

REVIEW ARTICLE

Management of anaphylaxis: a systematic review

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Abstract

To establish the effectiveness of interventions for the acute and long-term management of anaphylaxis, seven databases were searched for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before–after studies and interrupted time series and – only in relation to adrenaline – case series investigating the effectiveness of interventions in managing anaphylaxis. Fifty-five studies satisfied the inclusion criteria. We found no robust studies investigating the effectiveness of adrenaline (epinephrine), H1-antihistamines, systemic glucocorticosteroids or methylxanthines to manage anaphylaxis. There was evidence regarding the optimum route, site and dose of administration of adrenaline from trials studying people with a history of anaphylaxis. This suggested that administration of intramuscular adrenaline into the middle of vastus lateralis muscle is the optimum treatment. Furthermore, fatality register studies have suggested that a failure or delay in administration of adrenaline may increase the risk of death. The main long-term management interventions studied were anaphylaxis management plans and allergen-specific immunotherapy. Management plans may reduce the risk of further reactions, but these studies were at high risk of bias. Venom immunotherapy may reduce the incidence of systemic reactions in those with a history of venom-triggered anaphylaxis.

Anaphylaxis can be defined as a 'severe, life-threatening generalized or systemic hypersensitivity reaction' (1, 2). Several working definitions of anaphylaxis have been formulated to aid clinical diagnosis and management (3–6). The most well known of these is the consensus clinical definition proposed by Sampson et al., which involved representatives of a number of international allergy organizations, including the European Academy of Allergy and Clinical Immunology (EAACI) (7).

Care of patients with anaphylaxis involves consideration of both the acute, emergency treatment of reactions and long-term care, which aims to reduce the risk of further reactions and improve outcomes if, despite these measures, a further reaction ensues (8). It remains very difficult to predict the severity of a reaction and, in fatal episodes, death may occur within minutes of an anaphylactic reaction, these observations underscoring the importance of effective, emergency management.

EAACI is in the process of developing the *EAACI Guidelines for Food Allergy and Anaphylaxis*, and this systematic review is one of seven interlinked evidence syntheses that were undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life, which were used to inform clinical recommendations.

Aims

The aims of this systematic review were to assess the effectiveness of (i) interventions for the acute management of anaphylaxis and (ii) pharmacological and nonpharmacological approaches for the long-term management of anaphylaxis.

Methods

Details of the methodology for the identification, selection and inclusion of the studies have been previously reported (9, 10). In summary, our inclusion criteria were systematic reviews with or without meta-analyses, randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before–after (CBA) designs, interrupted time series (ITS) studies and case series, with a minimum of 10 patients, for studies investigating the use of adrenaline (Fig. 1).

Standard methods for performing systematic reviews were used. A descriptive summary with data tables was produced to summarize the literature. Quality assessments of studies were undertaken using appropriate tools (see online supplement). We preferentially extracted data on risk ratios and mean differences. Because data were not suitable for meta-analysis (11), a narrative synthesis of the data was undertaken.

Further details can be found in the online Supporting Information.

Results

The searches identified a total of 8929 potentially eligible studies, of which 55 satisfied our eligibility criteria and were therefore included in this review (Fig. 2). The key characteristics and main findings of all included studies are detailed in Table S1, and the quality assessment of these studies is summarized in Tables S2 (systematic reviews) and S3 (primary studies). The main findings are further discussed below.

Acute management of anaphylaxis

Adrenaline

We identified 15 studies: four systematic reviews (12–15) (including one update), four RCTs (16–19), two case series (20, 21) and five fatality register-based reports (22–26) (including two updates) on the effectiveness of adrenaline.

Effectiveness and timing

Three well-conducted systematic reviews (19–21) that looked at the use of adrenaline for the treatment of anaphylaxis and adrenaline auto-injectors found no RCTs or quasi-RCTs. Weaker evidence from a case series of 27 patients receiving emergency prehospital treatment found that prompt use of adrenaline may reduce the risk of fatality (26). The second case series found that a fifth of children experiencing anaphylaxis needed more than one dose of adrenaline; healthcare professionals administered this second dose in 94% of cases. The five fatality register-based reports (12–16) provided important insights into the difficulties of predicting the severity of subsequent reactions, risk factors for fatality, co-existing asthma and the under-issuing, poor carriage, under-use,

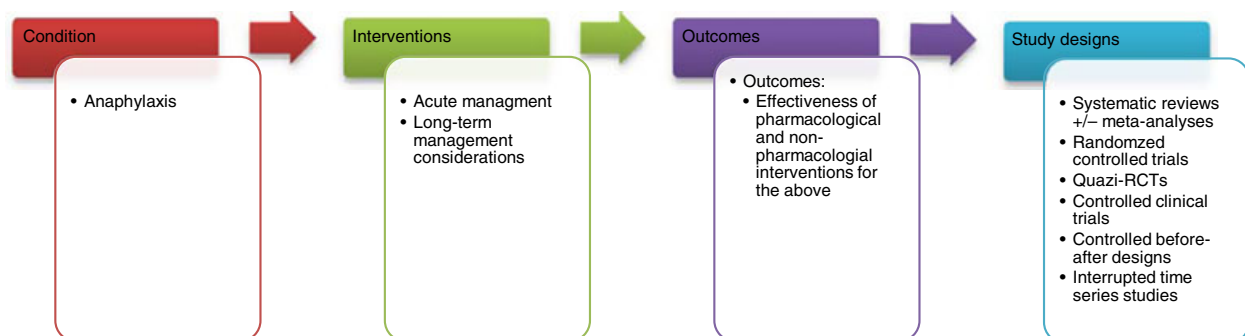


Figure 1 Conceptualisation of systematic review of interventions for the acute and long-term management of anaphylaxis.

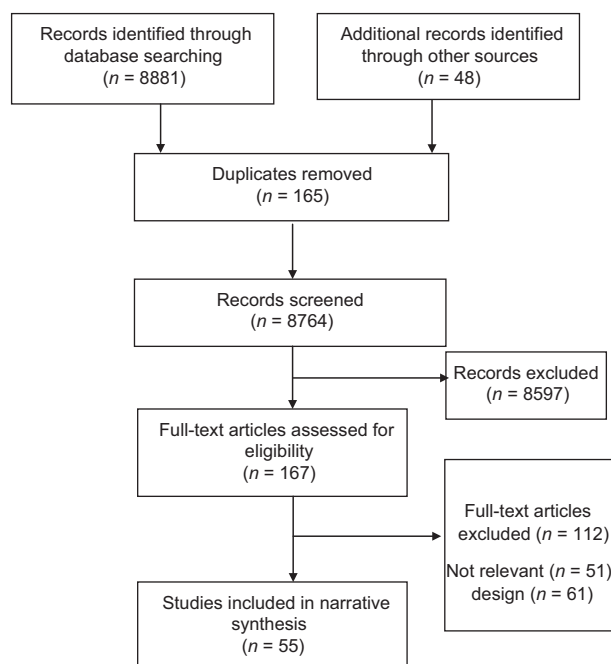


Figure 2 PRISMA diagram for searches on the acute and long-term management of anaphylaxis.

delayed use and incorrect use of adrenaline auto-injectors. These reports revealed that fatalities can occur, even if adrenaline is used correctly.

Site and route of delivery

Two RCTs (22, 24) found that, in both children and adults, maximal plasma concentration occurs quicker with the intramuscular than with subcutaneous route. The latter trial in adults also concluded that the optimum site of injection was the vastus lateralis muscle. A systematic review of poor quality found that the use of subcutaneous adrenaline was not contraindicated in patients older than 35 years without a history of coronary artery disease (17).

Dose in children

One RCT compared the effectiveness of the previous designs of the EpiPen Junior and EpiPen in children weighing 15–30 kgs. The authors concluded that children should be prescribed the 0.3 mg EpiPen from 30 kgs (17).

Glucocorticosteroids

Two systematic reviews investigating the use of glucocorticosteroids in the acute management of anaphylaxis (27, 28) failed to identify any RCTs or quasi-RCTs and so were unable to make any recommendations.

Antihistamines

Two systematic reviews investigating the use of H1-antihistamines in the acute management of anaphylaxis (29, 30) identified

no suitable RCTs or quasi-RCTs. Two RCTs that investigated the use of H1- and H2-antihistamines in acute allergic reactions (only a small proportion had anaphylaxis) (31, 32) revealed that the combination of H1- and H2-antihistamines was superior to H1-antihistamines alone in treating urticaria, but not angioedema; the second showed that pruritus was better controlled by H1-antihistamines than by H2-antihistamines and that combined treatment offered no advantage.

Methylxanthines

We found one systematic review investigating the effectiveness of methylxanthines in the acute management of anaphylaxis; this found no trials in humans (33).

Long-term management of anaphylaxis

Anaphylaxis management plans

We identified two systematic reviews investigating anaphylaxis management plans (34, 35). The first found no evidence from RCTs or quasi-RCTs investigating the clinical effectiveness of anaphylaxis management plans for the prevention of recurrences or improvement in outcomes from anaphylaxis. The second systematic review had a wider focus including qualitative, epidemiological and experimental studies undertaken with or without a control group. This demonstrated that there were no universally accepted anaphylaxis management plans. It, however, identified four studies, which suggested that anaphylaxis management plans may substantially reduce the risk of future, severe reactions.

Venom immunotherapy (VIT)

We found three systematic reviews and meta-analyses (36–38) and one further systematic review without a meta-analysis (39) investigating the effectiveness of VIT. These four systematic reviews included a total of 23 unique studies of varying quality. Twelve of these studied patients with a history of anaphylaxis using eligible study designs and have therefore also individually been assessed (see Tables S1 and S3) (40–51).

The high-quality systematic review by Boyle et al. identified six RCTs and 1 quasi-RCT (392 participants). Five studies involved subcutaneous immunotherapy and one sublingual immunotherapy. Patients treated with VIT had less systemic allergic reactions (RR = 0.10, 95% CI 0.03–0.28) and better quality of life (mean difference = 1.21 points on a 7-point scale (95% CI 0.75–1.67)). Subcutaneous VIT-treated patients had more systemic adverse reactions (RR = 8.16, 95% CI 1.53–43.46). One systematic review of low quality showed that VIT was effective in reducing the risk of further systemic reactions (49).

The systematic review by Hockenhull et al. (39) investigated the clinical and cost-effectiveness of a specific VIT subcutaneous preparation (Pharmalgen, ALK-Abello,

Reading, UK) and included nine trials (four RCTs and five quasi-RCTs), all judged to be of poor quality. They modelled cost-effectiveness showing a cost of £8–20 (€10–25) million/life year gained, assuming a base-case scenario of no improvement in quality of life. A sensitivity analysis showed that VIT was more cost-effective in those at high risk of further stings or if improvements in quality of life and anxiety associated with VIT were included in the model.

Educational interventions

A quasi-experimental trial evaluated whether an educational intervention could improve compliance with carrying an in-date adrenaline auto-injector in high school children with food allergy (52). The intervention failed to demonstrate any significant difference in carriage rates in the intervention and control groups.

Psychological interventions

One systematic review of low quality investigated the management of anxiety related to children with a history of anaphylaxis (53). It concluded that anaphylaxis can place a substantial psychological burden on children, adolescents and carers and that dealing with this anxiety may improve outcomes.

Prophylactic interventions

Interventions have been studied to prevent anaphylaxis. A major limiting factor with these studies is the fact that the groups studied were not known to be at high risk of anaphylaxis.

Adrenaline admixture with snakebite antivenom

A systematic review and meta-analysis demonstrated that adrenaline premedication reduces adverse reactions when administering snakebite antivenom (54) (RR = 0.32, 95% CI 0.18–0.58). A subsequent factorial designed RCT investigated the use of adrenaline, antihistamines and glucocorticosteroids given alone or in combination (55). This also found adrenaline, but not other interventions, to be effective in reducing the risk of anaphylaxis.

Pharmacological interventions for the prevention of anaphylaxis to iodinated contrast media

One systematic review of nine trials involving 10 011 unselected patients failed to demonstrate that premedication with glucocorticosteroids, H1-antihistamines or a combination of H1- and H2-antihistamines prevented anaphylaxis triggered by iodinated contrast media (56).

Discussion

This comprehensive review of the international literature has found little robust evidence for the acute or long-term management of anaphylaxis. The only trial evidence uncovered

for the emergency management of anaphylaxis was in relation to adrenaline, but these trials have been undertaken in patients who were at the time not experiencing anaphylaxis (22–25). Taken together with the methodologically lower-quality evidence from case series and fatality registers, there is some evidence to support the use of adrenaline for the emergency management of anaphylaxis. The evidence points to the importance of injecting this by the intramuscular route into the anterolateral aspect of the thigh. In relation to longer-term management considerations, anaphylaxis management plans may be effective in reducing the risk of recurrence. VIT reduces the severity of reactions to subsequent stings and improves quality of life, and concerns around cost-effectiveness remain.

Acute management of anaphylaxis

Case fatality register studies have demonstrated that deaths can occur within minutes of the onset of a reaction and have highlighted how difficult it is to predict the severity of reactions (12). It is therefore consistently advocated by guidelines that all reactions are promptly managed by initiating a range of pharmacological and nonpharmacological interventions. This review failed to identify any high-quality studies investigating the role of nonpharmacological interventions such as the role of cardiopulmonary resuscitation and posture. In contrast, we found some evidence investigating the role of adrenaline – the main drug treatment advocated in guidelines. This evidence was derived from case series, fatality registers and a limited number of trials in people not experiencing anaphylactic reactions. Overall, this body of evidence was weak, but pointed to the importance of the early administration of adrenaline, in an appropriate dose, administered by the intramuscular route into the anterolateral aspect of the thigh. Given the considerable ethical and logistical challenges in undertaking trials of parenteral adrenaline in patients experiencing anaphylaxis, it is unlikely that stronger evidence will be forthcoming.

We found no evidence from primary studies for other potential treatments, such as fluid replacement, oxygen, glucocorticosteroids, antihistamines, methylxanthines and bronchodilators, and it is therefore not possible to offer any recommendations for the use of these treatments.

Long-term management of anaphylaxis

The long-term management of anaphylaxis centres on the need to identify triggers and co-factors, providing advice on how to minimize further reactions, and equipping individuals with the skills and equipment needed to manage further reactions (57). Consideration also needs to be given to ameliorate any psychological consequences of a diagnosis of anaphylaxis. Researchers have therefore thus far focused attention on the role of anaphylaxis management plans, immunomodulatory interventions and a variety of educational and psychological interventions.

The formal experimental evidence in support of anaphylaxis management plans is limited. Studies that have,

however, used before–after designs and that therefore did not satisfy our inclusion criteria have found that these may result in substantial reductions in the risks of further reactions (58, 59). Given the high risk of confounding with such study designs, this evidence must be interpreted with caution.

The single educational study included failed to show a positive effect on carriage of in-date adrenaline auto-injectors by high school children with previous anaphylaxis. A study with a before–after design found that the input of a multidisciplinary allergy clinic was effective in improving parents' knowledge of food allergy and in reducing subsequent reactions (60). This evidence is encouraging, but due to the high inherent risk of bias associated with such a design, these findings need to be treated with caution until more evidence from studies employing more robust study designs is forthcoming. The systematic review on psychological interventions for children with a history of anaphylaxis and their parents/carers was difficult to interpret because of its poor quality and reporting. Whilst clearly demonstrating that a number of studies have found that a diagnosis of anaphylaxis can be associated with anxiety and impaired quality of life, there was very little in the way of primary evidence demonstrating that intervening could improve outcomes in such individuals/families.

Immunomodulatory approaches are of considerable interest as these have the potential to modify the disease course and may possibly prove curative. We found a modest body of evidence in relation to VIT in relation to the management of those with stinging insect anaphylaxis, although much of this was judged to be at high risk of bias. This body of evidence did, however, consistently demonstrate that VIT can significantly reduce the severity of subsequent systemic reactions to insect stings, but given the infrequency of further stings and the low number of fatalities, it was not possible to assess whether VIT reduced the risk of fatal reactions to insect stings. There were no formal cost-effectiveness studies identified, the only potentially relevant evidence emerging from modelling studies in relation to a specific product: this found that VIT is most likely to be cost-effective in populations at high risk of further exposure (e.g. bee keepers, their family members and those who live near bee farms) or if likely benefits to quality of life are accounted for. VIT is a treatment which has been shown to reduce subsequent reactions, and although the treatment may give rise to adverse effects, it is a treatment patients prefer over the long-term carriage of an adrenaline auto-injector. In state-funded health services, however, the cost implications of such an intervention may prevent widespread availability limiting its use to high-risk patients only where its cost-effectiveness profile is likely to be much more favourable.

We found no eligible studies investigating the role of desensitization therapy in the management of those with anaphylaxis to drugs or latex. Studies investigating the effectiveness of oral and sublingual immunotherapy have mainly been undertaken in those without a history of

anaphylaxis to foods; these studies are therefore reviewed in the companion systematic review on the management of food allergy.

Prophylactic approaches can also potentially play a role in those with a history of anaphylaxis. The evidence we uncovered did not, however, directly focus on this population. Rather, the approaches studied have been used in the general population and have found that prophylactic use of adrenaline can substantially reduce the risk of anaphylaxis associated with anti-snake venom, that adding antihistamines or glucocorticosteroids conferred no additional advantage and that antihistamines and glucocorticosteroids were of questionable value in preventing anaphylaxis associated with iodinated contrast media-based diagnostic investigations in unselected populations.

Implications for future research

This review has underscored the dearth of high-quality research to guide everyday clinical decision-making. There is then a pressing need to develop the evidence base for both the acute and long-term management of this potentially life-threatening disorder. In relation to acute management, it is widely accepted that it would be unethical to undertake studies investigating the effectiveness of adrenaline when compared with placebo, but trials could potentially be undertaken investigating the optimum dose, site, route and timing of administration of adrenaline. Other important questions that need to be addressed include establishing the role of H1- and H2-antihistamines and glucocorticosteroids, and these could also potentially be investigated using formal experimental designs. Similarly, there are a range of interventions delivered with the aim of improving longer-term outcomes – for example, provision of adrenaline auto-injectors, anaphylaxis management plans, immunotherapy – and these can all potentially also be studied using formal trial designs. Ideally, these studies should investigate the impact of interventions on the outcomes that have been carefully described in recent Cochrane and other systematic reviews (12, 14, 28, 29, 35). A fuller discussion of the research agenda will be made available in the forthcoming *EAACI Anaphylaxis Guidelines*.

Conclusions

There is at present little in the way of robust evidence to guide decisions on the acute or long-term management of anaphylaxis. Key recommendations from this review have been summarized in Box 1. Given the risk of death and the considerable morbidity associated with anaphylaxis, these evidence gaps need to be filled wherever possible (61). These gaps include the need for educational interventions for patients, carers and healthcare professionals, lack of data on the pharmacodynamics of adrenaline and the ideal dosage in children and to some extent adults, and a lack of effective study designs on the benefits of educational plans (62).

Box 1: Key recommendations

- There is some evidence that prompt administration of adrenaline may be life-saving; it should therefore be used as the drug of first choice in the acute management of anaphylaxis.
- Adrenaline should be administered by the intramuscular route into the anterolateral aspect of the mid-thigh.
- Anaphylaxis management plans may reduce the severity of subsequent reactions.
- VIT may reduce the severity of subsequent reactions and improve quality of life, but cost-effectiveness considerations should be considered, particularly in those at low risk of further stings.
- Adrenaline used prophylactically can reduce severe adverse effects associated with anti-snake venom administration.

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Contributorship

AS, AM and GR conceived this review. It was undertaken by SD with the support of SSP, GR and AS. SD, AS and GR led the drafting of the manuscript, and all authors critically commented on drafts of the manuscript.

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Ethical approval

Ethical approval was not required.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

Table S1. Key characteristics of included studies.

Table S2. Quality assessment of systematic reviews.

Table S3. Quality assessment of original studies.

Table S4. Ongoing/unpublished studies.

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ONLINE SUPPLEMENT

Management of anaphylaxis: a systematic review

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METHODS

Details of the methodology for the systematic review have been previously reported.¹

Search strategy

A highly sensitive search strategy was designed to retrieve all articles combining the concepts of anaphylaxis and epidemiology from electronic bibliographic databases.² We focused on the acute management of anaphylaxis by assessing the effectiveness of epinephrine, H1-antihistamines (versus placebo), systemic glucocorticosteroids, methylxanthines or any other treatments for the emergency management of people experiencing anaphylaxis. The main interventions that have been studied in the context of long-term management are anaphylaxis management plans and allergen-specific immunotherapy.

Inclusion criteria for study design

Details of the methodology for the identification, selection, and inclusion of the studies have been previously reported.¹ In summary, our inclusion criteria were systematic reviews with or without meta-analyses, randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), controlled before-after (CBA) designs, interrupted time series (ITS) studies, and case-series, with a minimum of 10 patients, for studies investigating the use of adrenaline (Figure 1).

We appraised the evidence by preferentially looking at higher levels of evidence such as systematic reviews and/or meta-analyses of RCTs and individual RCTs. However, in view of the anticipated limited information available, we decided *a priori* to include systematic reviews that included other non-RCT study designs (focusing on the studies that had used EPOC-endorsed study designs); quasi-RCTs and CCTs (i.e. where non-random allocation of patients had occurred); other EPOC study designs such as CBA studies (i.e. those in which observations were made before and after the implementation of an intervention) and ITS (i.e. where observations were made at multiple time-points before and after the intervention).³ Despite their representing much weaker forms of evidence, case series were eligible for inclusion in relation to adrenaline as expert advice pointed to the considerable ethical, scientific and logistical difficulties in mounting more rigorous study designs.

Exclusion criteria for study design

Reviews, discussion papers, non-research letters and editorials and case studies plus animal studies were excluded.

Study selection and quality assessment

The titles were independently checked by two reviewers according to the above criteria; any discrepancies were resolved by consensus and when necessary a third reviewer was consulted. Quality assessments of studies were undertaken using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews.⁴ We assessed the risk of bias of studies eligible for the review using the criteria suggested by EPOC.⁵ RCTs, CCTs and CBAs were assessed for: generation of allocation sequence; concealment of allocation; baseline outcome measurements; baseline characteristics; incomplete outcome data; blinding of outcome assessor; protection against contamination; selective outcome reporting; and other risks of bias. These assessments drew on the principles incorporated into the Cochrane EPOC guidelines for assessing intervention studies⁶ and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for assessing observational studies.⁷ Similarly, we drew on the quality assessment tool produced by the National Institute for Health and Clinical Excellence (NICE) to help critically appraise case series.⁸

Analysis, data synthesis and reporting

All assessments and data extraction were carried out independently by two reviewers; any discrepancies were resolved through discussion amongst the reviewers and, where necessary, arbitration by a third reviewer. A descriptive summary with data tables was produced to summarize the literature. We preferentially extracted data on risk ratios and mean differences. Data were not suitable for meta-analysis⁹ so a narrative synthesis of the data is reported.

RESULTS

Studies in progress

We are aware of two RCTs that are as yet unpublished (Table E4). The first is investigating the effectiveness of a 24-hour helpline offering direct access to specialist paediatric allergy advice in the context of supporting the management of allergic emergencies in children with life-threatening food allergies.^{10,11} The second is a multicentre RCT investigating the effectiveness of two x three hours standardised educational intervention aimed to increase practical knowledge on anaphylaxis, performance in a training anaphylaxis situation and reduce anxiety in patients with anaphylaxis and caregivers of affected children.

Table S1: Key characteristics of included studies

First author, year	Country	Design	Sample/ age N=no. of studies n=no. of participants	Intervention	Outcomes	Key findings	Quality	Comment
<i>Acute Management: Epinephrine</i>								
Bock, 2001 ¹²	USA	Case-series	n=32 2-33 years	Characteristics of anaphylaxis fatalities due to food	Numbers of food allergy-triggered deaths in the USA Treatment at the onset of reactions and emergency response treatment, with a particular focus on epinephrine	32 deaths from anaphylaxis to food investigated from a national USA register between 1994 and 1999. 31 with known food allergy. Good data on 21 subjects, 20 (95%) had active asthma, 2 (10%) received prompt i.m. epinephrine but died, 19 (90%) had no/delayed epinephrine. Suggest better education, availability of epinephrine auto-injectors	Low	Most anaphylactic fatalities to food occurred in those with a known history of food allergy so potentially avoidable. Suggestion that prompt administration of epinephrine may avoid fatalities. High proportion of fatal cases had co-existent asthma.
Bock, 2007 ¹³	USA	Case-series	n=31 5-50 years	Characteristics of anaphylaxis fatalities due to food	Numbers of food allergy-triggered deaths in the USA Treatment at the onset of reactions and emergency	31 deaths from anaphylaxis to food investigated from a national USA registry between 2001 and 2006 26 were known to have food	Low	Characteristics of deaths from anaphylaxis in food allergy patients remain largely unchanged. Still appears to be lack of

					response treatment, with a particular focus on epinephrine Any changes since previous recommendations	allergy but may have had a previous mild reaction. All (100%) subjects had asthma. Only 4/31 (13%) subjects had epinephrine promptly administered.		adequate awareness of allergen avoidance and poor access to readily-available epinephrine. All fatal cases had co-existent asthma.
Jarvinen, 2008 ¹⁴	USA	Case-series	n=78 0.5-17.5 years	Looking at use of multiple doses of epinephrine in children with food-induced anaphylaxis via anonymous questionnaires .	In food-induced anaphylaxis requiring epinephrine, how many doses were needed. Factors that may predispose to requiring multiple doses.	95 reactions treated with epinephrine in 78 children, from a food allergy referral centre, analyzed. 77 reactions needed one dose of epinephrine. (81%) 18 reactions needed multiple epinephrine doses (19%). The second dose was administered by a health professional in 17 of 18 reactions (94%). Patients needing multiple doses were more likely to have asthma (p=0.027). Symptom of 'throat closure' more common in those needing multiple doses of epinephrine (p=0.055). In those requiring multiple doses of epinephrine, the first dose was administered earlier (p=0.07), iv fluids were more	Low	A fifth of children with anaphylaxis receive more than one epinephrine auto-injector. Most (94%) of second doses are given by health care professionals. Co-existent asthma was associated with using more than one auto-injector.

						commonly used (p=0.031) and observation in hospital was longer (p=0.09). When 3 doses of epinephrine were administered , compared to two doses, features that were more frequently occurring were: hypotension (p=0.022); difficulty swallowing (p=0.022) and 'throat closure' (p=0.014).Peanut was the main trigger (p=0.013)		
Pumphrey, 2000 ¹⁵	UK	Case-series	n=164 40-89 years	Anaphylaxis fatalities from any cause	Number of deaths due to anaphylaxis in the UK Circumstances leading to fatal anaphylaxis	164 deaths identified due to probable anaphylaxis from any cause from UK death certificates between 1992 and 1998 (20/year). Half were iatrogenic, a quarter food induced and a quarter insect venom related. Paramedics and doctors had difficulty diagnosing anaphylaxis which led to a delay in epinephrine treatment Only 22% of patients with food allergy-triggered fatalities and 18% of venom allergy-triggered fatalities had experienced a previous severe reaction. Of the 14 who had experienced previous severe reactions, 9	Low	Fatalities may occur in those with only mild previous reactions. Diagnostic uncertainty, lack of issuing, carriage and use of epinephrine may increase risk of death. High dose i.v. epinephrine may increase risk of death. B2-agonists may be particularly important in those with food allergy-triggered reactions to help deal with respiratory compromise Death may still occur in those who have administered epinephrine

						(64%) had been issued epinephrine self-treatment. Of these 9: 3 (33%) used the epinephrine as instructed; the remaining 6 (67%) had a variety of reasons for non-use i.e. had not collected from pharmacy (n=1); non-carriage (n=1); found dead with unused epinephrine (n=2); used for someone else and not replaced (n=1); out-of-date (n=1). 56% of drug-triggered reactions occurred in hospitals with full resuscitative equipment available. 20% received epinephrine before cardiac arrest; the remaining 80% arrested before epinephrine administration. 2 patients given high dose i.v. epinephrine, both died. Over half the deaths occurred in those who had a previous mild reaction. such that it would have been unlikely that a doctor would have recommended auto-injector carriage Suggest optimizing allergen avoidance, optimal asthma		
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						management, and continuing patient awareness of risk factors.		
Pumphrey, 2007 ¹⁶	UK	Case-series	n=48 5 months to 85 years	Food-triggered anaphylaxis fatalities	Number of deaths due to food-triggered anaphylaxis in the UK Circumstances leading to fatal anaphylaxis	48 deaths from anaphylaxis due to food in the UK between 1999 to 2006. 43 (90%) had asthma; 10 (21%) had a degree of exacerbation prior to death 19 (40%) had been prescribed epinephrine auto-injectors. 9 correctly used; 2 had expired; 1 used 3 auto-injectors but still died. Auto-injectors were used too late, didn't have it with them or incorrectly used.	Low	Optimizing asthma control identified as important. Persisting issues with under-use of epinephrine. Overweight individuals may have epinephrine inadvertently administered s.c..
Safdar, 2001 ¹⁷	Worldwide	SR of any study design	N=Not known n=not known Older people (i.e. >35-40 years)	Safety of use of epinephrine during anaphylaxis in older patients without coronary artery disease in pre-hospital setting epinephrine	Risk of cardiovascular side effects of epinephrine in older patients	Authors only able to find 3 case reports demonstrating adverse cardiac effects (i.e. 1 transient ischemia; 1 had a myocardial infarction; and the last patient died of a cerebral hemorrhage) associated with use of epinephrine in anaphylaxis. This led the authors to conclude that there was very little evidence to contradict the use of s.c. epinephrine in patients older than 35-40 years without	Low	Poor quality SR that did not specify how many studies found.

						coronary heart disease in the management of asthma or anaphylaxis.		
Sampson, 1992 ¹⁸	USA	Case-series	n=13 2 to 17 years	Fatal and near-fatal episodes of anaphylaxis to food in children were collated over a 14 month period.	Survey of severe food induced anaphylaxis in children	6 children died and 7 had near fatal episodes requiring Intensive care admission, intubation, ventilation and vasopressor support. Of the 6 fatal cases, 5 accidentally ingested a known allergen, to which they had a previous mild reaction. All were atopic with asthma, allergic rhinitis and atopic dermatitis. Asthma was controlled on the day of death. Only 2 received epinephrine within 60 minutes of onset of symptoms, which began 3 to 30 minutes after ingestion of allergen Of the 7 near-fatal reactions, 6 of the children reacted to a known allergen the 7th had experienced several near fatal reactions in the past. All 7 had well controlled asthma: 2 had atopic dermatitis and 3 had allergic rhinitis. 6 of the children received epinephrine between 10 to 30 minutes after ingestion	Low	Delayed administration of epinephrine can lead to fatality. All patients had asthma some had other atopic disorders. None of the patients were aware of the need for strict avoidance of their food allergen Prescription of epinephrine auto-injectors is important but non-carriage of the medication can be fatal. Most of the fatal reactions took place in a public setting whereas all of the near-fatal reactions took place in a private home. Uniphasic (7/13), biphasic (3/13) and protracted (3/13) anaphylactic reactions were described.

						of the allergen; one received it 130 minutes after ingestion. All required intubation. 3 of the children who died had been prescribed self-injectable epinephrine but did not have it with them. Of the near fatal-cases 3 had been prescribed epinephrine and one self-injected.		
Sheikh, 2008 ¹⁹	World-wide	SR of RCT's and quasi-RCT'S	N=0 all ages eligible	Epinephrine vs no intervention, placebo or other adrenergic treatments	Primary-Death Secondary: Resolution of upper airway obstruction Resolution of lower airway obstruction Improvement in arterial blood pressure Resolution of urticaria Requirement of second dose of epinephrine Admission to hospital Length of emergency department stay Length of hospital stay Re-presentation for therapy within 24 hours Adverse events due to therapy, in either treatment arm	No RCT's or quasi-RCT's comparing epinephrine with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Recommend to continue use of epinephrine as first-line medication; such trials are unlikely to be forthcoming.

Sheikh, ^a 2012 ²⁰	World- wide	SR of RCT's and quasi- RCT's	N=0 all ages eligible	Epinephrine vs no intervention, placebo or other adrenergic treatments	Primary-Death Secondary Resolution of upper airway obstruction Resolution of lower airway obstruction Improvement in arterial blood pressure Resolution of urticaria Requirement of second dose of epinephrine Admission to hospital Length of emergency department stay Length of hospital stay Re-presentation for therapy within 24 hours Adverse events due to therapy, in either treatment arm	No RCT's or quasi-RCT's comparing epinephrine with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Updated review. Recommend to continue use of epinephrine as first-line medication; such trials are unlikely to be forthcoming.
Sheikh, ^b 2012 ²¹	World- wide	SR of RCT's and quasi- RCT's	N=0 all ages eligible	To assess the effectiveness of epinephrine auto-injectors in relieving the symptoms of anaphylaxis that occur in the community	Primary-Death Secondary: Proportion of participants carrying auto-injector Proportion correctly using auto-injector Proportion experiencing difficulty using auto-injector Proportion who failed to use auto-injector in a timely	No RCT's or quasi-RCT's comparing epinephrine auto- injectors with no intervention, placebo or other adrenergic agonists were identified. No new recommendations can be made.	High	Recommend to continue regarding epinephrine auto- injectors as the first-line treatment for the community management of anaphylaxis; such trials are unlikely to be forthcoming in economically- developed countries but may be possible in low resource settings.

					and appropriate manner. Resolution of airway obstruction Improvement in arterial blood pressure Hospital attendance or admission Re-presentation for treatment within 72 hours Cost-effectiveness Adverse events due to treatment, in either arm			
Simons, 1998 ²²	Canada	RCT	n=17 4-12 years	s.c. epinephrine vs i.m. epinephrine in well patients who had previously experienced anaphylaxis	Mean time to maximum plasma epinephrine concentration Terminal elimination half-life of epinephrine Adverse events	Administration of s.c. epinephrine to 9 children, mean time to maximum plasma epinephrine concentration, 34 (SEM 14) minutes. Administration of i.m. epinephrine to 8 children, mean time to maximum plasma epinephrine concentration 8 (2) minutes P<0.05 compared with mean time max plasma epinephrine concentration achieved in s.c. group. Absorption in s.c. group too variable to calculate reliable half-life values, clearance rates,	Moderate	IM is the best route for epinephrine. Study not performed during an acute allergic reaction or anaphylaxis.

						volume of distribution No serious adverse effects occurred in either group.		
Simons, 2000 ²³	Canada	RCT	n=19 6-14 years	Inhaled epinephrine vs placebo inhalations	Plasma epinephrine serially at baseline and up to 180 mins post-treatment Blood glucose concentration serially at baseline and up to 180 mins post-treatment Heart rate and blood pressure at baseline and up to 180 mins post-treatment Blood glucose concentration serially at baseline and up to 180 mins post-treatment Heart rate and blood pressure at baseline and up to 180 mins post-treatment Adverse effects	Few children were able to take the required number of inhalations because of adverse effects. Mean plasma epinephrine concentrations not significantly higher in inhaled epinephrine group when compared to placebo inhalation group at any time point ($p>0.05$). Mean heart rate and diastolic blood pressure did not differ significantly between the two groups. Systolic blood pressure significantly higher at 30 mins in epinephrine group. Adverse effects were common in both groups, particularly bad taste of inhalations; worse in treatment group: 10/11 vs 4/8 in placebo group. One child who nearly managed the required number of epinephrine inhalations had adverse effects lasting for 50 minutes post inhalation; these	Moderate	Small study with poor compliance because of adverse effects may have compromised ability to detect differences in epinephrine concentration. High rate of adverse events indicates that unlikely to represent a viable alternative route of administration.

						included apprehension, nausea, pallor, shaking, and intermittent muscle twitching.		
Simons, 2001 ²⁴	Canada	RCT, cross over study	n=13 18-35 years	Epinephrine absorption in adults, i.m. vs s.c.; also site of injection, vastus lateralis vs deltoid muscle and epinephrine vs placebo in well adults with a history of anaphylaxis	Plasma epinephrine serially at baseline and up to 180 mins post-treatment Heart rate and blood pressure Adverse effects	Mean plasma epinephrine concentration was significantly higher ($p<0.01$) after epinephrine i.m. in injection into the vastus lateralis vs. epinephrine i.m. or s.c. into the deltoid (or saline i.m. or s.c. into the thigh. Adverse effects reported were mild and transient: 21 after epinephrine, 3 after saline injection	Moderate	Supports i.m. injection or epinephrine auto-injector into thigh Limitation is however that not performed during severe acute allergic reaction
Simons, 2002 ²⁵	Canada	RCT	n=12 4-8 years	Epipen Junior vs Epipen in well children at risk of anaphylaxis	Plasma epinephrine serially at baseline and up to 180 mins post-treatment Blood glucose concentration serially at baseline and up to 180 mins post-treatment Heart rate and blood pressure at baseline and up to 180 mins post-treatment Adverse effects	153 families approached, 12 agreed to participate; 2 children subsequently withdrew consent. Of 10 children randomized and treated: 5 received Epipen (0.3mgs) and 5 received Epipen Jr (0.15mgs). Maximum plasma epinephrine concentration reached at 16 (SEM 3) minutes for Epipen 0.15mg, and 15 (3) minutes for Epipen 0.3mg; no significant difference. Mean systolic blood pressure	Moderate	No significant difference in peak plasma epinephrine concentration shown, may be due to small sample size. Children receiving Epipen Jr were significantly lower weight than those who received the Epipen.

						and blood glucose significantly higher in those who received Epipen 0.3mg compared to Epipen 0.15mg. Adverse effects were experienced by all children, mild and transient significantly higher in Epipen 0.3mg arm. One child who received Epipen 0.3mg had prolongation of QT interval lasting 120 mins post-injection.		
Soreide, 1988 ²⁶	Norway	Case-series	n=27 5-74 years	Etiology, symptoms and treatment of severe anaphylactic reactions outside hospital	Pre-hospital treatment Treatment delay Fatality	27 patients with anaphylaxis referred to air ambulance service over a 4-year period Epinephrine was the most commonly administered treatment, which was administered s.c., i.m. or i.v.. 2 deaths, both occurring in women who waited for >45 minutes for emergency treatment.	Low	Suggestive evidence that delays in epinephrine treatment may have contributed to fatality.
Acute Management: Glucocorticosteroids								
Choo, 2010 ²⁷	World-wide	SR of RCT's and quasi-	n=0	Glucocorticoid use in the treatment of anaphylaxis	Primary: Mortality rate Secondary: Prevention of biphasic or	No RCT's or quasi-RCT's comparing glucocorticosteroids with any control were identified for inclusion.	High	Cannot support or refute the use of glucocorticosteroids in the treatment of anaphylaxis.

		RCT's		compared with any control, placebo, epinephrine, antihistamine or any combination..	prolonged anaphylaxis Incidence of cardiovascular manifestations Incidence of respiratory manifestations Incidence of gastrointestinal manifestations Incidence of other clinical manifestations Hospitalization rate Length of emergency department visit Length of hospital stay Rate of re-presentation to hospital	No evidence from high quality studies for the use of steroids in the emergency management of anaphylaxis.		
Choo, 2012 ²⁸	World-wide	SR of RCTs and quasi-RCTs	n=0 all ages eligible	Glucocorticosteroids use in those experiencing anaphylaxis compared with any control, placebo, epinephrine, antihistamine or any combination.	Primary: Mortality rate Secondary Prevention of biphasic or prolonged anaphylaxis Incidence of cardiovascular manifestations Incidence of respiratory manifestations Incidence of gastrointestinal manifestations Incidence of other clinical	No RCT's or quasi-RCTs comparing glucocorticosteroids with any control were identified for inclusion. No evidence from high quality studies for the use of steroids in the emergency management of anaphylaxis.	High	Cannot support or refute the use of glucocorticosteroids in the treatment of anaphylaxis.

					manifestations Hospitalization rate Length of emergency department visit			
Acute management: Antihistamines								
Lin, 2000 ²⁹	USA	RCT	n=19 Adults >18 years	Parenteral administration of 50mgs of diphenhydrami ne and saline vs. 50mg of diphenhydrami ne and 50mgs of ranitidine in patients with acute allergic symptoms	Primary: Resolution of urticaria, angioedema or erythema at 2 hours Secondary: Areas of cutaneous involvement Heart rate Blood pressure Respiratory findings Symptom scores	Less urticaria at 2 hours in the ranitidine + diphenhydramine group vs diphenhydramine (p=0.02). Fewer areas of urticaria in ranitidine + diphenhydramine group vs diphenhydramine group (p=0.02). Less urticaria and angioedema at 2 hours in ranitidine + diphenhydramine group (p=0.02). Proportion of patients without angioedema at 2 hours did not differ between the 2 groups. No difference in proportion treated with epinephrine.	Moderate	Unclear if H2-antihistamines beneficial in anaphylaxis as only 2 patients had hypotension. Addition of H2- antihistamines to H1 use may improve cutaneous manifestations of acute allergic reactions, but benefit in more severe allergic reactions/ anaphylaxis remains unproven.
Runge, 1992 ³⁰	USA	RCT (3 arms)	n=39 18-50 years	300mg i.v. cimetidine and placebo vs 50mg i.v. diphenhydrami	Change in patients and physicians assessment of severity of acute allergic reactions using a visual- analog scale before and 30 minutes after treatment	Only pruritus and urticaria occurred often enough to allow any formal analysis. Diphenhydramine only group had greater symptom relief from pruritus than cimetidine only	Moderate	Small sample size: 39 patients across 3 arms Diphenhydramine group had less severe initial symptoms than the other 2 groups. Offers little insights into the

				ne and placebo vs. i.v. diphenhydramine plus i.v. cimetidine in patients experiencing acute allergic symptoms	Adverse effects	group (p=0.022); use of combined diphenhydramine +cimetidine did not offer any greater symptom relief. Greater relief of urticarial symptoms was achieved in the combined treatment group vs diphenhydramine alone (p=0.027).		effectiveness of treatments for life-threatening features of anaphylaxis.
Sheikh, 2007 ³¹	World-wide	SR of RCT's and quasi-RCT's	N=0 n=0 All ages eligible	H1 antihistamines vs placebo or no intervention in the treatment of anaphylaxis.	Primary Clinical improvement by any objective measure Mortality rate Secondary Hospitalization rate Length of emergency department visit Length of hospital stay Representation rate to hospital Iatrogenic adverse events Rate of persistent/delayed/biphasic reactions Costs to health services and patients	No RCT's or quasi-RCT's comparing H1-antihistamines with placebo or no intervention were identified for inclusion.	High	Unable to make any recommendations for clinical practice.
Sheikh, ^c 2012 ³²	World-wide	SR of RCT's and	N=0 n=0 All ages	H1 antihistamines vs placebo or	Primary Clinical improvement by any objective measure	No RCT's or quasi-RCT's comparing H1-antihistamines with placebo or no intervention	High	Unable to make any recommendations for clinical practice.

		quasi-RCT's	eligible	no intervention in the treatment of anaphylaxis	Mortality rate Secondary Hospitalization rate Length of emergency department visit Length of hospital stay Representation rate to hospital Iatrogenic adverse events Rate of persistent / delayed / biphasic reactions	were identified for inclusion.		
Acute management: Methylxanthines								
Ernst, 1999 ³³	USA	SR of controlled trials	N=0 All ages eligible	Methylxanthine use in anaphylaxis	Evidence to support or refute the use of methylxanthines in anaphylaxis Safety of use	No studies identified on the use of methylxanthines in the treatment of anaphylaxis. Until data are available on humans methylxanthines should not be recommended in the treatment of anaphylaxis.	High	
Long-term management: Anaphylaxis management plans								
Choo, 2007 ³⁴	World-wide	SR of RCT's and quasi-RCT's	N=0 All ages eligible	Effectiveness of anaphylaxis management plans in self-management of anaphylaxis	Primary: Clinical improvement by any objective measure Hospitalization rate Emergency department attendance Admission and	No RCT's or quasi-RCT's of anaphylaxis management plans on the management of anaphylaxis were identified.	High	Need to consider broadening searches.

					readmission rates Length of hospital stay Mortality rate Secondary: Symptoms Use of rescue medication Quality of life, functional health status Days off work/school Health service use: length of emergency department stay, primary care visits			
Nurmatov, 2007 ³⁵	World-wide	SR of epidemiological, qualitative and interventional studies	n=19 All ages eligible	Acceptability, effectiveness, facilitators and barriers to the use of anaphylaxis management plans	Any description of components of AMP's, barriers and facilitators to their use, clinical effectiveness and acceptability.	No consensus on what aspects of care should be covered in an anaphylaxis management plan. Written plans acceptable with training to increase knowledge and reduce anxiety. Four studies indicate that anaphylaxis management plans plus training to parents, patients, school staff may greatly reduce the frequency and severity of further reactions. Barriers to use of anaphylaxis management plan include lack of knowledge and skills among parents, schools and professionals in recognizing symptoms, giving epinephrine	Moderate	Weak but nonetheless encouraging evidence on the effectiveness of anaphylaxis management plans.

						and long-term management; lack of national guidelines for schools; indemnity concerns. Facilitators in use of anaphylaxis management plan include education and training that is regularly reinforced; on-going specialist follow-up.		
Long-term management: Venom immunotherapy								
Boyle, 2012 ³⁶	World-wide	SR of RCT's and quasi-RCT's All ages eligible	N=7 n=392 All ages eligible	Standardized venom extract vs. placebo, no treatment or back-up treatment	Primary: Systemic reaction(SR) to a 'field' insect sting or a sting challenge during treatment. Fatal SR due to a field or challenge insect sting over the same period. Secondary: Large local reactions to a field sting or sting challenge during treatment or during the 10 years following treatment. Quality of life or anxiety score, assessed using a published scale Adverse events to immunotherapy	6 RCT's and 1 quasi-RCT included. Included ant, bee, and wasp immunotherapy in children and adults with previous systemic or large local reactions to a sting, using subcutaneous (six trials) or sublingual (one trial) VIT. VIT is effective in preventing systemic allergic reaction to an insect sting but subgroup analysis by route showed that only subcutaneous VIT was effective. Fewer patients treated with VIT had a severe systemic reaction to a subsequent sting compared with untreated patients risk ratio [RR] 0.10 (95%CI 0.03, 0.28).	High	Only subcutaneous VIT was shown to be effective. VIT reduced subsequent systemic reactions and improved quality of life.

						Unable to confirm whether VIT prevents fatal reactions to insect stings due to rarity of outcome. Increased risk of systemic adverse reactions to treatment with subcutaneous VIT compared to placebo (RR=8.16, 95%CI 1.53, 43.46). Undertook additional analysis of 11 observational studies to estimate risk of adverse events.		
Brown, 2003 ³⁷	Australia	RCT crossover design	n=68 20-63 years	Healthy patients with a previous Grade II-IV hypersensitivity to ant were randomly allocated to semi-rush immunotherapy or placebo with crossover	Primary: Systemic reaction to a sting challenge defined by objective measures Secondary: any systemic symptoms in the absence of objective physical signs; a grade IV reaction; treatment with epinephrine; changes in serum mast cell tryptase or plasma histamine after the sting challenge.	Only patients with positive skin tests were included, 33 in placebo group and 35 received VIT. After 52 sting challenges, objective reactions were found in 21 of 29 (72%) in the placebo group and none of 23 in the VIT group. (p<0.0001). In the placebo group 15 anaphylactic reactions occurred following the first sting challenge and 6 after the second. In the VIT group only one systemic reaction occurred on sting challenge, urticaria which settled without treatment. Of 30 patients from the placebo group who chose to crossover to	Moderate	Venom immunotherapy, in those with positive intradermal skin tests, was effective in preventing life threatening sting anaphylaxis. The severity of reaction to the deliberate sting in the placebo group could not be predicted from the worst Grade reaction in the field.

						VIT, 26 were sting challenged of these only one had a systemic reaction, Grade I urticaria.		
Golden, 1980 ³⁸	USA	RCT	n=64	Patients with a positive history of sting-anaphylaxis and positive intradermal skin test were randomized to 3 treatment groups. Group I, slow immunotherapy over 16 weeks, maintenance reached at 14 weeks; Group II, rush immunotherapy 7 bimonthly injections, maintenance reached at 6 weeks; Group III stepwise increment of doses,	Study of clinical efficacy, frequency and patterns of adverse reactions, and immunological responses.	Efficacy: 52 patients had sting challenges in hospital 4 were accidentally stung, none had a systemic reaction. Adverse reactions- during immunotherapy from all groups, 50% had at least one large local reaction average rate of 9.6 reactions/100 injections; 16% of all patients had systemic reactions during immunotherapy, 1.6 reactions per 100 injections. In both cases Group I, slow regime, had more reactions per patient as more injections were administered. IgG levels were significantly higher in Group II (rush) than the slow group $p<0.08$ at 18 weeks.	Low	Indicates that rush regimens of venom immunotherapy are equally as efficacious as more slower forms and are associated with less adverse effects due to the fewer number of injections administered. 7.8% of patients required epinephrine during treatment. Most local reactions occurred at doses of 15-50ug and decreased at higher doses and maintenance dose.

				maintenance dose reached at 11 weeks.				
Golden, 1981 ³⁹	USA	CBA	n=36	To prolong the interval between maintenance doses of VIT. 30 patients were randomly selected from a group of 81 patients who were already receiving the recommended maintenance dose of VIT following successful desensitization with whole-body extract therapy. 80% of the 81 had a history of previous anaphylaxis to insect sting. These 30	IgG venom specific antibody levels. Challenge stings. Adverse reactions	No increase in adverse reactions occurred between the 4 and 6 weekly maintenance dosing groups. At 6-9 months of maintenance therapy 29 of the 30 patients were sting challenged. 28 had no systemic effects and 1 had anxiety which settled with reassurance. These 30 patients plus 26 from the control group were stung after 1 year of maintenance injections followed by the 30 and 12 from the control group at 2 years. One systemic reaction occurred in each group, 98% success. IgG antibody levels did not differ significantly during the study.	Low	A 6 week maintenance interval should be considered in those who are successfully maintained on the conventional 4 week interval regime. longer interval should be considered in those who are successfully maintained on the conventional 4 week interval regime.

				patients had the interval between maintenance doses increased from 4-6 weeks.				
Hockenhull, 2012 ⁴⁰	UK	SR of RCTs and quasi-RCTs and health economic modeling	N=9, 4 RCT's, 5 quasi-experimental trials n=Not stated	Clinical effectiveness and cost effectiveness of Pharmedgen VIT for the treatment of bee and wasp venom allergy compared to other active treatment.	Clinical effectiveness outcomes: Systemic reactions Local reactions Mortality Anxiety related to the possibility of future reactions Health-related quality of life Adverse reactions to treatment Cost-effectiveness Cost per QALY gained	All trials small and of poor quality. Eight studies reported re-sting data after PhVIT, rate of systemic reactions ranged from 0-36.4%. AR's to PhVIT were recorded in 8 studies, systemic reactions between 0.0-38.1%, none was fatal. 17 non-comparative studies of PhVIT showed post VIT systemic reaction rates between 2-12.5%. Quality of life of people receiving VIT improved more than the quality of life of those using an EpiPen (p<0.00001). Cost effective only for high risk groups or if VIT is assumed to improve quality of life.	High	Evidence supports a decrease in reactions to stings following PhVIT. PhVIT is associated with AR's, these are treatable and may be acceptable due to the overall quality of life improvement perceived by the patients. Unable to assess impact on fatality because of small numbers of fatal events. Cost-effectiveness only likely in high-risk subgroups or if improved quality of life associated with VIT taken into account.
Hunt, 1978 ⁴¹	USA	RCT	n=59	Patients with a history of a	Challenge by hospital based stings after a series	Venom group after achieving a maintenance dose of 100ug VIT	Low	Of 59 patients, 58 successfully achieved

				generalized allergic reaction to a sting included, some had a previous anaphylactic reaction to a sting. Three matched groups were given placebo, whole-body extract or venom immunotherapy.	of immunotherapy injections had failed to cause a reaction. IgE antibody to honeybee and yellow jacket measured before and after the intervention.	were sting challenged. 18 stung, one had mild urticarial. 1 patient was not challenged as failed to tolerate treatment. Whole-body extract group, of 11 patients 7 were stung, 64% had systemic symptoms to the challenge. Placebo group, of 12 patients 7 were challenged and 58% had systemic symptoms to the sting. Last two groups, no statistical difference but significantly greater than the venom treated group, $p<0.01$. Control arm of study was aborted when second patient experienced a severe systemic reaction 14 patients who were treatment failures from the placebo and whole-body extract group and a further 17 patients who were not challenged were then given VIT and re-stung .Of these, 1 patient had urticaria following sting challenge. IgG antibody level increased in all venom treated patients but not in the other 2 groups.		desensitization with VIT Advocate use of venom immunotherapy over whole-body extract for the prevention of life-threatening reactions to insect stings. Advocate use of venom immunotherapy over whole-body extract for the prevention of life-threatening reactions to insect stings.
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Mosbech, 1985 ⁴²	Denmark	RCT	n=32	Patients with known systemic reactions to yellow jacket stings randomized to 3 groups: 1. Pharmalgen-yellow jacket venom (YJV) reconstituted in albumin 2. YJV without low molecular component, non-adsorbed., ALK 3. YJV adsorbed to aluminum hydroxide; Alutard.	Assessment of skin prick test size. Specific YJV IgE and IgG antibody levels	Of the 32 patients, 26 completed 2 years of treatment. Skin prick tests diminished for most patients in Pharmalgen and Alutard arms. No significant difference found in IgE levels between the 3 treatment groups IgG levels significantly increased in the Alutard arm and Pharmalgen arm. Between treatments significant difference in IgG levels when comparing Alutard and Pharmalgen and Alutard and ALK. All patients who had sting challenges had no systemic reactions.	Low	Small number of patients distributed among 3 arms. Treatment regimens different, difficult to blind. No statistical values given.
Muller, 1979 ⁴³	Switzerland	CBA	n=56	Patients with immediate type hypersensitivity (onset within	IgE and IgG antibodies levels to bee venom before treatment and at 1, 2, 6, and 12 months of treatment.	31 patients received bee venom and 25 whole bee extract. 24 patients, 12 from each group were re-stung, 23 accidental and one controlled. 8 of the WBE	Low	Venom is more effective than whole body extract in successful desensitization of highly allergic patients. Maintenance dose of 100ug

				30 mins) to bee stings, and positive specific IgE antibodies to bee venom were randomized to immunotherapy with bee venom (BV) or whole-body extract (WBE). Half of each group had intra-cutaneous injections and half subcutaneous into the upper arm.	Results of subsequent stings were compared.	patients and all of the BV patients had a reduced or no general reaction on re-sting. Difference between the 2 groups is significant ($p<0.05$). No general reaction on re-exposure ($p<0.025$). IgE levels of both groups were significantly lower at the end of treatment, greater reduction in the venom group. IgG levels increased significantly in the BV group, most pronounced in the first 2 months but maintained after 1 year of treatment ($p<0.001$). In the WBE group IgG levels decreased after 1 year of treatment. 8% of WBE and 39% of BV patients had severe local reactions during treatment; 16% of WBE and 39% of BV patients had general reactions. 4 had dyspnea needing epinephrine.		is recommended.
Muller, 1985 ⁴⁴	Switzerland	RCT	n=24	Patients were randomized to honey bee venom (HBV) or	Honey bee sting challenge. HBV- specific IgE antibodies measured before treatment and at 1 and 3 months of treatment	Of 12 HBV patients, 1 had a systemic reaction and 4 local reactions were noted on sting challenge. On PEG-HBV of 12 patients 3 had systemic	Low	Small sample size. No statistical analysis. Maintenance dose was changed during the study due to treatment failures.

				monomethoxy polyethylene glycol-coupled honey bee venom (PEG-HBV)	plus pre-sting and 2 weeks post-sting.	reactions and 7 local reactions. Specific HBV-IgE initially increased mildly in the HBV group no change illustrated in the PEG-HBV group. Increase in HBV specific IgG in both groups.		
Muller, 1987 ⁴⁵	Switzerland and South Africa	RCT	n=35	Patients with known systemic reactions to Honey Bee sting were randomized to receive honey bee venom (HBV) or monomethoxy polyethylene glycol modified (PEG) HBV doses received by PEG HBV patients increased quicker and maintenance dose was double	Sting challenge at week 14. HBV specific IgE and IgG levels taken at the start and after 4, 9, 14 weeks of treatment .and at 6 and 12 months. Adverse events recorded. Skin prick test results.	17 patients in each arm. Systemic reactions occurred in 2 of the PEG-HBV patients and 4 of the HBV. All 17 patients from PEG-HBV were sting challenged, 4 had systemic reactions. Of HBV arm only 14 had a sting challenge, 2 patients stopped treatment due to severe adverse reactions, 2 had a systemic reaction on re-sting. After 1 year there was a significant reduction in HBV specific-IgE in PEG-HBV arm ($p<0.01$) and HBV arm ($p<0.001$). Specific-IgG levels increased significantly in both groups over the year.		

				(200ug) that of HBV patients				
Oude Elberink, 2002 ⁴⁶	Canada	RCT	n=74	The effect of VIT on health-related quality of life in patients allergic to yellow jacket venom. Patients block-randomized to VIT or Epipen	HRQL measured with a disease specific instrument (VQLQ) before and 1 year post treatment. Mean change in VQLQ in both groups compared	36 received VIT, 38 Epipen Mean change in VQLQ score in VIT group 1.07 (95% CI, 0.68-1.46). Mean change in VQLQ score in Epipen group -0.43 (95%CI, -0.71 to -0.16), significantly different from VIT group (p<.0001). Expectation of outcome score, changed in the VIT group from 5.66 to 2.88 (p<0.0001), no change in the Epipen group Improvement of VQLQ score of greater than 0.5 was 74% in VIT group and 9% in Epipen group. Overall proportion of patients benefiting from VIT over Epipen is 0.72 which corresponds to an NNT of 1.4. 94% rated VIT as extremely or very positive when taking into consideration the positive and negative effects of this treatment	Low	Half of patients approached refused to be randomized, 80% of whom chose VIT over Epipen. Improvement in HRQL scores indicates that this is clinically important and relevant to patients. NNT of 1.4 to achieve an improvement in VQLQ scores is favorable.
Oude Elberink, 2006 ⁴⁷	Canada	RCT	n=94 18 to 65	To examine negative aspects of the Epipen when	Measurement of VQLQ, BoT and Epipen statements at the onset of treatment and 1 year later.	47 received VIT and 47 had an Epipen. 2 patients were stung in the field during the study one from each	Moderate	Suggests that carrying an Epipen is more of a burden than VIT.

				compared to VIT in patients with anaphylaxis to yellow jacket stings by using a burden of treatment questionnaire (BOT) and statements about the Epipen. Patients were randomized to VIT or carry an Epipen for 1 year.	Epipen group given choice to continue with Epipen or have VIT.	group, VIT patient had no symptoms, and the other patient used the Epipen. 91.5% of the VIT group were positive about treatment, none were negative. 47.7% of the Epipen group were positive compared to 29.5% who were negative After 1 year of carrying the Epipen when given the choice 78% wanted to start VIT.		
Quercia, 2001 ⁴⁸	Italy	RCT	n=55	Patients with systemic reactions Grade II or more, positive skin prick and RAST to Apis Mellifera were assigned to 1 of 3 groups: Aluminium hydroxide-	Tolerance of aqueous cluster or rush VIT vs cluster depot VIT. Adverse reactions during the induction phase.	20 patients had aqueous-rush VIT, 20 aqueous-cluster, 15 received depot-cluster VIT. Significantly lower number of patients with adverse events in both cluster arms compared to the rush arm ($p<0.009$). Frequency of adverse events also significantly lower in both cluster groups ($p<0.003$) No significant difference in both number of patients and	Low	Aqueous cluster and depot cluster VIT have fewer side effects than rush schedule VIT. Small sample size may have influenced results. No reference to randomization of patients to various arms.

				adsorbed honey bee venom was used as an aqueous cluster, rush VIT or cluster depot VIT.		frequency of adverse events between the two cluster groups.		
Ross, 1999 ⁴⁹	World-wide	SR of all studies	N=8 n=453	Meta-analysis of all studies to compare the effects of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity.	To assess the effectiveness of specific venom immunotherapy for Hymenoptera venom as a protection against a major systemic reaction.	Studies included involved patients with severe venom hypersensitivity. All 8 studies concluded that SIT was clinically effective. Significantly greater likelihood of a reduced rate of systemic symptoms on re-sting.	Low	Most of the studies were open with no placebo or control group.
Thurnher, 1983 ⁵⁰	Sweden	CBA	n=42	Patients with previous systemic allergic reactions to hymenoptera stings were randomized to receive rush or conventional	Primary outcomes were treatment tolerance; skin tests; specific-IgE and IgG antibodies before treatment and at 3, 6, 12, 24 and 36 months after commencing treatment.	21 patients had rush and 21 conventional therapy, 2 patients failed to complete treatment. Adverse reactions occurred in both groups with no statistical difference between groups ($p>0.1$). 4 patients, 3 from the rush group and 1 on conventional therapy, had Grade II-IV reactions requiring	Low	Patients were randomized to rush treatment if they lived at a distance to the hospital or had a high risk of re-sting. Skin tests and specific IgE antibodies became negative in 15 patients in whom desensitization was successful..

				VIT. Patients received honeybee venom (HBV), yellow jacket venom (YJV) or both dependent on their allergy profile.		epinephrine and antihistamine. 24 patients were re-stung, 22 accidental and 2 were challenged. 17 had no reaction, 6 had reduced systemic reactions and 1 had a prolonged delayed reaction and discontinued treatment. 96% success rate. Skin test to honeybee venom and yellow jacket venom decreased over the 3 year treatment period for all patients but more in the conventional treatment group. More became negative on conventional treatment but only statistically significant for YJV ($p<0.05$). After 3 years treatment, 3/30 were specific IgE negative to HBV, 17/29 negative to YJV and 5/30 negative to both who were on combined treatment. More patients negative on conventional treatment but only significant for those on YJV treatment ($p<0.01$).		
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Watanabe, 2010 ⁵¹	World-wide	SR of RCT's	N=4 n=286 All ages eligible	VIT vs placebo or patient follow-up	Risk of systemic reactions after specific immunotherapy was evaluated using odds ratios and their 95% confidence intervals	4 RCTs satisfied inclusion criteria. It was possible / appropriate to undertake meta-analyses of 2 trials in children which showed OR=0.29 (95%CI 0.10, 0.87) for systemic reactions after further accidental stings in VIT treated children. No indication for VIT in children who have only had cutaneous reactions following a sting. Conclude that specific VIT should be recommended for children with previous moderate-to-severe reactions and adults with previous systemic reactions	High	Lack of allocation concealment and the fact that the trials were not double-blind may have led to an over-estimation of the effects of treatments.
<i>Long-term management: Educational interventions</i>								
Spina, 2012 ⁵²	USA	Quasi-experimental trial	n=77 14-18 years	Effectiveness of school nurse-delivered educational intervention to high-school students with	Primary: To increase carriage of epinephrine auto-injector. Secondary: To increase carriage of in-date epinephrine auto-injector	Ineffective at improving carriage rate (p=0.189). Suggestion that those who carry epinephrine may be more likely to carry unexpired auto-injectors.	Moderate	Within arm analysis of expired / unexpired auto-injectors.

				food allergy vs standard checks				
Long-term management: Psychological interventions								
Manassis, 2012 ⁵³	World-wide	SR of studies of any design	Children and adolescents	Reviews anxiety and anaphylaxis in children and youth and principles to manage anxiety in children and parents.	Aspects of anxiety assessed: Physiological Cognitive Behavioral Parental anxiety	Physical, cognitive and behavioral aspects of anxiety related to anaphylaxis needs to be addressed to allow children to function well. Parents need to be involved in children's care. On-going follow up is needed of psychological as well as medical management.	Low	Poor quality SR with limited transparency of searches, assessment of quality of included studies. Conclusions drawn mainly from weak primary evidence.
Long-term management: Prophylactic interventions for snake anti-venom								
De Silva, 2011 ⁵⁴	Sri Lanka	RCT	n=1007	Immediately before receiving snake anti-venom patients experiencing envenomation were randomized to either s.c.	The incidence of severe reactions following pretreatment with epinephrine, promethazine or hydrocortisone up to and including 48 hours after anti-venom administration.	752(75%) patients had acute reactions to anti-venom within the 48 hour period; 43% of these were severe and 83% of the severe reactions took place in the first hour. Epinephrine reduced the rate of severe reactions compared to placebo significantly at 1 hour (p<0.001) and at 48 hours (p<0.001).	High	Pretreatment with epinephrine significantly reduces the incidence of acute adverse effects following administration of anti-venom. A dose of epinephrine 0.25mls given s.c. appears to be safe and no adverse effects of the pretreatment were noted.

				epinephrine (0.25mls 1:1000), i.v. promethazine 25mgs or i.v. hydrocortisone 200mgs alone or in combination or placebo. Patients were randomized to 8 possible groups using a 2x2x2 factorial blinded design.		No significant benefit was seen by using hydrocortisone or promethazine in the incidence of adverse effects at 1, 6 24 or 48 hours. Combination of hydrocortisone with epinephrine appeared to negate the beneficial effects of epinephrine (p=0.013).		Routine pretreatment with glucocorticosteroids and antihistamines was not shown to significantly reduce adverse effects. There is a need to produce better anti-venoms to deduce the incidence of adverse reactions.
Fan, 1999 ⁵⁵	Brazil	RCT	n=101 >2 years	Patients bitten by bothrops snakes needing anti-venom were randomized to i.m. promethazine (25mgs for adults, 0.5.kg for children) or placebo, 15-20 mins prior to iv	Incidence and severity of anaphylactic reactions occurring within 24 hours of anti-venom treatment.	Anaphylactic reactions occurred early in 25 patients, 12 from the treatment group 13 from the placebo group. All needed epinephrine. A further 8 developed anaphylaxis 1-2 hours after the anti-venom infusion, 3 from the treatment group and 5 from the placebo group. No difference in the severity of reactions between the two groups.	High	No evidence to suggest use of H1 antihistamine to reduce severe adverse reactions to snake anti-venom.

				infusion of anti-venom.		No statistical difference illustrated in between the 2 groups.		
Gawarammana, 2004 ⁵⁶	Sri Lanka	RCT	n=52 >12 years	Patients with snake envenoming randomized to hydrocortisone infusion (n=15), hydrocortisone infusion with chlorpheniramine bolus (n=21) or placebo (n=16) prior to and during treatment with snake anti-venom.	Occurrence and severity of adverse reactions to anti-venom	Adverse reactions in 80% receiving hydrocortisone alone; in 52% receiving hydrocortisone and chlorpheniramine and in 81% of the placebo group. No significant difference in the severity of reactions between groups. 21 patients needed treatment with epinephrine. Hydrocortisone infusion with a 10mg chlorpheniramine bolus had significantly less adverse effects when compared to placebo (p=0.04). Using hydrocortisone alone did not significantly reduce adverse reactions when compared to placebo.	High	Evidence that a combination of hydrocortisone and chlorpheniramine reduces the likelihood of adverse reactions with anti-venom.
Habib, 2011 ⁵⁷	World-wide	SR of RCT's	N=7 n=833 All ages eligible	Effect of pre-medication following anti-venom use in snake bite	Risk of early adverse reactions Epinephrine pre-medication	3 randomized and 4 non-randomized trials Epinephrine pre-medication resulted in a reduced risk of early adverse reactions: overall RR=0.32 (95%CI 0.18, 0.58) .	High	Only one author, unclear whether quality assessment of studies carried out by more than one person.

						No significant reduction in early adverse reactions associated with use of H1-antihistamines and glucocorticosteroids.		
Premawardhena, 1999 ⁵⁸	Sri Lanka	RCT	n=105 12-70 years	Patients with envenomation randomized to receive epinephrine 0.25mls (1:1000) s.c. into the forearm or placebo prior to treatment with snake anti-venom serum.	Acute adverse reactions to snake anti-venom serum. Side-effects associated with use of epinephrine.	56 patients received epinephrine and 49 placebo. No of patients experiencing mild, moderate or severe adverse reactions significantly reduced in the epinephrine group (p=0.0002). No adverse effects noted due to epinephrine use.	High	Treatment so effective study had to be aborted after recruiting 105 patients, power calculations stated needed 228 patients but results at halfway point so significant. Patients at high risk of adverse effects with epinephrine excluded e.g. people with atopy, wheezing, ischemic heart disease.
Long-term management: Prophylactic interventions for contrast media								
Bertrand, 1992 ⁵⁹	France	RCT	n=400 >18 years	Patients needing i.v. contrast media were randomized to receive oral Hydroxyzine (H1 antihistamine)	Adverse reactions to i.v. contrast media	No anaphylactic reactions occurred in either group. Hydroxyzine compared to placebo reduced the number of mild adverse reactions occurring significantly (p<0.0001).	Low	Patients with any allergy, atopy, drug sensitivities or previous allergic reaction to contrast media were excluded. Patient numbers too small to show if effective to prevent anaphylaxis plus high risk patients actively excluded.

				100mg 12 hours before i.v. contrast media or placebo				
Chevrot, 1988 ⁶⁰	France	RCT	n=221	Assess the protective effect of betamethasone 8 mg injected or not (1:1) to patients at the same time as the contrast media. 221 patients, 68 had the steroid injected with the contrast medium.	Occurrence of an allergic reaction	133 patients had allergic reactions, weak difference between the treatment and no treatment group, 61% versus 79%.	Low	Open randomization.
Ginsberg, 1996 ⁶¹	UK	RCT	n=86	Patients requiring myelography were randomized to receive oral dexamethasone 4mgs, 4 times a day or	To investigate the usefulness of glucocorticosteroids to alleviate adverse reactions to contrast media Analysis of post-myelography symptom pathogenesis.	No significant difference was illustrated between the 2 groups in terms of adverse effects.	Low	Patient size small may have contributed to lack of difference illustrated between treatment and control group.

				placebo 24 hours before and after myelography with intra-thecal contrast medium.				
Lasser, 1987 ⁶²	USA	RCT	n=6763 >18 years	Patients undergoing x-rays with iv contrast media were randomized to 4 arms: 1 Oral methylprednisolone 32mg, 12 and 2 hours prior to iv contrast media 2. Oral methylprednisolone 2 hours prior to i.v. contrast media or 3. Placebo 2 tablets to match group 1 4. Placebo 1 tablet to match group 2	Reduction of adverse events with pretreatment with corticosteroids prior to iv contrast media administration	No significant difference was found in the adverse reaction rate between the two placebo groups, or between placebo and one dose of methylprednisolone. The two dose methylprednisolone group had a reduced adverse reaction rate ($p<0.05$). compared to the other 3 groups.	Low	Patients with previous severe reactions to contrast media were excluded.

Lasser, 1994 ⁶³	USA	RCT	n=1155 18 years or older	Patients were randomized to: - oral methylprednisolone 32mgs, 6-24hrs and 2 hours prior to i.v. contrast media administration or - placebo tablets administered at the same times.	To determine whether patients receiving 2 doses of corticosteroids before i.v. injection of non-ionic contrast media would have reduced adverse effects. Grade I reactions-single episode of emesis, nausea, sneezing, and vertigo. Grade II reactions- hives, erythema, emesis more than once, fever or chills. Grade III reactions- clinical 'shock', bronchospasm, laryngospasm, edema, loss of consciousness, convulsions, decrease in BP, increase in BP, cardiac arrhythmias, angina, angioedema, pulmonary edema.	107 patients had a history of previous adverse reaction to contrast media, 12 (11%) had an adverse reaction in this study. Of 565 patients who had received contrast media in the past with no adverse effect, 12 (2%) had a reaction. 28 (5%) of patients who received placebo had reactions compared to 10 (2%) in the treatment group (p=0.005). Methylprednisolone decreased the number of Grade I reactions (p=0.004), but not Grade II (p=0.63) or Grade III (p=0.11) reactions.	Low	Patients excluded if they had used antihistamines in the previous 12 hours Patients with previous reactions to contrast media were included in the study. Previous adverse reaction is associated with a greater risk of a further adverse reaction (p<0.0001). Study was aborted early due to lack of funding, ideal patient size was 6000. Methylprednisolone failed to show any reduction in severe adverse reactions such as those fulfilling the criteria for anaphylaxis.
Small, 1982 ⁶⁴	Canada	RCT	n=220	Patients requiring an IVP were randomized to 3 arms: 1. no premedication, 2. s.c. of saline 15 minutes prior to	Incidence of allergic and non-allergic reactions. Changes in serum total hemolytic complement and immune complexes at 0, 1, 5, 10, 20 minutes after injection of contrast media.	42 patients had a reaction. Reduced number of reactions in chlorpheniramine group compared to other 2 groups (p<0.05). No statistical difference between the 2 control groups. Allergic reactions were hives or generalized pruritus. There was	Low	Patients currently taking antihistamines were not included in the study. Allergic reactions which occurred were mild no cardiovascular or respiratory compromise occurred.

				receiving i.v. contrast media or 3. s.c. chlorpheniramine 10mgs 15 minutes prior to receiving i.v. contrast media.		a significant reduction in allergic reactions in the chlorpheniramine group ($p<0.05$).		
Tramer, 2006 ⁶⁵	World-wide	SR of RCT's	N=9 n=10,011 All ages eligible	Efficacy of pharmacological prevention of anaphylactic reactions to iodinated contrast media vs placebo or no treatment	Distinct allergy related symptoms Symptom categories (grades) Non-specific symptoms Adverse drug-reactions	H1-antihistamines, H1+H2-antihistamines and glucocorticosteroids trialled. Anaphylactic reactions to iodinated contrast media were rare, e.g. no deaths or cardio-pulmonary resuscitation Oral prednisolone reduced the risk of less severe cardio-respiratory outcomes OR=0.28 (95%CI 0.13, 0.60) Overall risk of serious adverse reactions was low, so the NNT to treat even with effective interventions is likely to be very high	High	Prophylactic premedication in unselected patients to prevent allergic reactions is of doubtful value This approach may however be useful in selected high risk patients who have a history of allergy but no trials in such high risk groups.
Wicke, 1975 ⁶⁶	German	RCT	n=208 adults	Patients requiring	Does the intervention reduce side effects for the	Side effects with the contrast material Uravison and	Low	

				urography (148) or cholangiography (60) were randomised to receive an antihistamine, Clemastine iv (92) or placebo (116) with contrast media	patients while/after diagnostic x-ray examination	Clemastine were 13% Side effects with the contrast material Uravison and placebo were 25% Side effects are significantly reduced with use of clemastine ($p < 0, 1$) Side effects with the contrast material Biligradin and clemastine were 4% Side effects with the contrast material Biligradin and placebo were 24% Side effects are significantly reduced with use of clemastine ($p < 0,05$)		
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Table S2: Quality assessment of systematic reviews

Author, year	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Appropriateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms/costs	Overall quality assessment
Boyle, 2012 ³⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Choo, 2007 ³⁴	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Choo, 2010 ²⁷	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Choo, 2012 ²⁸	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Ernst, 1999 ³³	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Habib, 2011 ⁵⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Hockenhull, 2012 ⁴⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Manassis, 2012 ⁵³	✓	X	✓	X	✓	✓	✓	✓	✓	Low
Nurmatov, 2008 ³⁵	✓	X	✓	✓	✓	✓	✓	✓	✓	Moderate
Ross, 1999 ⁴⁹	✓	X	✓	X	X	✓	✓	✓	✓	Low
Safdar, 2000 ¹⁷	X	X	X	✓	X	✓	✓	✓	✓	Low
Sheikh,	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High

2007 ¹⁹										
Sheikh, 2009 ²⁰	✓	✓	✓	N/A	N/A	✓	✓	✓	N/A	High
Sheikh, ^a 2012 ³¹	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Sheikh, ^b 2012 ³²	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Sheikh, ^c 2012 ³²	✓	✓	✓	N/A	N/A	✓	✓	✓	✓	High
Tramer, 2006 ⁶⁵	✓	✓	✓	Unclear	✓	✓	✓	✓	✓	High
Watanabe, 2010 ⁵¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	High

Table S3: Quality assessment of original studies

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding/ patient-related outcomes	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias*	Overall quality assessment
Bertrand, 1992 ⁵⁹	RCT	Unclear	Unclear	Yes	Yes	Yes	No	Low
Bock, 2001 ¹²	Case series	No	No	No	No	No	No	Low
Bock, 2007 ¹³	Case series	No	No	No	No	No	No	Low
Brown, 2003 ³⁷	RCT	Yes	Yes	Unclear	Yes	Yes	Yes	Moderate
Chevrot, 1988 ⁶⁰	RCT	Unclear	No	No	Unclear	Unclear	Unclear	Low
De Silva, 2011 ⁵⁸	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Fan, 1999 ⁵⁹	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Gawarammana, 2004 ⁶⁰	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Ginsberg, 1996 ⁶¹	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Golden, 1980 ³⁸	RCT	Unclear	Unclear	No	No	No	Yes	Low
Golden, 1981 ³⁹	CBA	No	No	No	Unclear	No	Yes	Low
Hunt, 1978 ⁴¹	RCT	Yes	Unclear	No	Yes	Unclear	No	Low
Jarvinen, 2008 ¹⁴	Case series	No	No	No	No	No	No	Low
Lasser, 1987 ⁶²	RCT	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Lasser, 1994 ⁶³	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Lin, 2000 ²⁹	RCT	Yes	Yes	Yes	Yes	Yes	No	Moderate
Mosbech, 1986 ⁴²	RCT	Unclear	Unclear	No	Yes	Yes	Yes	Low
Muller, 1979 ⁴⁵	CBA	No	No	No	Unclear	Unclear	No	Low
Muller, 1985 ⁴³	RCT	Unclear	Unclear	No	Yes	Yes	No	Low
Muller, 1987 ⁴⁴	RCT	Unclear	Unclear	Unclear	No	Yes	No	Low
Oude Elberink,	RCT	Yes	Yes	No	Yes	Yes	Yes	Moderate

2002 ⁴⁶								
Oude Elberink, 2006 ⁴⁷	RCT	Unclear	Unclear	No	Yes	Yes	No	Low
Premawardhen, 1999 ⁵⁸	RCT	Yes	Yes	Yes	Yes	Yes	Yes	High
Pumphrey, 2000 ¹⁵	Case series	No	No	No	No	No	No	Low
Pumphrey, 2007 ¹⁶	Case series	No	No	No	No	No	No	Low
Quercia, 2001 ⁴⁸	RCT	No	No	No	Yes	Yes	No	Low
Runge, 1992 ³⁰	RCT	Yes	Yes	Yes	Yes	No	No	Moderate
Sampson, 1992 ¹⁸	Case series	No	No	No	No	No	No	Low
Simons, 1998 ²²	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2000 ²³	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2001 ²⁴	RCT	Yes	No	Yes	Yes	Yes	No	Moderate
Simons, 2002 ²⁵	RCT	Yes	Yes	Yes	Yes	Yes	No	Moderate
Small, 1981 ⁶⁴	RCT	Unclear	Unclear	Yes	Yes	Yes	Yes	Low
Soreide, 1988 ²⁶	Case series	No	No	No	No	No	No	Low
Spina, 2012 ⁵²	Quasi- RCT	No	Yes	No	Yes	No	No	Moderate
Thurnheer, 1983 ⁵⁰	CBA	No	No	No	No	No	No	Low
Wicke, 1975 ⁶⁶	RCT	No	Yes	No	No	Yes	No	Low

Table S4: On-going/unpublished studies

PI, country	Title	Study design	ClinicalTrials.gov identifier	No. of participants	Intervention	Primary outcome measures	Started reporting	Estimated study completion date	Status
Brockow, Germany	Effects of a structured educational intervention on knowledge and emergency	RCT	None	130	Two 3-hour schooling modules of group education; the waiting control group received no intervention	Knowledge of anaphylaxis and emergency management competence at baseline and 3 months after	2009	2011	Closed, submitted for publication
Hourihane, Ireland	A 24-hour helpline for access to expert management advice for food allergy-related anaphylaxis in children: protocol for a pragmatic RCT	RCT	ISRCTN29793562	47	24-hour telephone access to specialist paediatric allergy expert advice for children <16 years with food allergy who carry an epinephrine auto-injector vs. usual care	To compare the difference in food allergy related quality of life between the 24-h telephone access and usual care at 1 and 6 months post-randomization	July 2012	Early 2013	Closed, data as yet unpublished

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