Oral and sublingual immunotherapy for egg allergy (Review)

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[Intervention Review]

Oral and sublingual immunotherapy for egg allergy

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ABSTRACT

Background

Clinical egg allergy is a common food allergy. Current management relies upon strict allergen avoidance. Oral immunotherapy (OIT) might be an optional treatment, through desensitization to egg allergen.

Objectives

We aimed to assess the successful desensitization and development of tolerance to egg protein and the safety of egg oral and sublingual immunotherapy in children and adults with immunoglobulin E (IgE)-mediated egg allergy as compared to a placebo treatment or an avoidance strategy.

Search methods

We searched 13 databases for journal articles, conference proceedings, theses and unpublished trials using a combination of subject headings and text words (the last search was on 5 December 2013).

Selection criteria

Randomized controlled trials (RCTs) were included. All age groups with clinical egg allergy were to be included.

Data collection and analysis

We retrieved 83 studies from the electronic searches. We selected studies, extracted data and assessed the methodological quality. We attempted to contact the study investigators to obtain the unpublished data, wherever possible. We used the I^2 statistic to assess statistical heterogeneity. We estimated a pooled risk ratio (RR) with 95% confidence interval (CI) for each outcome using a Mantel-Haenzel fixed-effect model if statistical heterogeneity was low (I^2 value less than 50%).

Main results

We included four RCTs with a total of 167 recruited individuals (OIT 100; control 67 participants), all of whom were children (aged four to 15 years). One study used a placebo and three studies used an avoidance diet as the control. Each study used a different OIT protocol. Thirty nine per cent of OIT participants were able to tolerate a full serving of egg compared to 11.9% of the controls (RR 3.39, 95% CI 1.74 to 6.62). Forty per cent of OIT participants could ingest a partial serving of egg (1 g to 7.5 g; RR 5.73, 95% CI 3.13 to 10.50). Sixty nine per cent of the participants presented with mild-to-severe adverse effects (AEs) during OIT (RR 6.06, 95% CI 3.11 to 11.83). Five of the 100 participants receiving OIT required epinephrine. We cannot comment on whether over- or under-reporting of AEs was a concern based on the available data. Overall there was inconsistent methodological rigour in the trials.

Authors' conclusions

The studies were small and the quality of evidence was low. Current evidence suggests that OIT can desensitize a large number of egg-allergic patients, although it remains unknown whether long-term tolerance develops. A major difficulty of OIT is the frequency of AEs, though these are usually mild and self-limiting. The use of epinephrine while on OIT seems infrequent. There are no standardized protocols for OIT and guidelines would be required prior to incorporating desensitization into clinical practice.

PLAIN LANGUAGE SUMMARY

Daily administration of small, incremental amounts of egg protein for treatment of egg allergy

Until recently, the only practical option for people with food allergies was a strict avoidance of allergen-containing food. It is difficult to avoid egg because it is found in many foods. Even with avoidance, the fear of accidental ingestion from mislabelled foods or cross-contamination is an ever-present fear for even the most careful of food-allergic individuals. Accidental consumption of egg-containing foods might cause a life-threatening event. Although there are only a small number of published studies, there is a new type of treatment for egg allergy called 'oral immunotherapy' (also known as 'oral desensitization' or 'vaccination'). This is comprised of daily consumption of a small amount of egg protein, which is gradually increased over time until a full serving is reached. This method could alter the allergic response to the egg protein by the body's immune system, increasing the amount of egg that can be eaten without inducing an adverse reaction.

We identified randomized controlled trials that compared oral immunotherapy to a placebo or avoidance diet in people with egg allergy. A total of 167 children (100 in the oral immunotherapy group and 67 in the control group) who were aged 4 to 15 years were studied. The evidence to date showed that oral immunotherapy for egg allergy might help a majority of egg allergic children to tolerate a partial serving of egg, as long as they continued to consume a daily amount of egg protein. Side effects were frequent during the oral immunotherapy but they were usually mild to moderate. Nevertheless, five of 100 patients treated with oral immunotherapy for egg allergy required epinephrine administration because of a serious hypersensitivity reaction. Of note, the trials involved small numbers and there were problems with the way they were done, therefore further research is needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oral and sublingual immunotherapy compared to no therapy for egg allergy

Patient or population: patients with egg allergy
Settings:
Intervention: oral and sublingual immunotherapy
Comparison: no therapy for egg allergy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No therapy for egg allergy	Oral and sublingual immunotherapy				
increase in the amount of egg that can be tolerated	Study population		RR 5.73 (3.13 to 10.5)	167 (4 studies)	⊕⊕◯◯ low[1,2]	
	134 per 1000	770 per 1000 (420 to 1000)				
	Moderate					
	100 per 1000	573 per 1000 (313 to 1000)				
complete recovery	Study population		RR 3.39 (1.74 to 6.62)	167 (4 studies)	⊕⊕◯◯ low[1,2]	
	119 per 1000	405 per 1000 (208 to 790)				
	Moderate					
	50 per 1000	170 per 1000 (87 to 331)				

serious adverse events	See comment	See comment	Not estimable	167 (4 studies)	⊕⊕◯◯ **low**[1,2]
mild to severe adverse reactions	**Study population**		**RR 6.06** (3.11 to 11.83)	167 (4 studies)	⊕⊕◯◯ **low**[1,2]
	90 per 1000	**543 per 1000** (279 to 1000)			
	Moderate				
	100 per 1000	**606 per 1000** (311 to 1000)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] all studies at high or unclear risk of bias in at least one domain
[2] few events

BACKGROUND

Description of the condition

Clinical egg allergy is one of the most common food allergies in western countries, affecting up to approximately 2% of young children (Savage 2007). Osborne 2011 showed an 8.9% prevalence of challenge-proven egg allergy in 12-month old infants in Australia. Natural tolerance, developing tolerance to egg over time, is common but some children will remain allergic until adulthood, and egg-allergic reactions might persist throughout adulthood even though the symptoms may be milder. It has been shown that 75% to 85% of young children with egg allergy could tolerate heat-denatured (baked) egg products, showing mild or no symptoms (Leonard 2012; Osborne 2011); most of these children will 'outgrow' their allergy. Despite this trend, recent data have shown that milk and egg allergies are becoming more persistent and that children may not be outgrowing these allergies until adolescence rather than during the first five to six years of life as previously thought (Savage 2007). It appears that the longer the egg allergy persists the less likely it is that tolerance will develop (Wood 2003 B). Thus, it has become imperative to understand individualized prognoses of egg allergy and develop clinical management that may improve the quality of life of egg-allergic children and, ideally, promote the earlier development of tolerance. It is likely that the vast majority of children who tolerate baked-egg products will develop tolerance after undergoing oral immunotherapy (OIT), perhaps more rapidly if treated with OIT. Those who do not tolerate heat-denatured egg are likely to be very different, and more difficult to treat. Consequently, an adequate placebo group is needed to investigate the ability of OIT to induce long-term tolerance.

An immunoglobulin E (IgE)-antibody mediated allergic reaction to egg is based on soluble IgE, which is produced by B cells, circulating levels and what is bound to the surface of mast cells and basophils. Mast cells are found in the skin, gut, and respiratory tract and are situated adjacent to nerves and blood vessels. Among the most important of their immune functions is the propensity to bind IgE, utilising the high-affinity IgE receptor FcåR1. When egg allergen is re-encountered and recognized by cell-bound IgE, adjacent FcåR1-IgE complexes move closer together and bring their signalling machinery into close proximity, which sets off a cascade of phosphorylation ultimately resulting in calcium influx. When calcium enters the cell, the activated mast cell undergoes degranulation and the contents of these granules are released into the extracellular space. The immediate liberation of preformed powerful vasoactive compounds such as histamine, platelet activating factor, tryptase, carboxypeptidase, chymase, and heparin elicit the acute symptoms of type 1 hypersensitivity reactions in the skin, gut, respiratory, and cardiovascular systems (Galli 2010). These symptoms include urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhoea, wheezing, coughing and bronchospasm, rhinorrhoea, and hypotension or syncope, which can occur alone or in combination and typically begin within minutes up to two hours after food ingestion (Burks 2008; Simons 2011). There is no interventional therapy currently approved by the US Food and Drug Administration, nor by the European Medicines Agency (EMA). Current management relies upon strict allergen avoidance, including the small quantities present in a variety of foods as well as obvious sources such as dessert. In the US, European Union, Australia, Japan, and Singapore, food-labelling laws require food manufacturers to label packaging in plain language, listing the presence of common allergens and products. However, similar laws are not in place in many other countries and in these settings care is required to identify hidden forms of egg allergens, such as ovalbumin or ovomucoid (Burks 2012a). Studies that evaluated growth measurements against dietary records have suggested that food allergy puts children at risk of inadequate nutrition (Christie 2002). Specifically, where paediatric food allergy is concerned it is advisable to involve a dietician in formulating a nutritionally adequate, allergen-free diet. The quality of life of affected persons and their caregivers is reduced due to the fear of incorrect labelling or accidental egg-containing food ingestion and the ever-present threat of anaphylaxis (Cummings 2010). The management of clinical egg allergy consists of teaching individuals and caregivers to recognize the symptoms and signs of severe reaction, the prompt use of epinephrine auto-injection, and activation of emergency medicine (Simons 2009).

Therefore, therapeutic interventions that might provide lifelong protection against potential egg ingestion are needed. Traditional subcutaneous immunotherapy (also known as 'allergy shots') was studied over 10 years ago and was able to induce desensitisation. However, this type of treatment is not feasible due to the high rate of systemic reactions during the immunotherapy (Nelson 1997; Oppenheimer 1992). Given the safety issues from subcutaneous immunotherapy, oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) have recently been studied as optional treatments. Although there have been scattered reports in the literature over the last 100 years on the use of OIT for food allergy, the majority of research has occurred in the last 25 years, beginning with Patriarca 1984, who demonstrated the successful treatment of allergies to cow's milk, egg, fish, and fruits with standardized OIT protocols. In a pilot study of OIT for egg allergy in children, Buchanan demonstrated the safety of a 24-month egg OIT protocol involving a modified rush desensitization phase, build-up phase, and maintenance phase (Buchanan 2007). A randomized, double-blind study showed that 75% of children in the OIT group were desensitised (Burks 2012). A small randomized controlled study (Dello Iacono 2013) was published recently showing that 90% of children with severe egg allergy achieved a partial level of tolerance after six months of treatment. Similar results were published in the study by Meglio 2013. The initial aim of OIT is to provide clinical desensitization, that is to achieve a state in which effector cells involved in a specific immune response develop reduced reactivity or become non-reactive upon increased

introduction of an allergen. In a desensitized state, an individual may be non-reactive while regularly receiving the allergen. However, when regular administration ends the previous amount of reactivity returns. The goal of immunotherapy is to reach a state of tolerance where the non-reactive state remains present permanently through down-regulation of the TH2 response to egg, and which will endure irrespective of whether a previously clinically reactive patient continues to consume egg products or not (Land 2011).

There are different types of OIT protocols. OIT involves the regular administration of small amounts of allergen by the oral route to first rapidly induce desensitization then over time induce tolerance to the allergen. Some reports have considered immunotherapy that is ingested and immunotherapy that is administered sublingually as two forms of oral immunotherapy. For the purposes of this review, OIT will refer specifically to ingested immunotherapy and sublingual immunotherapy (SLIT) will refer to immunotherapy that is administered under the tongue. Patients undergoing OIT generally ingest a mixture of protein powder in a vehicle food (for example apple sauce). Patients undergoing SLIT generally receive a small amount of liquid extract under the tongue. Both treatments are typically initiated in a controlled setting where gradually increasing doses of allergen are given up to a targeted dose. Following this, in standard protocols the majority of dosing is done at home.

Description of the intervention

Therapeutic interventions that may provide lifelong protection against accidental allergen ingestion are needed. OIT is of particular interest as a possible treatment for egg allergy. The aim of the treatment is initially to desensitize patients to egg allergen by increasing the threshold dose of exposure, to reduce the risk of anaphylaxis. However, the longer-term goal is to induce a state of tolerance to an allergen following the completion of the treatment. More importantly, Jones 2009 demonstrated that underlying the clinical benefits of OIT were changes to multiple aspects of the immune system, leading to a dampened allergic response. These changes included not only the decrease in allergen-specific IgE and increase in allergen-specific IgG4, previously demonstrated (Buchanan 2007; Itoh 2010; Patriarca 2003; Staden 2007), but also a suppression of mast cells and basophils, an increase in T regulatory cells (TRegs), and a change in cytokine profile. Additionally, microarray analysis of patient T cells has revealed changes in several apoptotic pathways, although the significance of this result is still unknown (Jones 2009). Cytokine analysis demonstrated a clear decrease in TH2 cytokines without a concomitant increase in TH1 cytokines, causing a shift in TH1 and TH2 skewing and arguing against OIT. Rather, a decrease in IL-2 was noted possibly suggesting clonal anergy or deletion as a possible mechanism of OIT (Land 2011). However, one should be cautious of interpreting these results as both studies had small cohorts of participants and the selection criteria for the immunological studies were not sufficiently clear.

How the intervention might work

OIT involves the administration of initially very small doses (usually micrograms or milligrams) of food allergen to food-allergic patients in a controlled clinical setting. The dose of the administered food allergen is then systematically increased until a maximum tolerated dose is achieved (Jones 2009). Regular dosing with this maximal dose is then maintained at home by the patient. Successful desensitization is thought to induce immunological tolerance by generating allergen specific IL-10 secreting Tr1 or TGF- secreting TH3 regulatory T cells, or both (Sicherer 2010).

Why it is important to do this review

Food allergy is an IgE-mediated immediate-type hypersensitivity that is thought to be the result of a breakdown in the normal process of oral tolerance. Although the prevalence of food allergy continues to rise, avoidance remains the standard of care as no disease-modifying treatments are readily available. Although questions regarding the safety of the treatments and the potential for the development of long-term immunological tolerance remain, OIT and SLIT offer a potential hope for the future treatment of egg allergy. Thus, there is a need to systematically identify, critically appraise, and summarize the available evidence on the benefits and risks that are associated with OIT and SLIT for the management of persons with egg allergy.

OBJECTIVES

To assess the successful desensitization and development of tolerance to egg protein and the safety of egg oral and sublingual, immunotherapy in children and adults with IgE-mediated egg allergy as compared to a placebo treatment or an avoidance strategy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), quasi-RCTs, and controlled clinical trials (CCT) were included.

Types of participants

Children and adults diagnosed with an immediate-type egg allergy were included. Egg allergy was defined as a history of systemic clinical reaction within minutes to hours after the ingestion of egg in patients with objective evidence of sensitization to egg. Objective evidence was:

1. a positive skin prick test (SPT) or the presence of specific IgE;
2. a positive open or double-blind, placebo-controlled food challenge. The positive reaction to the challenge should be the immediate onset of symptoms suggestive of IgE-mediated mechanisms such as urticaria, angioedema, vomiting, diarrhoea, abdominal pain, and any alteration in the level of consciousness.

Types of interventions

Egg OIT or SLIT administered by any protocol compared with a placebo group, an alternative way of administering desensitization therapy, or treatment with a continued avoidance diet.

Types of outcome measures

Primary outcomes

Successful desensitization or achieved tolerance defined as:

- an increase in the amount of egg that can be ingested and tolerated (absence of adverse reactions) while receiving allergen-specific OIT or SLIT (i.e. evidence of desensitization);
- a complete recovery from egg allergy after completion of OIT or SLIT whether or not egg is eaten (i.e. induction of immunologic tolerance).

Secondary outcomes

1. Immunological changes suggestive of the induction of tolerance (e.g. decreased wheal diameter on SPT testing with egg, decreased egg-specific IgE levels, increased egg-specific IgG4 levels)
2. Serious adverse events
3. Mild-to-severe adverse reactions
4. Satisfaction
5. Change in quality of life
6. Cost effectiveness

We presented the main outcomes of the review in a summary of findings table.

Search methods for identification of studies

We conducted systematic searches for RCTs, quasi-RCTs, and CCTs regardless of language, geographical area, or publication status. The date of the last search of all databases was 5 December 2013.

Electronic searches

We searched the following databases: EMBASE, PubMed, MEDLINE, The Cochrane Library, ISI Web of Science, Google Schoolar, AMED, BIOSIS, CAB, CINAHL, Global Health, TRIP, and WHO Global Health Library. The MEDLINE search strategies are detailed in Appendix 1 and the search strategies used for other databases are found in Appendix 2. We combined subject search strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomized controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b (Higgins 2011).

Searching other resources

We found unpublished studies, ongoing work and research in progress by searching key internet-based relevant databases (controlled-trials.com, clinicaltrials.gov, and www.anzctr.org.au). We also searched the proceedings of conferences important to allergy and immunology and not included in the electronic databases. We used key articles retrieved from the electronic database searches (including seminal research studies and review articles) to conduct citation searches in Web of Science and Scopus. We searched for grey literature via Google Scholar (scholar.google.com) and contacted experts in the field.

Data collection and analysis

Selection of studies

One author screened the retrieved titles and abstracts of records and excluded irrelevant ones. We retrieved full texts of reports of potentially relevant studies. Multiple reports from the same study were identified and grouped under a single study identifier. Two authors independently undertook the examination of studies and selection based on the eligibility criteria. If required, study investigators were contacted to clarify eligibility. If the two authors did not agree on including a study, even after discussion, the third author acted as an arbiter.

Data extraction and management

We created a data extraction form and included the following items: trial characteristics (setting, OIT regimen, eligibility criteria); methodological quality (randomization, blinding, selective reporting); patient characteristics; results and outcomes. The form was piloted using two sample studies. Data extraction was undertaken by two authors working independently. Correspondence with study investigators was required when not all information was available from the reports. Disagreements between review authors were resolved with discussion and, if required, arbitration by the third author.

Assessment of risk of bias in included studies

Two authors indepemdently used the Cochrane Collaboration's risk of bias tool to evaluate each included study. We considered the following types of potential bias: selection bias (adequacy of randomization and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); and attrition bias (loss to follow-up). Any disagreements were discussed and the third author acted as an arbiter if necessary. The results of the assessments are summarized in the 'Risk of bias' table. To determine the influence of the studies with a high risk of bias on the results of the meta-analysis, sensitivity analyses were performed.

Measures of treatment effect

The outcomes were collected and analysed as dichotomous data, for example the presence or absence of tolerance, partial tolerance, adverse effects. The effect measure of choice was the risk ratio (RR).

Unit of analysis issues

We did not anticipate that we were likely to come across unit of analysis issues with this particular intervention. For example, cross-over trials would not be a rational approach to assessing immunotherapy as the goal of treatment is to induce tolerance, and a patient would not be able to serve as their own control if their immune response had been altered. We also did not expect large numbers of egg-allergic patients to arise from various cohorts and so cluster-randomization was unlikely to be encountered.

Dealing with missing data

When addressing missing data we attempted to contact study investigators to request them. When possible, we classified missing data as random and non-random. For the non-random missing data it was necessary to input replacement values based on reasonable clinical assumptions. If this was required, a sensitivity analysis was performed to ensure that any assumptions made did not greatly change the results. Data were analysed on an intention-to-treat (ITT) basis whenever possible.

Assessment of heterogeneity

We anticipated clinical heterogeneity in the studies that were reviewed, including the ages of the study population and differences in the immunotherapy protocol. However, despite these potential differences we believe that we were able to analyse the studies together to assess the efficacy of OIT. We assessed statistical heterogeneity using the I^2 statistic (Higgins 2011), where an I^2 value greater than 50% implies substantial heterogeneity. If statistical heterogeneity was detected, we explored the possible causes through sensitivity analyses.

Assessment of reporting biases

If appropriate, a funnel plot was created to assess whether there was evidence of asymmetry indicative of possible publication or other types of bias.

Data synthesis

We intended to use the Mantel-Haenszel fixed-effect model for meta-analysis, and we summarized the evidence in a summary of findings table. All analyses were conducted using Review Manager (RevMan 5).

Subgroup analysis and investigation of heterogeneity

Depending on the data available, we undertook subgroup analyses for presence of asthma, other food allergies, history of previous anaphylaxis, the OIT or SLIT regimen, duration of treatment, time since completion of treatment, and RCT versus non-RCT.

Sensitivity analysis

A sensitivity analysis was performed for reviewed studies that were deemed at high risk of bias.

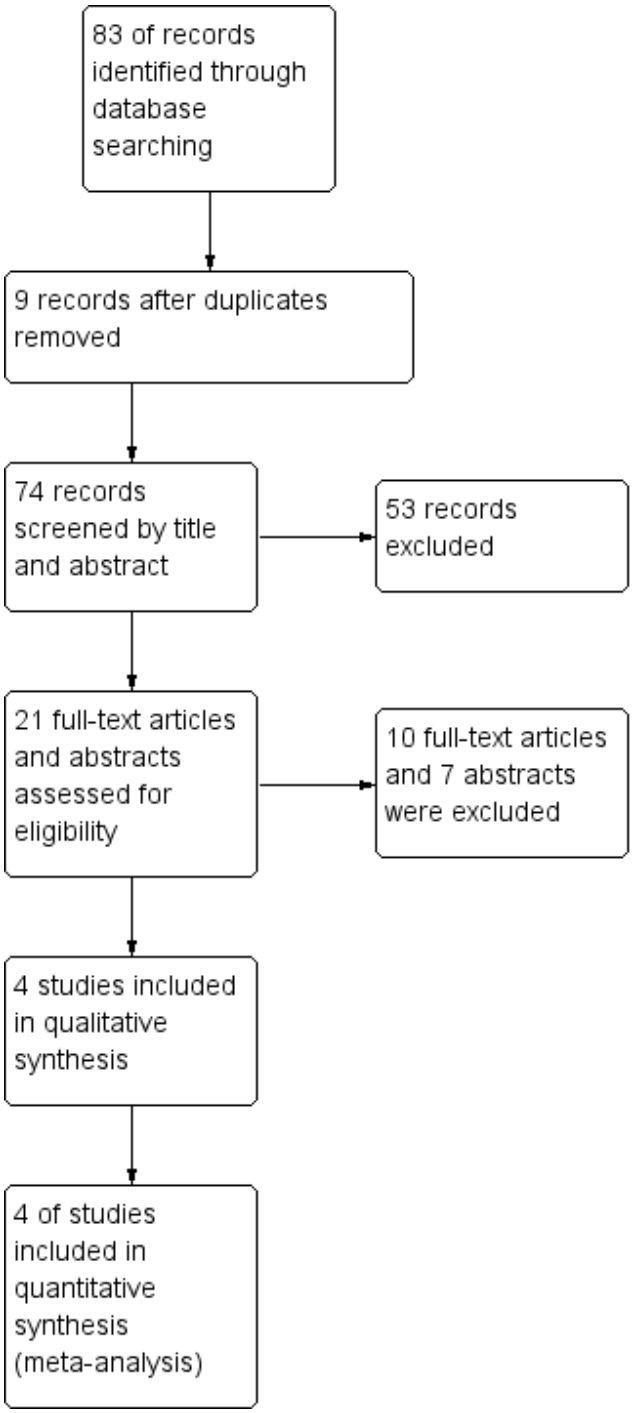
RESULTS

Description of studies

Results of the search

The electronic searches retrieved 83 studies, from which 74 remained after removing duplications. A review author screened these and excluded 53 records based on title and abstract information. We then retrieved full-text articles for the remaining 21 records. For conference abstracts and trial registries, all available information was included in a citation database along with full-text articles. Two authors independently assessed these records for eligibility for inclusion. We contacted article authors if there was insufficient information to assess eligibility. We resolved discrepancies through discussion. See the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

We identified four published RCTs that satisfied the inclusion criteria. The methods, participants, interventions, and outcomes of the included studies are listed in the Characteristics of included studies table. A total of 167 patients were recruited (intervention group 100 patients; control group 67 patients). All patients were children aged four to 15 years. One study used a placebo control (Burks 2012) and three studies used an avoidance diet as the control (Dello Iacono 2013; Fuentes-Aparicio 2012; Meglio 2013). One study excluded children with a history of anaphylaxis (Burks 2012), two studies excluded children with unstable asthma and any other immunotherapy (Dello Iacono 2013; Meglio 2013), two studies included children with a history of anaphylaxis (Dello Iacono 2013; Fuentes-Aparicio 2012), one study excluded children with parents with a history of unreliable management of complications and treatment (Dello Iacono 2013). Finally, one study administered an antihistamine treatment as a co-intervention (Meglio 2013).

Of note, the egg immunotherapy protocols differed from each other. However, all of them included a build-up phase in an institution (hospital, day hospital, research centre) followed by gradual up-dosing (hospital or home) and a maintenance phase at home. The Burks 2012 protocol was characterized by an increasing dose in research settings followed by an approximate doubling every 30 minutes, up to 50 mg. The maximum tolerated single dose of egg was given in the clinic on the following day and it was the starting dose for the build-up phase. Attainment of a minimum dose of 3 mg of egg white powder was required to continue dosing. The participants then continued a build-up dosing at home. For participants who did not achieved a dose of 50 mg on the first day, the doses were doubled every 2 weeks up to 50 mg. Therefore, the dose was increased to 75 mg with following increases by 25% up to 2 g. The maximum time allowed for the build-up phase was 10 months; the dose achieved at 10 months was considered the maintenance dose. In Dello Iacono 2013 children started with one drop of undiluted raw hen's egg (HE) emulsion (0.015 mL) in a day hospital then continued at home with gradually increasing doses and six doubling doses in hospital (on days 8, 29, 64, 92, 134, 176). Dose increases were customized based on the frequency and severity of side effects and in cases of intercurrent illness or worsening asthma. The Fuentes-Aparicio 2012 protocol included in-hospital administration of 1 mg of egg and was continued by triplicating the dosage every 30 minutes. On the second day 30 mg was administered in one single dose, with treatment continuing at home at the same dosage. Subsequently, weekly increases were made in the clinic until 10 g of powdered egg, the equivalent of one egg, was reached. The OIT protocol in Meglio 2013 started with 0.27 mg of HE proteins and the doses were doubled every eight days until day 80. Subsequently, the doses were doubled every 16 days to achieve a total daily intake of 25 mL in six months. In Burks 2012 and Fuentes-Aparicio 2012, at 22 months and 6 to 12 months, respectively, the target maintenance dose was 10 g (a small egg serving); Dello Iacono 2013 aimed for 40 mL after six months but none of the children managed this amount. Ninety per cent achieved partial tolerance (< 40 mL but > 10 mL) and 25 mL should have been achieved in six months in Meglio 2013; 80% of children were able to tolerate the target dose of 25 mL.

Raw egg was used in the OIT group in three studies (Burks 2012; Dello Iacono 2013; Meglio 2013). Burks 2012 used raw egg powder; Dello Iacono 2013 and Meglio 2013 used raw egg emulsion. Fuentes-Aparicio 2012 used powdered pasteurized egg.

A double-blind, placebo-controlled food challenge (DBPCFC) was performed at the end of the OIT protocol in two studies (Dello Iacono 2013; Meglio 2013). In Burks 2012 and Fuentes-Aparicio 2012 an open food challenge was performed at the end of treatment.

The follow-up period varied for each study, ranging from 24 (Burks 2012), 12 (Fuentes-Aparicio 2012), to 6 months (Dello Iacono 2013, Meglio 2013). All patients were on daily maintenance at the time of follow-up.

In our searches of the clinical trials registers we found another trial that could potentially meet our criteria for future updates of this review once the trial is completed (Wood 2013).

Excluded studies

We excluded 17 of the 21 studies identified from screening the search results as they did not meet our specific inclusion criteria. The reasons for exclusion were: no previous history of exposure to egg (one study); comparison group not placebo or a continued avoidance diet (seven studies); met our inclusion criteria but the results were for combined egg and milk-allergic patients (two studies); the abstracts did not provide enough information to assess eligibility (seven studies). Further details can be found in Characteristics of excluded studies.

Risk of bias in included studies

We analysed six domains of potential risk of bias for the included studies; all four studies were rated at low risk of attrition bias; three and two studies were rated at low risk of selection and selective reporting bias, respectively. All four studies were rated at high risk of performance and detection bias. The risk of bias decisions are shown in Figure 2 and Figure 3. Aspects of the assessment of risk of bias are summarized for the primary outcome under the following headings.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

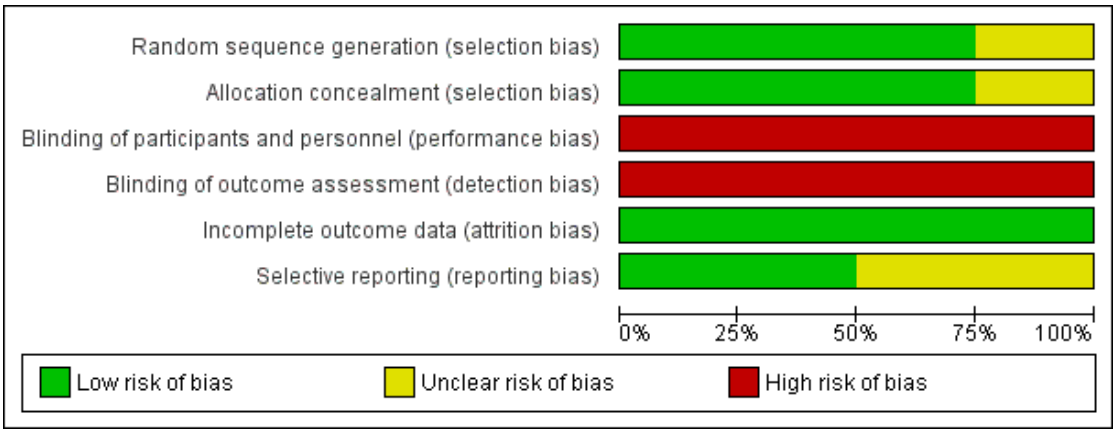
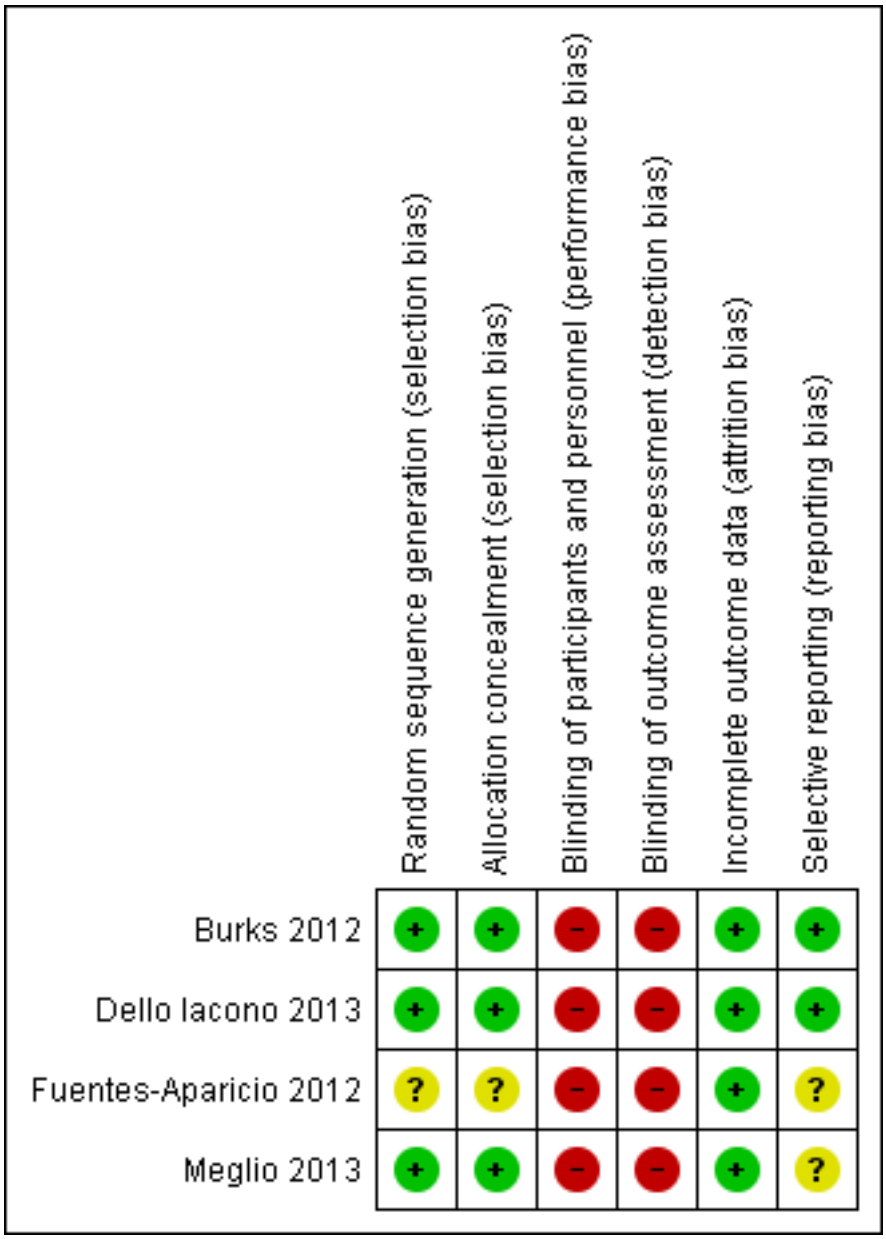


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All the included studies except one (Fuentes-Aparicio 2012) provided a description of an adequately generated allocation sequence and adequately concealed allocation.

Blinding

None of the studies contemplated blinding of the participants and investigators.

Incomplete outcome data

All the studies reported on the main outcomes.

Selective reporting

Pre-specified outcomes were available for two of the studies, both in the form of protocols (Burks 2012; Dello Iacono 2013). Unfortunately the data were not clear nor in the form of protocol or in the manuscript of pre-specified outcomes for the other two studies (Fuentes-Aparicio 2012; Meglio 2013). Given the small number of included studies, the majority of which detected statistically significant results, we cannot rule out the presence of reporting bias.

Other potential sources of bias

The studies appeared free of other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Oral and sublingual immunotherapy compared to no therapy for egg allergy
See Summary of findings for the main comparison

Desensitization

Two studies conducted a DBPCFC at baseline to confirm a diagnosis of IgE-mediated egg allergy (Dello Iacono 2013; Meglio 2013). Fuentes-Aparicio 2012 required a positive open oral challenge test. Burks 2012 included participants on the basis of a positive history after ingestion of egg and positive specific IgE antibody levels of more than 5 kU/L for children six years of age or older, or 12 kU/L or more for those five years old; moreover, all children underwent a skin prick test (SPT). All studies set out to assess the participants' ability to tolerate a full serving of egg. The final quantities achieved were: 10 mL (Dello Iacono 2013), 13.6 g (Meglio 2013), and 10 g (Burks 2012; Fuentes-Aparicio 2012). A total of 167 children were analysed (100 children in the intervention group; 67 children in the control group). Thirty nine per cent of children receiving OIT were able to tolerate a full serving of egg compared to 11.9% of the control group, with a pooled relative risk ratio (RR) of 3.39 (95% CI 1.74 to 6.62, Analysis 1.2). Spontaneous tolerance was achieved in nine children: two participants were from Meglio 2013 and seven from Fuentes-Aparicio 2012.

Meglio 2013 was the only study that administered an antihistamine throughout OIT. Regardless of age, history of anaphylaxis, or antihistamine co-intervention there was still a significant effect favouring OIT.

Partial desensitization

Seventy nine per cent (79%) of patients in the OIT group could ingest a partial serving of egg (1 to 7.5 g), resulting in a pooled RR of 5.73 (95% CI 3.13 to 10.50, Analysis 1.1). In two studies (Dello Iacono 2013; Meglio 2013) a DBPCFC was performed on all patients in the control group at the end of the study. In Fuentes-Aparicio 2012 an open challenge test was performed at the end of the study. It was not clear whether an open oral food challenge (OFC) or DBPCFC was performed at the end of the Burks 2012 study. There was one patient in Meglio 2013 who could digest 13.6 g of egg (the cut-off for complete tolerance by the authors) but who presented with throat pruritus. There were no participants in the control groups in Burks 2012 and Dello Iacono 2013 who were able to digest even a small amount of egg without presenting with allergic symptoms.

Adverse effects (AEs)

While all studies provided somewhat detailed reports of AEs there was much heterogeneity in the methods of reporting. AEs occurred most frequently in association with OIT dosing. Sixty nine per cent of children presented with some mild-to severe AEs during OIT treatment, with a pooled RR of 6.06 (95% CI 3.11 to 11.83, Analysis 1.4). Five participants in Fuentes-Aparicio 2012 required epinephrine treatment. There were no serious adverse reactions or need for epinephrine use in the other three studies.

In Burks 2012 the rates of AEs were highest during the first 10 months of OIT. However, no serious AEs or need for epinephrine were reported. AEs, most of which were oral or pharyngeal, were associated with 25% of 11,860 doses of OIT with egg and 3.9% of 4018 doses of placebo. In the OIT group 78% of children had oral or pharyngeal AEs as compared with 20% of those in the placebo group ($P < 0.001$). After 10 months the rate of symptoms in the OIT group decreased to 8.3% of 15,815 doses (data not shown). In addition to dosing-related symptoms, 437 other AEs

were reported; 96% were considered to be unrelated to dosing on the basis of the timing and types of symptoms.

Fuentes-Aparicio 2012 described 21 children (52.5%) who had symptoms at some stage of the dosage with OIT. In eight of the children (20%) the symptoms were very mild; in eight other children (20%) the symptoms were severe and five children (12.5%) required epinephrine treatment.

Dello Iacono 2013 reported that all children who received OIT experienced AEs, with a total of 53 events; though none resulted from accidental HE exposure. According to Sampson's classification (Sampson 2003) 3 (5.6%) were grade 1, 10 (18.9%) were grade 2, 35 (66%) were grade 3, and 5 (9%) were grade 4. No child in the OIT group had a grade 5 reaction, needed oral or intramuscular steroids or epinephrine, or had access to emergency services. Eighty one per cent of adverse reactions occurred during administration of the first 6 mL, and 100% occurred with administration of 20 mL HE. The children in the OIT group had a RR of 4.96 (95% CI 3.30 to 7.45) for incurring an AE but there were no significant differences in the severity of the reactions. No child discontinued treatment because of adverse reactions. Three (30%) control children had a total of five adverse reactions because of accidental ingestion of trace amounts of HE. The severity grade was 3 or 4 and none required intramuscular epinephrine.

In Meglio 2013 70% of patients presented with some mild-to severe AEs. Nevertheless, there were non-serious AEs reported.

Based on the available data we cannot comment on whether over- or under-reporting of AEs is a concern, although this is always a possibility. In total, 5 (5%) of the 100 patients receiving OIT required epinephrine.

Medication used

The data for medications used were somewhat poor. Burks 2012 mentioned only one participant who received prednisone but without specifying the route, dosage, or duration of the treatment. As mentioned previously all patients in Meglio 2013 received cetirizine treatment orally (0.25 mg/kg/day) for the duration of the study, but no other administration of therapy was reported (Meglio 2013). In Fuentes-Aparicio 2012 antihistamine therapy was administrated in 10 cases, steroids in nine cases, b2-agonists in five cases, and epinephrine treatment in five cases. The adminstration route, dosage, and duration of these medications were not reported. However, they did report the exact correlation with the OIT dosage. In Dello Iacono 2013 information on medication use was reported for both groups, in association with OIT dosage for the experimental group and for traces of egg in the control group. Unfortunately the number of cases in which antihistamine treatment was used remained unclear in the OIT group. In the control group there were three cases requiring treatment. Nebulized epinephrine was used in two cases in the OIT group and in two cases in the control group. There were three patients in the OIT group who needed b2-agonists, and no cases were documented for steroid administration. Additionally, there were two children in the control group who required oral steroid therapy. Information about the dosage and duration was missing.

Skin prick test (SPT)

All four studies had performed a SPT on participants before and after OIT. There were non-significant differences between the OIT and control groups before starting immunotherapy. A significant difference in the SPT wheal size was found at the end of OIT by all studies (Burks 2012; Dello Iacono 2013; Fuentes-Aparicio 2012; Meglio 2013). Moreover, Burks 2012 showed that a decrease in wheal size from baseline to 22 months was correlated with sustained unresponsiveness at 24 months.

Serologic testing

Specific IgE at baseline and after the intervention was investigated in each study using different laboratory methods. Dello Iacono 2013 and Fuentes-Aparicio 2012 used the Phadia CAP System fluorescence enzyme immunoassay (FEIA) (Phadia Diagnostics); Burks 2012 used the Thermo Immuno-CAP100 (Fisher Scientific), and Meglio 2013 used the Realtest Reverse Enzyme Allergo Sorbent Test (REAST) (Lofarma) and an allergen microarray assay (Immuno Solid-phase Allergen Chip ISAC; VBC Genomics Bioscience Research, Vienna, Austria) in accordance with the manufacturer's recommendations. A panel of 104 allergens (inhalants and foods), which also contained the following five purified natural HE allergens: ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4), and serum albumin (Gal d 5) were used. Specific IgG4 for ovomucoid (Gal d 1) and ovalbumin (Gal d 2) were also determined. Because of the differences in the upper limit of measurement it was impossible to combine the data. Nevertheless, three studies reported significantly decreased levels of egg-specific IgE antibody after OIT (Burks 2012; Dello Iacono 2013; Meglio 2013). There was no significant change of egg-specific IgE antibodies in Fuentes-Aparicio 2012. In Dello Iacono 2013 the difference in the reduction of IgE between pre- and post-OIT therapy was -14.4 (-27.6 to 0.1) in the OIT group and 2 (-8.9 to -13.8) in the control group ($P < 0.001$). Meglio 2013 used two tests; according to the REAST test results there was a significant reduction in egg-specific IgE antibody for ovomucoid, expressed as an average (SD) of 14.4 (± 30.7), and there was no significant reduction for ovalbumin. However, the ISAC test revealed a significant reduction for both ovomucoid and ovalbumin egg-specific IgE antibodies, expressed as average (SD) of 1.78 (± 1.74) and 0.74 (± 1.22), respectively; no significant changes were reported in the control group. It was not possible to extrapolate the data in Burks 2012.

Three studies evaluated changes in egg-specific IgG4 antibodies (Burks 2012; Fuentes-Aparicio 2012; Meglio 2013) and all three showed a significant increase in the titre of these antibodies. In

Burks 2012 the median in the OIT group was 48.5 kUA/L (range -0.1 to 162.1, P < 0.001). Meglio 2013 showed a significant increase in ovalbumin egg-specific IgG4 antibodies in the OIT group (average 2.95 (± 0.4) kUA/L, P = 0.02). It was not possible to extrapolate precise data from Fuentes-Aparicio 2012.

The study by Meglio 2013 reported a statistically significant increase in IL-5 levels in the OIT group (mean 28.13 ± 14.7 pg/mL, range 12.00 to 56.00, P = 0.03). Finally, Burks 2012 reported a significant reduction in CD 63+ basophil levels in the OIT group at the end of treatment (0.01 μg/mL, P = 0.002).

Withdrawal rate

We calculated the withdrawal rate for each study. In Burks 2012 it was 15% for the OIT group and 13% for placebo group, so the overall withdrawal rate for both study groups was 14.5%. Fuentes-Aparicio 2012 reported a 4% overall dropout rate (0% for the placebo group and 7.5% for the OIT group). Meglio 2013 reported an overall 5% dropout rate, with 10% in the OIT group (one of 10 children treated).

DISCUSSION

Summary of main results

Egg oral immunotherapy (OIT) appears to be an effective treatment option to induce desensitization in patients with IgE-mediated egg allergy, despite a difference in immunotherapy protocols. However, the long-term effect of OIT on tolerance is currently unclear. There have been concerns that unpreventable interruptions, such as illness, adverse reactions, lifestyle or habits might induce immune changes and alter the benefits achieved. Thus, it is important to emphasize that the regular introduction of a tolerated dose of egg at home is crucial to maintain a successful desensitization and eventually to reach tolerance. Nevertheless, OIT is an alternative to the current therapeutic mainstay of an avoidance diet. It may have a positive effect on overall quality of life, including positive nutritional consequences and the potential avoidance of allergy related emergencies.

It is important to note that a large percentage of the children (69%) in the intervention groups experienced at least one adverse event during the OIT. Most of the symptoms were related to the build-up phase in association with OIT dosing. However, the majority of symptoms were mild and self-limiting. Only Fuentes-Aparicio 2012 reported serious adverse reactions requiring epinephrine treatment. As adverse events were classified differently amongst the studies, it is difficult to comment on whether they were under- or over-estimated. Thus, the possiblity of serious adverse events should be discussed with a patient being offering OIT, with clear guidelines regarding the perception and acceptance of these risks. The risks associated with administering OIT need to be evaluated against the 'real life' risks of standard care, namely an avoidance diet, though it is difficult to accurately estimate the true rate of accidental allergic reactions.

Information regarding the different potential medications was poor. Even though Fuentes-Aparicio 2012 and Dello Iacono 2013 provided detailed information about antihistamine, steroid, epinephrine, and b2-agonists administration in association with the dosage of OIT, and the occurring symptoms on those specific occasions, information on the administration route, dosage and duration of use was missing. The Meglio 2013 protocol was the only one that administrated antihistamine treatment as a co-intervention with OIT, hence it is difficult to assess from this study whether OIT-induced adverse allergic reactions can be avoided. Likewise, as Burks 2012 did not provide specific information regarding the medications used for adverse allergic reactions (antihistamines, steroids, epinephrine, b2- agonists) it is difficult to assess the extent of OIT-induced allergic reactions. Sclar 2014 shows that anaphylaxis is often under-estimated. In a study of paediatric food-related allergic reactions the most common reason given for lack of epinephrine administration to patients experiencing a severe reaction is that the reaction was not recognized as severe (47.7% of cases in which epinephrine was not used) (Fleischer 2012).

Surprisingly only Fuentes-Aparicio 2012 used denatured egg for the OIT group (the other three studies used raw egg) and this study was the only one reporting serious adverse events. This finding differs from the Leonard 2012 data which showed overall tolerance of denaturated egg (baked egg) without reports of acute allergic reactions; they reported only one participant who passed a baked egg re-challenge then subsequently developed vomiting and diarrhoea hours after accidental exposures to regular egg (in icing and cookie dough ice cream). The authors suggested that this reaction was consistent with atypical food protein-induced enterocolitis syndrome, however the child was reverted to complete egg avoidance. Curently we can not explain such contradictory data. Futher studies are needed to explore the safety issues.

Importantly, the four included studies reported a significant reduction in wheal diameter from skin prick tests (SPTs) after completion of OIT. Moreover, three of the four studies (Burks 2012; Dello Iacono 2013; Meglio 2013) showed a reduction in egg-specific IgE antibodies levels and increased egg-specific IgG4 antibodies. Therefore, it appears that OIT might induce tolerance through specific immunological mechanisms.

In most OIT trials there is a 15% to 20% dropout rate due to frequent adverse reactions (Khoriaty 2013). The dropout rate data from Burks 2012 agrees with the information reported previously (Khoriaty 2013). However, the withdrawal rate in the other three studies (Dello Iacono 2013; Fuentes-Aparicio 2012; Meglio 2013) was surprisingly low, with Dello Iacono 2013 having no dropouts, for which we cannot find an explanation. It may be that patient collaboration is easier in a smaller study, perhaps because

there is more medical attention. Dello Iacono 2013 did not discuss their high adherence rate within the study. Meglio 2013 discussed the high adherence rate in their study, giving as the possible explanation a longer intervention period; the protocol took longer than the expected period (planned 181 days) with a mean of 219 days (range 178 to 287 days). The very gradual protocol that was adopted may guarantee more safety and more parental collaboration as the percentage increment between doses was the same and there were not dose 'jumps' in the egg daily administrations for the entire period of desensitization. Moreover, co-intervention with antihistamine was used in their study. More studies are needed to confirm or to disprove such an hypothesis.

Overall completeness and applicability of evidence

All of the studies addressed the primary outcome of complete tolerance of one egg serving. There are four studies published so far, which include a very specific patient group (children). Recruitment selection bias is possible. The study population characteristics suggest that these studies might be generalizable for a larger population group. For instance, OIT appears to be effective both in young children and in later childhood. To date, none of the studies have reported on children less than three years of age or adults. Another factor which may influence the development of desensitization is the presence of anaphylaxis. Out of the four studies that were in this review there were two studies that included patients with a history of anaphylaxis (Dello Iacono 2013; Fuentes-Aparicio 2012), and OIT appeared to be effective regardless of the history of anaphylaxis. Interestingly, OIT both with and without co-intervention with an antihistamine was included in the review, which did not seem to affect the treatment effect. Of note, 39% of patients from all four studies achieved full tolerance after OIT, which means that they did not need to continue daily ingestion of a serving of egg in their everyday life diet. However, concerns about compliance and interruption due to sickness should be addressed.

Forty per cent of the patients were able to tolerate a partial serving of egg, reducing limitations in their diets and the risk of a serious adverse event. Despite a follow-up period of up to two years, none of the studies commented on difficulties in continuing OIT during illness but this concern needs to be clarified for the everyday clinical counselling of the parents.

Adverse effects are likely to be the most important factors to be considered when applying evidence to practice. The vastly different reporting methods for symptoms during OIT make them complicated to quantify. As previously mentioned, there is a risk of both under- or over-estimation. The need for parenteral epinephrine treatment could be a reflection of serious adverse effects, and only one study (Fuentes-Aparicio 2012) reported 20% of patients in the OIT group who needed epinephrine treatment. This could be due to a different definition of adverse effects and the clinical practice in their unit. On the other hand, frequent, milder symptoms during OIT might influence the patients' quality of life and compliance. Inquiring about the study participants' acceptance of this therapy would be insightful. If applied to practice, physicians would have to cautiously consider, and discuss with the patient at length, whether the risks are acceptable; and to ensure good compliance of the children's parents or guardians.

According to the different OIT protocols, all patients started the protocol during hospital admission, as day patients, or in a research centre. During the build-up phase patients were closely monitored during the visits to the clinic or research centre; moreover, close follow-up and individualized guidance was provided. Whether these time and personnel commitments are feasible in practice could be a factor, and they are dependent on the institution providing the OIT.

Quality of the evidence

According to the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the overall judgement of the quality of the body of evidence contributing to the results of the review is low. The reasons for double-downgrading from high are 1) the high likelihood of bias, and 2) the imprecision of results (a small number of studies with a small number of participants). High likelihood of bias is suspected because of the methodological limitations of the studies, resulting in possible selection, performance, and detection bias. The confidence intervals were wide because of small sample sizes and variability in the estimated treatment effect. Two studies (Fuentes-Aparicio 2012; Meglio 2013) did not perform a sample size calculation and this could be a source of random error risk. The random error is closely related to the imprecision. The results of smaller studies are subject to greater sampling variation and hence are less precise. Indeed, imprecision is reflected in the confidence interval around the intervention effect estimate from each study and in the weight given to the results of each study in the meta-analysis (Higgins 2011).

We did not find sufficient studies to create a funnel plot as a means to assessing publication bias. Given the small number of included studies, the majority of which detected statistically significant results, we cannot rule out the presence of reporting bias. The strength of the evidence was that there was a consistently positive treatment effect, despite clinical heterogeneity in the patient characteristics and the OIT protocols.

Potential biases in the review process

A strength of this review is the thorough search strategy, including searching several databases as well as conference papers and ongoing trial registries, to minimize the possibility of missing studies.

The fact that several iterations of the same studies were retrieved supports this. One possible source of bias relates to the exclusion of potentially relevant studies when requests to the authors for additional information went unanswered. Moreover, some studies which fulfilled our criteria were excluded because they combined results for immunotherapy for two or more foods. For example, one study (Staden 2007) fulfilled the eligibility criteria but results for both egg and milk immunotherapy were combined in the published article. It is possible that the inclusion of such data would have altered the results of the meta-analysis. The ongoing eligible study (Wood 2013) emphasizes the need for frequent updates of this review as OIT for egg allergy continues to be a topic of active research. Ongoing and future studies could potentially affect our conclusions.

Agreements and disagreements with other studies or reviews

To date this is the first systematic review on immunotherapy specifically for egg allergy. The findings of our review are in agreement with the study by Nurmatov (Nurmatov 2014). In their systematic review with meta-analysis on food allergies they evaluated egg OIT as a subgroup. There were four studies in their egg OIT subgroup (Burks 2012; Dello Iacono 2013; Meglio 2013; Morisset 2007). They excluded Fuentes-Aparicio 2012, and we did not include Morisset 2007 as the results for egg and milk allergy were combined. They found that OIT substantially reduced the risk for egg allergy (RR 0.19, 95% CI 0.04 to 0.99). The serologic changes caused by OIT in our analysis are similar to those of Nurmatov's review, for the skin prick test, egg-specific IgE antibodies, and IgG4 antibodies. Of note, the safety data remain a challenge. Regarding Burks 2012, Meglio 2013, and Dello Iacono 2013, the safety data were the same; the allergic adverse events reported by these three studies were mild to moderate and there was no need for intramuscular epinephrine treatment. The major difference between our review and that of Nurmatov 2014, was the documentation of serious adverse effects of OIT treatment as reported by Fuentes-Aparicio 2012 (12.5% of children on OIT required intramuscular epinephrine). Although our review specifically analysed immunotherapy for egg allergy there was only one study with a 24-month follow-up (Burks 2012). Clearly more studies are needed to clarify whether oral immunotherapy is efficacious in the longer term, whether it is safe, and whether some co-therapy, like an antihistamine, could be helpful.

AUTHORS' CONCLUSIONS

Implications for practice

Studies to date have involved small numbers of participants and the quality of evidence is generally low. Despite that, the majority of the children in the four included studies had reached partial tolerance of egg. Moreover, some participants were able to achieve full tolerance, and therefore improved their quality of life and nutritional requirements. To date, OIT has not been studied in toddlers. Given that some proportion of young egg-allergic children tolerate heat-denatured (baked) egg products, and the addition of these products to the diet appears to accelerate the development of tolerance with minimal adverse side effects, it may be safer and easier to identify such children and simply add baked-egg products to their diets (more studies are needed in this area). OIT is very labour intensive and induces adverse allergic reactions in virtually all children who are treated (although with mostly mild symptoms) and eosinophilic esophagitis (EoE) in 10% to 15% of those treated with immunotherapy. A major difficulty of OIT is the frequency of adverse effects even thoughmost of them seem to be mild to moderate and self-limiting. The use of parenteral epinephrine, as suggested by the guidelines in the case of a life-threatening adverse event, is infrequent while on OIT. However, physicians along with their patients have to verify the risks of OIT and their acceptance of them. Because there are no standardized protocols guidelines would be required prior to incorporating desensitization into clinical practice.

Implications for research

The quality of evidence is limited by small sample sizes and a lack of methodological rigour. A larger randomized controlled trial that attempts to eliminate selection, performance, and detection bias would provide a more precise estimate of the treatment effect. Investigators should be encouraged to utilize a standard DBPCFC protocol, such as described by Sampson 2012, to enable better comparison of clinical trial outcomes and to facilitate transition into practice. In this review, adverse effects were difficult to quantify because of the variability in reporting. Future studies should attempt to report them in a standardized fashion and the development of a consensus severity scale of adverse effects could facilitate this. Co-interventions to decrease the rate of adverse effects might be key and need to be explored.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Burks 2012

Methods	RCT, double-blind Placebo-controlled
Participants	55 participants, aged 5 to 11 years, a convincing clinical history of egg allergy (shown by the development of allergic symptoms within minutes to 2 hours after ingesting egg) and a serum egg-specific IgE antibody level of more than 5 kU per litre for children 6 years of age or older, or 12 kU per litre or more for those 5 years old
Interventions	The protocol for oral immunotherapy consisted of three phases: an initial-day dose escalation of median 18.5 mg (range 6 to 50 mg) a build-up phase of median 9 mg (range 3 to 50 mg) a maintenance phase during which participants ingested up to 2 g of egg white powder per day
Outcomes	The primary endpoint of the study was the induction of sustained unresponsiveness after 22 months The secondary endpoints were: an oral food challenge consisting of 5 g (cumulative dose) of egg white powder at 10 months after the oral immunotherapy an oral food challenge consisting of 10 g of egg powder at 22 months after oral immunotherapy an oral food challenge at 24 months of 10 g of egg white powder, followed 1 hour later by feeding of a whole cooked egg for children who passed the second oral food challenge adverse effects change in skin prick test (assessed at month 10, 22 and 24) egg-specific IgG4 antibody (assessed at month 10, 22 and 24) total IgE antibody (assessed at month 10, 22 and 24) egg-specific IgE antibody (assessed at month 10, 22 and 24) CD63+ basophils (assessed at month 10, 22 and 24)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomly assigned by means of a centralized computer algorithm
Allocation concealment (selection bias)	Low risk	Randomization by means of a centralized computer algorithm

Burks 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was blinded only for the first 10 months: the primary endpoint was evaluated after 22 months
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was blinded only for the first 10 months: the primary endpoint was evaluated after 22 months
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants accounted for
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the protocol (NCT00461097, ClinicalTrials.gov number) were reported

Dello Iacono 2013

Methods	RCT Control: an egg-free diet for 6 months
Participants	Twenty children, aged 5 to 11 yr, with severe IgE-mediated hen egg (HE) allergy, were recruited. Inclusion criteria were as follows: (i) at least 1 anaphylactic reaction (grade 3, 4 or 5 according to Sampson's grading) after accidental exposure to trace amounts of HE or egg-derived products, within 12 months of pre-enrolment (ii) previous SPT/IgE positive for HE (iii) a positive double-blind placebo-controlled food challenge (DBPCFC) at a dose of 0.9 ml of raw HE emulsion
Interventions	Oral immunotherapy protocol consisted of starting with 1 drop of undiluted raw HE emulsion (0.015 mL) flavoured with vanilla and cacao in day hospital then continued at home with gradually increasing doses mixed by the parents in the child's breakfast (cow's milk, soy milk, fruit juice or other) and 5 doubling doses in day hospital. Dose increases were customized based on the frequency and severity of side effects, and in the case of intercurrent illness or asthma worsening
Outcomes	'maximum tolerance': 40 mL of raw HE emulsion in a single dose, which roughly corresponds to a small egg 'partial tolerance': less than 40 mL but at least 10 ml in a single dose 'persistence of HE allergy': less than 10 mL in a single dose adverse reactions skin prick test prick by prick test egg-specific IgE antibody
Notes	Blindness not clear

Risk of bias

Dello Iacono 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer scientist not involved in the study was responsible for the computerized randomization of the children to each group
Allocation concealment (selection bias)	Low risk	Computerized randomization of the children to each group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Healthcare staff and parents were aware of the treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Healthcare staff and parents were aware of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes accounted for
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified in the protocol (NCT01379651, ClinicalTrials.gov number) were reported

Fuentes-Aparicio 2012

Methods	RCT Control: elimination diet
Participants	Seventy-two children, aged 4 to 15 years, with persistent egg allergy with positive to cutaneous tests and specific IgE tests to egg and its fractions (white, yolk, OVA, and OVM)
Interventions	On the first day, fractionated doses were administered until reaching 31 mg of egg, beginning with 1 mg and continuing with 3, 9, and 18 mg at 30 min intervals. On the second day, 30 mg in one single dose was administered, with the treatment continuing at home at this same dosage. Subsequently, weekly increases were made in the clinic until 10 g of powdered egg, the equivalent of one egg, was reached. Lastly, tolerance of the natural food was checked
Outcomes	clinical egg tolerance adverse effects skin prick test egg-specific IgE antibody
Notes	Blindness not clear

Fuentes-Aparicio 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants accounted for
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and therefore selective outcome reporting could not be assessed

Meglio 2013

Methods	RCT, controlled open study Control: hen egg-free diet
Participants	Twenty children, aged 4 to 14 years, with mild-to-severe IgE-mediated HEA, according to Clark's severity classification, were admitted. All fulfilled the inclusion criteria of being more than 4 yrs of age and having an IgE-mediated HEA: positive HE skin prick tests (SPTs) or HE IgE > 0.35 kUA/l confirmed by means of double-blind, placebo-controlled food challenge (DBPCFC) or a convincing history
Interventions	The schedule consisted of administering increasing amounts of raw HE starting from one drop (mixed egg white and yolk) diluted 1:100 with water, corresponding to 0.27 mg of HE proteins. The HE doses were doubled every 8 days until day 80. Subsequently, the HE doses were doubled every 16 days to achieve a total daily intake of 25 ml, in 6 months The protocol was suspended when the child reached 25 ml/ day or the maximum tolerated dose, that is to say the dose that did not induce any symptom and that was established after the third attempt to continue with the desensitization protocol (the parents tried to administer the same dose, which caused symptoms three times, so the previous tolerated dose was considered the maximum tolerated dose)
Outcomes	to desensitize children with moderate-severe IgE-mediated HE allergy over a 6-month period the skin prick tests with egg white and yolk-specific serum IgEs (REAST method) to

	ovomucoid (Gal d 1) and ovalbumin (Gal d 2) specific serum IgEs (ISAC method) to ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4) and serum albumin (Gal d 5) serum-specific IgG4 to ovomucoid (Gal d 1) and ovalbumin (Gal d 2) serum cytokine levels adverse effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By means of a computerized randomization schedule, the children were randomly assigned to either intervention or control
Allocation concealment (selection bias)	Low risk	Computerized randomization schedule
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants accounted for
Selective reporting (reporting bias)	Unclear risk	Study protocol not available and therefore selective outcome reporting could not be assessed

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Buchanan 2007	No control group
Caminiti 2013	Abstract only; not enough information to assess; authors contacted but no response received
García Rodríguez 2011	No control group
Itoh 2010	No control group

(*Continued*)

Itoh 2013	Abstract only; not enough information to assess; authors contacted but no response received
Jones 2010	Abstract only
Masayuki 2009	Abstract only; not enough information to assess; authors contacted but no response received
Meglio 2011	Not control group
Morisset 2007	Meets inclusion criteria, but results combined egg and milk- allergic patients
Pajno 2012	Abstract only; not enough information to assess; authors contacted but no response received
Palmer 2013	No history of immediate egg-induced allergy
Patriarca 2007	No control group
Ruiz Garcia 2012	No control group
Staden 2007	Meets inclusion criteria, but results combined egg and milk-allergic patients
Takahashi 2013	Abstract only; not enough information to assess; authors contacted but no response received
Vickery 2010	Open-label study, no control group
Yanagida 2013	Abstract only; not enough information to assess; authors contacted but no response received

Characteristics of studies awaiting assessment *[ordered by study ID]*

Vazquez-Ortiz 2014

Methods	Non-randomised, controlled, parallel group intervention study Control: elimination diet
Participants	Fifty children, aged 5 to 18 yrs, with IgE-mediated egg allergy confirmed by double-blind placebo-controlled challenge (DBPCFC) and sIgE or skin prick test (SPT) to egg white (EW), ovalbumin (OVA), or ovomucoid (OVM) above 0.35 kU/L and 3 mm, respectively, were included
Interventions	Pasteurized liquid EW containing 8.3 g of protein per 100 mL was used, whose allergenicity is equivalent to raw egg white. Induction phase involved 16 weeks and started with a 2-day in-hospital rush phase, in which increasing doses were given hourly. Patients were then discharged home and continued having the last tolerated dose once daily throughout the week. Weekly increases were given at the outpatient clinic, as follows: 0.5 mL, 0.7 mL, 1 mL, 1.3 mL, 2 mL, 2.5 mL, 3.2 mL, 4 mL, 5 mL, 8 mL, 11 mL, 15 mL, 22 mL, 30 mL, and finally, one raw egg (60 g of the fresh product). In maintenance phase, children continued having one raw egg (or their maximal tolerated dose) twice weekly uninterruptedly

Outcomes	Efficacy: open challenge to one raw egg (3.8 g raw egg white protein or, if not reached, to the highest tolerated dose) at 12 months after OIT start. Complete desensitization was defined as clinical unresponsiveness to one raw egg, whereas partial desensitization as increase in reaction threshold not reaching one raw egg Safety: all allergic reactions occurring within 2 h after OIT doses, as well as delayed gastrointestinal or skin symptoms suggesting a non-IgE-mediated mechanism, were recorded. Severity was assessed according to Sampson's Grading
Notes	Subgroup analysis of safety data

Characteristics of ongoing studies *[ordered by study ID]*

Wood 2013

Trial name or title	Oral Desensitization to Egg With Subsequent Induction of Sustained Unresponsiveness for Egg-Allergic Children Using Baked Egg or Egg Oral Immunotherapy (OIT)
Methods	Open-label, parallel group, RCT The purpose of this study is to compare baked foods with egg versus egg OIT. The intent of the study is to investigate if participants will be able to consume egg after taking baked foods with egg or egg OIT for a period of time and then stopping for a certain period. This is referred to as tolerance or sustained unresponsiveness. This study will evaluate the effectiveness of the egg OIT versus baked egg by having each participant ingest egg white solid or baked foods with egg. This will be done over 2 years This study will last 2 years. All eligible subjects will receive a baked egg oral food challenge (OFC). Those who pass the baked egg OFC will then have a 2 gm egg OFC. Those who react to the egg OFC will be randomized to baked egg or egg OIT. Individuals who do not pass the initial baked egg OFC will be assigned to egg OIT. Those who pass the egg OFC will not be eligible for the study and will be followed per site standard of care. All eligible and enrolled subjects will have a 1-year and a 2-year OFC At selected visits, blood and urine collection, physical examination, prick skin tests, and atopic dermatitis and asthma evaluations will occur
Participants	Inclusion criteria: • Age 3 through 16 years with a serum IgE to egg of ≥ 5 kUA/L within the past 12 months • Reacting to the initial baked egg OFC with dose-limiting symptoms OR • Reacting on a 2 gm egg OFC with dose-limiting symptoms to a cumulative dose of 2 gm or less after passing the initial baked egg OFC • Written informed consent from subject or parent or guardian • Written assent from all subjects as appropriate • All females of child bearing age must be using appropriate birth control Exclusion criteria: • History of anaphylaxis to egg resulting in hypotension, neurological compromise or mechanical ventilation • Chronic disease (other than asthma, atopic dermatitis, rhinitis) requiring therapy (e.g., heart disease, diabetes) • Active eosinophilic gastrointestinal disease in the past 2 years • Participation in any interventional study for the treatment of food allergy in the past 6 months • Subject is on 'build-up phase' of immunotherapy (i.e., has not reached maintenance dosing). Subjects tolerating maintenance allergen immunotherapy can be enrolled • Severe asthma, or uncontrolled mild or moderate asthma. More information on these exclusion criteria

	can be found in the protocol • Inability to discontinue antihistamines for initial day escalation, skin testing or OFC • Use of omalizumab or other non-traditional forms of allergen immunotherapy (e.g., oral or sublingual) or immunomodulator therapy (not including corticosteroids) or biologic therapy (e.g., infliximab, rituximab, etc.) within the past year • Use of beta-blockers (oral), angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB) or calcium channel blockers • Use of investigational drug within 90 days or plan to use investigational drug during the study period • Pregnancy or lactation
Interventions	Egg oral immunotherapy (OIT) in the form of egg white solid with up to four oral food challenges as directed by protocol. Baked egg in the form of home-baked goods and 'safe' commercial products with up to four oral food challenges. Commercially available egg white solid dispensed by the central manufacturer. Study product will be dispensed in vials for low doses, capsules for mid-range doses, and bulk powder with dosing scoops for the higher doses
Outcomes	Primary outcome: the development of sustained unresponsiveness to egg consumption at 2 years Secondary outcome: incidence of all serious adverse events during the study; changes in egg-specific mechanistic measures and prick skin test results
Starting date	July 2013
Contact information	Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute
Notes	http://www.cofargroup.org

DATA AND ANALYSES

Comparison 1. Oral and sublingual immunotherapy versus no therapy for egg allergy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 increase in the amount of egg that can be tolerated	4	167	Risk Ratio (M-H, Fixed, 95% CI)	5.73 [3.13, 10.50]
2 complete recovery	4	167	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.74, 6.62]
3 serious adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 mild to severe adverse reactions	4	167	Risk Ratio (M-H, Fixed, 95% CI)	6.06 [3.11, 11.83]

Analysis 1.1. Comparison 1 Oral and sublingual immunotherapy versus no therapy for egg allergy, Outcome 1 increase in the amount of egg that can be tolerated.

Review: Oral and sublingual immunotherapy for egg allergy

Comparison: 1 Oral and sublingual immunotherapy versus no therapy for egg allergy

Outcome: 1 increase in the amount of egg that can be tolerated

Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burks 2012	30/40	0/15		6.5 %	23.80 [1.55, 366.48]
Dello Iacono 2013	9/10	0/10		4.5 %	19.00 [1.25, 287.92]
Fuentes-Aparicio 2012	32/40	7/32		70.7 %	3.66 [1.87, 7.17]
Meglio 2013	8/10	2/10		18.2 %	4.00 [1.11, 14.35]
Total (95% CI)	**100**	**67**		**100.0 %**	**5.73 [3.13, 10.50]**

Total events: 79 (Immunotherapy), 9 (Control)

Heterogeneity: $Chi^2 = 3.81$, df = 3 (P = 0.28); $I^2 = 21\%$

Test for overall effect: Z = 5.66 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Oral and sublingual immunotherapy versus no therapy for egg allergy, Outcome 2 complete recovery.

Review: Oral and sublingual immunotherapy for egg allergy

Comparison: 1 Oral and sublingual immunotherapy versus no therapy for egg allergy

Outcome: 2 complete recovery

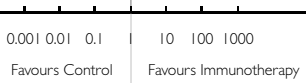
Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burks 2012	11/40	0/15		7.6 %	8.98 [0.56, 143.50]
Dello Iacono 2013	0/10	0/10			Not estimable
Fuentes-Aparicio 2012	20/40	7/32		81.9 %	2.29 [1.11, 4.72]
Meglio 2013	8/10	1/10		10.5 %	8.00 [1.21, 52.69]
Total (95% CI)	**100**	**67**		**100.0 %**	**3.39 [1.74, 6.62]**

Total events: 39 (Immunotherapy), 8 (Control)

Heterogeneity: $Chi^2 = 2.41$, df = 2 (P = 0.30); $I^2 = 17\%$

Test for overall effect: Z = 3.58 (P = 0.00034)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Oral and sublingual immunotherapy versus no therapy for egg allergy, Outcome 3 serious adverse events.

Review: Oral and sublingual immunotherapy for egg allergy

Comparison: 1 Oral and sublingual immunotherapy versus no therapy for egg allergy

Outcome: 3 serious adverse events

Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Burks 2012	0/40	0/15		Not estimable
Dello Iacono 2013	0/10	0/10		Not estimable
Fuentes-Aparicio 2012	5/40	0/32		8.85 [0.51, 154.37]
Meglio 2013	0/10	0/10		Not estimable

Analysis 1.4. Comparison 1 Oral and sublingual immunotherapy versus no therapy for egg allergy, Outcome 4 mild to severe adverse reactions.

Review: Oral and sublingual immunotherapy for egg allergy

Comparison: 1 Oral and sublingual immunotherapy versus no therapy for egg allergy

Outcome: 4 mild to severe adverse reactions

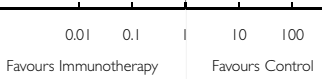
Study or subgroup	Immunotherapy n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burks 2012	31/40	3/15		48.9 %	3.88 [1.39, 10.81]
Dello Iacono 2013	10/10	3/10		39.2 %	3.00 [1.25, 7.19]
Fuentes-Aparicio 2012	21/40	0/32		6.2 %	34.61 [2.18, 550.19]
Meglio 2013	7/10	0/10		5.6 %	15.00 [0.97, 231.84]
Total (95% CI)	**100**	**67**		**100.0 %**	**6.06 [3.11, 11.83]**

Total events: 69 (Immunotherapy), 6 (Control)

Heterogeneity: $Chi^2 = 5.16$, $df = 3$ ($P = 0.16$); $I^2 = 42\%$

Test for overall effect: $Z = 5.29$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. MEDLINE search strategy

Search term

1. "Egg Hypersensitivity"[Mesh]
2. "Immunotherapy"[Mesh]
3. 1 AND 2
4. "administration"[All Fields]
5. "sublingual"[All Fields]
6. 4 AND 5
7. "mouth"[MeSH Terms]
8. "mouth"[All Fields]
9. "oral"[All Fields]
10. "administration, sublingual"[MeSH Terms]
11. "sublingual administration"[All Fields]
12. "sublingual"[All Fields]
13. OR/6-12
14. Clinical Trial[ptyp]
15. 3 AND 13 AND 14

Appendix 2. Other databases search strategies

1. randomz.ti,ab.
2. factorial.ti,ab.
3. (cross over or crossover or cross-over).ti,ab.
4. placebo.ti,ab.
5. (double adj blind).ti,ab.
6. (single adj blind).ti,ab.
7. assign.ti,ab.
8. allocat.ti,ab.
9. volunteer.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE-BLIND PROCEDURE.sh.
14. or/1-13
15. egg allergy/
16. egg hypersensitivity.mp.
17. (egg and hypersensitivity).mp.
18. immunotherapy/ or oral immunotherapy/ or sublingual immunotherapy/
19. immunotherapy.mp.
20. 15 or 16 or 17
21. 18 or 19

22. 20 and 21
23. 14 and 22

CONTRIBUTIONS OF AUTHORS

Protocol draft: OR, MB, ODCA, MGC

Develop a search strategy: MB, MGC

Search for trials: OR, MAT

Obtain copies of trials: OR

Select which trials to include: OR, MAT; arbiter: MB

Extract data from trials: OR, MAT

Enter data into RevMan: OR, MB, SZ

Carry out the analysis: OR, MGC, SZ

Interpret the analysis: OR, MGC, SZ

Draft the final review: OR, MB, MAT, MGC, SZ, ODCA

Update the review: OR, MB

DECLARATIONS OF INTEREST

All review authors declare they have no competing financial conflicts of interest.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Desensitization, Immunologic [adverse effects; *methods]; Egg Hypersensitivity [*therapy]; Egg Proteins, Dietary [*administration & dosage; immunology]; Epinephrine [therapeutic use]; Immunoglobulin E [immunology]; Randomized Controlled Trials as Topic; Sublingual Immunotherapy [adverse effects; methods]

MeSH check words

Child; Child, Preschool; Humans