52.5%) of patients had symptoms. Severe reactions in 13, epinephrine was required in 5 children. -Reduction in weal size in all patients at the end of SOTI ($p<0.001$) at all dilutions. -Significant change in IgG ($p<0.05$) with EW. -Nine patients had previously undergone milk oral therapy induction protocol successfully. -One patient in SOTI suffered anaphylactic reactions.	<u>Strengths:</u> -Older participants, indicating that tolerance achieved was due to the treatment and not spontaneous tolerance (seen in younger patients). -Antihistamines or corticosteroids were only given during adverse reactions. <u>Limitations:</u> -Open OFC rather than DBPCFC. -Tolerance to raw egg was not tested in all patients. -Exclusion criteria not well defined.

			<p>protocol, if the child had good tolerance they were recommended to follow a normal diet.</p> <p>-Open OFC to raw egg done after at least 6 months of completing SOTI.</p> <p>- SPSS used for statistical analysis. Wilcoxon test conducted.</p>		
<p><u>Escudero et al.</u> (2015) Madrid, Spain "Early sustained unresponsive ness after short-course egg oral immunotherapy: a randomized controlled study in egg- allergic children" (12)</p>	<p>-Assessing the efficacy of a short course of egg oral immunotherapy to induce SU to egg.</p> <p>-Evaluate safety of OIT.</p> <p>- Assess desensitisation induction.</p> <p>-Assess the possible predictors to develop sustained unresponsiveness.</p>	<p>N=61 Children aged 5-17 years.</p> <p>Inclusion:</p> <p>-History of symptomatic allergic reaction.</p> <p>-Male and female.</p> <p>-IgE egg allergy.</p> <p>-Egg avoidance diet/baked egg/extensively heat- treated egg.</p> <p>-SPT ≥ 3 mm and sIgE for EW, OVA and/or OVM ≥ 0.7 kU/L.</p> <p>-Positive DBPCFC to dehydrated EW during enrolment.</p> <p>Exclusion:</p> <p>-History of severe anaphylaxis.</p> <p>-Non-IgE mediated egg reaction.</p> <p>-Eosinophilic oesophagitis.</p> <p>-Allergy to placebo- controlled challenge or contraindication to epinephrine use.</p> <p>-Severe immune deficiency.</p> <p>-Autoimmune /malignant disease.</p>	<p>Randomised Control Trial</p> <p>-Randomised into OIT group(OITG)=30 patients, control group(CG)=31 patients. -CG on 4 months egg avoidance. OITG on 3-month OIT, then egg avoidance for 1 month.</p> <p>-Initial-day dose escalation of EW protein (cumulative dose 280 mg) administered at 20 min intervals in a single day.</p> <p>-Phase ended when patient had a reaction.</p> <p>-Build-up phase: weekly increase in dose until 2808 mg.</p> <p>-If a dose was tolerated, the following week the patient continued daily intake of this dose at home.</p> <p>-Maintenance phase: At least 1 undercooked egg every 48 hrs. Child allowed to consume other egg foods.</p> <p>-Personalised strategies during adverse effects.</p> <p>-OITG passing DBPCFC at 4 months asked to incorporate egg into the diet ad libitum.</p> <p>-Fisher's exact test, Wilcoxon</p>	<p>-SU defined as consuming 2808mg EW protein without symptoms, at 4 month DBPCFC.</p> <p>-Desensitisation achieved in 28/30(93%) of OITG (median 32.5 days).</p> <p>-At 4 month DBPCFC 37% of the OITG passed and 3% of the CG passed.</p> <p>-OITG who did not pass the 4th month DBPCFC had increased their threshold to a mean dose of 481.3 mg compared to CG's threshold mean dose of 256.2 mg at 4 months (P = 0.02).</p> <p>-During OIT, 145 adverse effects, most in build up phase.</p> <p>-Decreased SPT size in OITG at 4 months, compared to baseline (P = 0.001).</p> <p>-Decreased OVA-sIgE, at 4 months in the OITG (P < 0.001)</p> <p>-Higher baseline sIgE in those who had adverse reaction (P < 0.05).</p> <p>-In maintenance phase, 57% of the OITG reported difficulty with egg intake due to disliking the appearance, texture and/or taste.</p>	<p><u>Strengths:</u></p> <p>-Safe consumption after protocol.</p> <p>- Higher dose of egg (2808 mg protein) as compared to previous studies, to eliminate risk of accidental exposure.</p> <p>- Allergenicity of eggs maintained by giving undercooked eggs.</p> <p><u>Limitations:</u></p> <p>-Risk of lack of adherence due to difficulty consuming egg.</p> <p>-No placebo group.</p> <p>-Patients had lower sIgE levels to egg protein as compared to patients in other studies, which could influence success ratio.</p>

			test, Youden index and likelihood ratio calculated.		
<p>Palosuo et al. (2021)</p> <p>Finland</p> <p>"A</p> <p>Randomized, Open-Label Trial of Hen's Egg Oral Immunotherapy: Efficacy and Humoral Immune Responses in 50 Children"</p> <p>(13)</p>	<p>To determine efficacy of raw EW powder OIT in persistent egg allergic children and its effects on humoral responses.</p>	<p>N=50 commenced. <u>Inclusion:</u></p> <ul style="list-style-type: none"> -Age: 6-17 years. -History of hen's egg allergy. -EW-sIgE ≥ 0.35 kU/L. -Mild/moderate reaction during baseline DBPCFC. -Referred to Department of <u>Allergology</u> in Helsinki University Central Hospital. <p><u>Exclusion:</u></p> <ul style="list-style-type: none"> -Uncontrolled/severe asthma. -Poor adherence. -Autoimmune disease. -Pregnancy. -Severe systemic illness. -Malignant neoplasia. 	<p>Open Label Randomised Trial</p> <ul style="list-style-type: none"> -Randomly, 23 assigned to egg avoidance, 33 to OIT. -OIT 8 months or avoidance 6 months. -At 6 months, rechallenge in avoidance group, at 8 months crossed over to OIT. <p>OIT: -Build up phase (8 months): daily dosing of pasteurised EW powder.</p> <p>-Antihistamine dose until 2nd week of maintenance phase.</p> <p>-Dose escalations weekly then biweekly.</p> <p>-Maintenance dose target =1g EW protein.</p> <p>-Maintenance phase: 1/3rd EW daily.</p> <p>-After 3 months on target dose, open oral egg challenge conducted in fully desensitised patients.</p> <p>-T-test, Spearman Rank and Pearson correlation tests and Mann-Whitney U or the Kruskal-Wallis test.</p>	<ul style="list-style-type: none"> -Desensitisation: consuming maintenance dose target without symptoms. -In control group 1/20 passed the rechallenge in 6 months. -In OIT group 22/50(44%) reached desensitisation. -Symptoms in 82% during build up phase. -After 18 months of OIT 44/50 (88%) of all patients were consuming egg. 36/50 were considered desensitised. -Throughout OIT IgG4 concentration increased ($P < .001$). -At 8 months: decrease in IgE for Gal d 2 ($P < .01$). -Of those fully desensitised at 8 months, 21/22 had baseline IgE < 57 kU/L for EW. -At baseline 54% of the 50 participants were sensitised to all Gal d 1-4. Significant correlation between this and their tolerated dose at 8 months ($r = -0.477$; $P < .001$) and discontinuation of protocol. 	<p><u>Strengths:</u></p> <ul style="list-style-type: none"> -Raw EW to desensitise to allergens. -First study to show that sensitivity to all 4 allergens (Gal d 1-4) correlates with poor desensitisation. <p><u>Limitations:</u></p> <ul style="list-style-type: none"> -Not controlled trial, no placebo. -OFC with avoidance group could cause misclassification bias. -Possibility of participants outgrowing allergy in the 2 months before commencement of OIT. -Occurrence of dosing symptoms could be underestimated as no daily log kept. -No antibody analysis at 18 months.
<p>Caminiti et al. (2015)</p> <p>Palermo, Italy</p> <p>"Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo- Controlled Study, with Postdesensitization</p>	<p>Investigate the efficacy of egg OIT for desensitisation and assess if tolerance can be maintained post desensitisation.</p>	<p>N=31</p> <p><u>Inclusion:</u></p> <ul style="list-style-type: none"> -Male and female. -Age: 4-11 years. -Hen's egg allergy: positive DBPCFC, clinical history, SPT, sIgE positive assay for hen's egg. 	<p>Randomised Control Trial</p> <ul style="list-style-type: none"> -Seventeen randomised to OIT with dehydrated egg white (DEW), 14 into placebo. -DBPCFC at baseline and at 4 months to assess desensitisation. -Those desensitised, put on hen's egg-containing diet for 6 months and then egg avoidance for 3 months. -DBPCFC repeated to 	<ul style="list-style-type: none"> -Tolerance defined as passing last DBPCFC. -In the OIT group 16/17 desensitised. -No participant in control group passed DBPCFC after placebo ($P < .001$ vs OIT group). -Sustained tolerance achieved in 31%. -Eleven of 16 desensitised (69%), lost desensitisation and reacted again at DBPCFC ($P = .05$). -In the placebo group, 77% of participants had symptoms at 	<p><u>Strengths:</u></p> <ul style="list-style-type: none"> -Doses prepared by nurses rather than physician administering the dose, ensuring double-blind. -Similar results to other studies <p><u>Limitations:</u></p> <ul style="list-style-type: none"> -DEW may not contain all of the

Follow-Up" (18)			<p>assess maintained tolerance.</p> <p>OIT: Doses of DEW, diluted in saline, administered weekly.</p> <p>-Starting dose = 0.1mg and doubled weekly until cumulative dose of 4g reached at 4 months.</p> <p>-Cooked/boiled egg given to children tolerating 4g DEW dose.</p> <p>-IgG4, SPT and IgE tested at baseline and at 4 months in both groups. Assays repeated 10 months from baseline.</p>	<p>final DBPCFC.</p> <p>-Mean sIgG4 levels higher in the OIT group than placebo after protocol. 29.2 mcg/mL and 1.5 mcg/mL respectively (P = .001).</p> <p>-Three patients in OIT group had adverse reactions, 1 discontinued protocol.</p>	<p>allergens present in cooked or raw egg.</p> <p>-Possibility of spontaneous tolerance.</p> <p>-Small sample size.</p> <p>-Exclusion criteria not well defined.</p>
<p>Akashi et al. (2016)</p> <p>Tokyo, Japan</p> <p>"Randomized controlled trial of oral immunotherapy for egg allergy in Japanese patients" (19)</p>	<p>To conduct the first randomised control trial using OIT for patients with egg allergy in Japan.</p>	<p>N=36</p> <p>Recruited from outpatient department of National Center for Child Health and Development, Tokyo.</p> <p>Inclusion:</p> <p>-Age: 3-15 years.</p> <p>-Total elimination of egg in diet.</p> <p>-Egg-sIgE ≥ 0.7 UA/mL.</p> <p>-Positive immediate allergic reaction during egg DBPCFC after hospital admission.</p> <p>-Desire to join the</p>	<p>Randomised Control Trial</p> <p>-Participants randomly assigned to egg elimination (EE) or OIT. 18 patients in each group.</p> <p>-EE group continued regular diet.</p> <p>-Both groups underwent DBPCFC, after 6 months and EW-sIgE and IgG4 levels measured at both DBPCFCs. OIT:</p> <p>-Powdered egg starting dose 0.1mg, escalated every 3-4 days until 4g reached.</p> <p>-Antihistamines with OIT for repeated reactions.</p> <p>-Upon reaching 4g dose, study.</p> <p><u>Exclusion:</u></p> <p>-Anaphylaxis (hypotension or dyspnea) on egg challenge.</p>	<p>-OIT group: 17/18 had symptoms during protocol. Three patients withdrew due to repeated anaphylaxis/symptoms/refusal to ingest product.</p> <p>-Second DBPCFC: 8/14 in OIT group had no reaction, none in EE group had reaction (P < 0.01).</p> <p>-Increased median cumulative tolerated dose at 2nd DBPCFC compared to baseline in OIT group (P < 0.01).</p> <p>-IgG4 increased at 2nd DBPCFC in OIT group (P < 0.01). patients continued 4g intake until 2nd DBPCFC.</p> <p>-Adherence to protocol assessed during each outpatient visit.</p>	<p><u>Strengths:</u></p> <p>-Demonstrates possibility for OIT in Japan.</p> <p><u>Limitations:</u></p> <p>-Small sample size.</p> <p>-No placebo group.</p> <p>-Center based bias not excluded.</p> <p>-OIT not stopped before 2nd DBPCFC, cannot measure SU.</p> <p>-Food labelling laws, genetic factors and excessive avoidance of egg</p>

Table 3: Summary of results.

	Giavi et al. (22)	García Rodríguez et al. (20)
Did the study address a clearly focused issue?	Y	Y
Was the cohort recruited in an acceptable way?	Y	Y

Was the exposure accurately measured to minimise bias?	Y	Y
Was the outcome accurately measured to minimise bias?	Y	C, no control group.
Have the authors identified all important confounding factors?	Y	Y
Have they taken account of the confounding factors in the design and/or analysis?	Y	C
Was the follow up of subjects complete enough?	N	Y
Was the follow up of subjects long enough?	N	Y
What are the results of this study?	No significant difference in the maximum cumulative dose tolerated between placebo and OIT group. Increased IgG4 and decreased CD63+ and CD203c+ cells in OIT group.	Most achieved tolerance in 5 days. IgE levels decreased over 6 months.
How precise are the results?	Confidence intervals not calculated.	Confidence intervals not calculated.
Do you believe the results?	Y	Y
Can the results be applied to the local population?	N	N
Do the results of this study fit with other available evidence?	Y	Y
What are the implications of this study for practice?	Desensitisation can be initiated with a low allergenic egg product at home.	Tolerance can be achieved through short OIT protocols in hospital settings in symptomatic allergic patients.

Table 4: CASP Checklist for cohort studies. Y= Yes, N= No, C= Can't tell

	Jones et al. [16]	Megli et al. [21]	Kim et al. [11]	Palosu et al. [13]	Fuentes - Aparicio et al. [17]	Escudero et al. [12]	Camini et al. [18]	Akashiet al. [19]
Did the study address a clearly focused research question?	Y	Y	Y	Y	Y	Y	Y	Y

Was the assignment of participants to interventions randomised?	Y	Y	Y	Y	Y	Y	Y	Y
Were all participants who entered the study accounted for at its conclusion?	Y	Y	Y	Y	Y	Y	Y	Y
Were the participants 'blind' to the intervention they were given?	Y	Y	N	N	N	N	Y	N
Were the investigators 'blind' to the intervention they were giving to participants?	Y	N	C	N	N	C	Y	C
Were the people assessing/analysing outcome/s 'blinded'?	C	Y	Y	Y	Y	Y	Y	Y
Were the study groups similar at the start of the randomised controlled trial?	Y	Y	Y	Y	Y	Y	Y	Y
Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	N	Y	Y	Y	Y	Y	Y	Y
Were the effects of intervention reported comprehensively?	Y	Y	Y	Y	Y	Y	Y	Y

Was the precision of the estimate of the intervention or treatment effect reported?	Y	C	C	Y	N	C	N	N
Do the benefits of the experimental intervention outweigh the harms and costs?	Y	Y	Y	Y	Y	Y	Y	Y

Table 5: CASP Checklist for randomised control trials.

Discussion

The introduction of OIT for children with IgE egg allergy appears to be an effective method to induce desensitisation and, in some cases, tolerance. Each study used a different egg product and their duration and end points differed. The approach of dose escalation, followed by maintenance was utilised by five studies [11-13,16,22].

Meanwhile, Giavi et al. used a consistent daily dose of 9 ± 1 g HyDE throughout their protocol. They reported increased IgG4 and decreased CD63+ and CD203c+ cells post protocol, however did not find a significant difference in the maximum cumulative dose tolerated by the control and intervention group [22]. All studies adopting the escalation and maintenance phase strategy, except Palosuo et al, reported a significant increase in the proportion of participants in the OIT group who were desensitised or had a greater cumulative tolerated dose as compared to the control group after protocol [11-13,16,22].

Jones et al's protocol lasted for 4 years and García Rodríguez et al used a rush protocol lasting 5 days [16,20]. Jones et al argue that a longer protocol increases the proportion of participants achieving tolerance, as they found that greater percentage of participants reached SU at year 4 as compared to year 2 [16]. Giavi et al also suggested using longer protocols to enhance clinical outcomes [22]. Despite their short protocol, García Rodríguez et al reported 14/20 of their participants achieving tolerance in 5 days and significantly decreased sIgE at 6 months [20]. Hence, it is difficult to determine the most effective protocol based on duration. Furthermore, varying definitions of tolerance/desensitisation used across studies makes it tougher to determine the quantity of egg that needs to be consumed to ascertain tolerance achievement. Kim et al defined SU as passing DBPCFC with a cumulative dose of 7444 mg EW protein 8-10 weeks post intervention, while Escudero et al defined it as consuming 2808mg EW protein without symptoms at the 4 month DBPCFC [11,12].

Regardless of definitions, of the seven studies reporting tolerance, only four conducted egg avoidance in the OIT group prior to testing tolerance [11,12,16,18]. Having an egg avoidance phase is important to accurately state whether tolerance has been achieved as tolerance is permanent and independent

of repetitive allergen exposure [9]. This may reduce the validity of the other studies.

When tolerance is induced, sIgE levels decrease, while IgG4 levels rise. This aligns with the results of several studies in this review [14]. Seven studies showed increased IgG4 in the OIT group and three showed decreased sIgE [11-13,17-22]. Giavi et al, showed a decrease in CD63+ cells which was also found in other studies testing egg and peanut OITs [19,23,24]. Four studies reported decreased SPT values post protocol, aligning with studies on peanut OIT [12,17,18,20,21,25].

Allergic reactions during protocol were noted by nine studies. Escudero et al reported that most reactions occurred during the escalation phase. According to Escudero and García Rodríguez et al, most reactions were mild but Fuentes-Aparicio reported severe reactions with 5 requiring epinephrine administration [12,17,20]. However, other research indicates that reactions in the initial phase of OIT are common and tend to reduce over the course of the protocol [11,16,21,26,27]. The use of antihistamines during Meglio and Palosuo et al's protocols could have reduced their number of adverse reactions [13,21].

Higher baseline sIgE levels were associated with adverse effects and termination of protocol while lower levels were associated with greater achievement of desensitization [12,13,20,28]. Tolerance to baked egg also seemed to increase the likelihood of SU/desensitisation [4,11]. Escudero et al reported that 57% of patients had difficulty ingesting the product which could have affected compliance. Yet, they showed a high desensitisation rate [12,20]. A limitation of most trials was that they could not account for spontaneous tolerance.

Critical appraisal of the included studies

Control groups in many trials were not placebos but rather egg avoidance groups [12, 13,17,21,22]. Hence, participants were often not blinded to the interventions. Rodriguez et al had no control group [20]. Placebo groups would exclude bias of spontaneous tolerance. In Kim et al's trial, the OIT group were informed about risks related to missing doses, while the baked egg group were not. This could have increased compliance and introduced performance bias in the OIT group [11]. While statistical significance was calculated by all, estimating precision through confidence intervals was only done in two studies [13,16]. In Jones et al's study, the OIT group continued dosing for longer than the placebo group and no OFCs were conducted in the placebo group, making it difficult to fairly compare results [16]. Two studies were multicenter, with Kim et al's study including participants with different egg tolerance phenotypes, making their results more generalisable [11,16]. The sample size of several studies was too small to make definitive conclusions [11,13,18-22].

Impact on current knowledge

This review highlighted several different OIT methods and their results. Overall, the results demonstrate support for OIT as a useful method for the development of desensitisation and/or tolerance to egg in allergic patients. They also suggest both protocol and patient factors that may influence the success of OIT seen in patients, and potential drawbacks of OIT. Taking these studies into account, OIT can be considered a potential therapy to be used for paediatric egg allergic patients in the future, as in many

countries egg avoidance is still the primary form of treatment. The studies show that it can be implemented both in clinical settings and at home. The use of OIT to induce desensitisation/tolerance could also make it preferable to egg avoidance diets, as it would limit the need for caution with food intake and allow children to consume foods containing egg more readily.

Suggestions for future research

It is essential to explore whether reactions during OIT are an acceptable risk and whether they outweigh the risk of reactions that may otherwise occur from accidental egg exposure in non-desensitised patients. Investigation of predictive markers for the achievement of SU/desensitisation would also help guide clinicians on which patients should be started on OIT. Future studies should additionally identify the most palatable egg product for OIT. Research on the impact of the OIT on quality of life, would be important to assess its long-term benefits.

Strengths and limitations of this review

This review appraised and condensed literature regarding OIT to improve tolerance in children with IgE egg allergy, the most common type of egg allergy. Two databases were searched, ten OIT protocols were highlighted, and their outcomes were evaluated against current knowledge regarding immune tolerance.

The restriction of the review to ten articles and a strict inclusion criterion could have led to some valuable articles being missed. Egg allergic patients often also have other food allergies, but this review looked solely at studies where patients only had egg allergy. Only articles with full text availability in English were included.

Conclusion

OIT stands out as an upcoming, potential method for the management of IgE egg allergy in paediatric populations. A variety of protocols have been trialed with many indicating that it has a role in inducing desensitisation and increasing patient's tolerated doses. Some have reported tolerance. However, reactions commonly occurred during protocols. Hence, it is imperative to evaluate whether these are acceptable risks in comparison to the risks with accidental egg exposure. Factors such as previous baked egg tolerance and baseline humoral immunity may affect the protocol's outcomes, however further research needs to be conducted to ascertain predictive factors for the success of OIT.

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