Diagnosing, managing and preventing anaphylaxis: systematic review

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Abstract

Background This systematic review used the GRADE approach to compile evidence to inform an anaphylaxis guideline from the
European Academy of Allergy and Clinical Immunology (EAACI). Methods We searched five bibliographic databases from 1946 to 20 April 2020 for studies about the diagnosis, management and prevention of anaphylaxis. We included 50 studies with 18,449 participants: 29 randomised controlled trials, seven controlled clinical trials, seven consecutive case series and seven case-control studies. Findings were summarised narratively because studies were too heterogeneous to conduct meta-analysis. Results It is unclear whether the NIAID/FAAN criteria or Brighton case definition are valid for immediately diagnosing anaphylaxis due to the very low certainty of evidence. Adrenaline is the cornerstone of first-line emergency management of anaphylaxis but, due to ethical constraints, little robust research has assessed its effectiveness. Newer models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce time to administration. Face-to-face training for laypeople may slightly improve anaphylaxis knowledge and competence in using autoinjectors. Adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis but the impact of prophylactic corticosteroids and antihistamines is uncertain. There was insufficient evidence about the impact of other anaphylaxis management strategies. Conclusions Anaphylaxis is a potentially life-threatening condition but, due to practical and ethical challenges, there is a paucity of robust evidence about how to diagnose and manage it.

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Diagnosing, managing and preventing anaphylaxis: systematic review

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Author contributions

All authors conceptualised the work, commented on the work and approved it for submission. DdS and CS searched for studies, extracted data and drafted the review.

Potential conflict of interests related to the manuscript content

Some of the authors have professional affiliations related to the content of the review. These authors were not involved in decisions about study selection, data extraction or analysis of studies in fields where they had a declared commercial interest.

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ADG: Research: Aimmune Therapeutics, National Children’s Research Centre Ireland, DBV Technologies, SafeFood Ireland. Consultant: Aimmune Therapeutics, Atlanta Clinical Trials in Food Ireland;
AM: Research: Aimmune; Speaker: DVB, Aimmune, Mylan, ALK, Nestle;
AS: Consultant: Aimmune Therapeutics;
BJ: Speaker: Novartis;
BV-B: Consultant: Marfo Food Groups. Research: Nutricia. Speaker: Mead Johnson, Nutricia, Thermofisher;
CB-J: Research: Hal Allergy, Termofischer, Aimmune, Novartis, Allergy Therapeutics, Allakos;
EA: Consultant: BSACI member, Anaphylaxis Campaign scientific board member;
GR: Editor: Editor in Chief Clinical & Experimental Allergy;
KB: Research: Aimmune, ALK, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, Infectopharm, Thermofisher, VDI, EU, German Research Foundation, BMBF. Consultant/Speaker: Aimmune, ALK, Allergopharma, Bausch & Lomb, Bencard, Danone, DBV, Hycor, Jenpharma, Infectopharm, Mabylon, Mylan, Nestle, Novartis, Nutricia, Thermofisher;
KBr: Consultant: Thermofisher; Speaker: Meda;
LHG: Consultant: Novo Nordisk, Merck, Thermofisher Scientific;
LJM: Consultant/speaker: Danone Nutricia, Sanofi; Speaker: Novartis; Allergy Therapeutics; Research: Danone Nutritica, Sanofi; BSACI member;
LOM: Consultant: Alimentary Health Ltd. Research: GSK. Speaker: Nestle, Nutricia;
LR: Employee of Anaphylaxis Campaign, UK.
MBB: Speaker: ALK, Allergy Therapeutics, Astra, GSK, Sanofi;
MW: Consultant: ALK Abello, Aimmune, DBV Technologies, Regeneron Pharmaceuticals, Sanofi Aventis, Leo Pharma, Mylan, WAO co-chair anaphylaxis committee;
SH: Speaker: ARLA, Nestle. Research: ALK, GAP study;
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vi. Abstract and keywords
Background
This systematic review used the GRADE approach to compile evidence to inform an anaphylaxis guideline from the European Academy of Allergy and Clinical Immunology (EAACI).
Methods
We searched five bibliographic databases from 1946 to 20 April 2020 for studies about the diagnosis, management and prevention of anaphylaxis. We included 50 studies with 18,449 participants: 29 randomised controlled trials, seven controlled clinical trials, seven consecutive case series and seven case-control studies. Findings were summarised narratively because studies were too heterogeneous to conduct meta-analysis.

Results

It is unclear whether the NIAID/FAAN criteria or Brighton case definition are valid for immediately diagnosing anaphylaxis due to the very low certainty of evidence.

Adrenaline is the cornerstone of first-line emergency management of anaphylaxis but, due to ethical constraints, little robust research has assessed its effectiveness. Newer models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce time to administration.

Face-to-face training for laypeople may slightly improve anaphylaxis knowledge and competence in using autoinjectors.

Adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis but the impact of prophylactic corticosteroids and antihistamines is uncertain.

There was insufficient evidence about the impact of other anaphylaxis management strategies.

Conclusions

Anaphylaxis is a potentially life-threatening condition but, due to practical and ethical challenges, there is a paucity of robust evidence about how to diagnose and manage it.

Keywords: Anaphylaxis, Prevention, Management, Diagnosis, Adrenaline, Epinephrine

Word count: 226

vii. Main text

INTRODUCTION

Rationale

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released guidelines for managing anaphylaxis. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, Eigenmann PA, Grimshaw KE, Hoest A, Lack G, O’Mahony L. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy 2014;69(5):590-601. Since that time, new research has been published and the EAACI guideline is being updated. This manuscript describes a systematic review to support the guideline.


Objectives

This systematic review focuses on three questions:

1. What is the effectiveness of any approach for the immediate diagnosis (intervention) of anaphylaxis (outcome) in children and adults (population) compared with expert panel consensus or any other approach (comparator)?
2. What is the effectiveness of any approach for the emergency management (intervention) of anaphylaxis (outcome) in the community or in hospital in children and adults (population) compared to any other intervention, placebo or no intervention (comparator)?
3. What is the effectiveness of any approach (intervention) for the prevention or long-term management of anaphylaxis (outcome) in children and adults (population) compared to any other intervention, placebo or no intervention (comparator)?

METHODS

The review was undertaken by a task force representing allergists, anaesthetists, emergency medicine clinicians, paediatricians, paramedics, pharmacists, primary care doctors, psychologists, nurses, other clinicians, patient representatives, teachers and methodologists from seven countries.

Eligibility criteria

Studies were eligible for the review if they included:

- **Population**: children (aged under 18 years) and/or adults (18+ years) with or without a history of anaphylaxis.
- **Comparator**: any comparator, including placebo, no intervention or any intervention or combination of interventions.
- **Outcomes**: anaphylaxis incidence, sensitivity and specificity of diagnostic approaches, mortality or near fatal incidents, hospital admissions, quality of life and other pre-set outcomes.
- **Study types**: full publications of randomised controlled trials (hereafter trials), controlled clinical trials, controlled before-and-after studies and case-control studies in humans and, in the case of diagnosis and adrenaline (epinephrine) only, consecutive case series with a minimum of 20 participants. There were no language or geographical restrictions.
- **Timeframe**: published from 1946 to 20 April 2020.


**Study selection and data extraction**

An information specialist/methodologist (CS) searched five databases using a search strategy developed with clinicians and patient representatives (see online supplement S1). Two methodologists identified additional references by searching the reference lists of previous reviews, guidelines and identified studies and seeking recommendations from experts (CS, DdS). Two methodologists independently screened titles and abstracts and the full text of any studies deemed potentially relevant (CS, DdS). Shortlisted studies were rescreened by all clinicians, allied health professionals and patient representatives on the task force (all authors). We excluded studies where it was unclear that the reactions described were anaphylaxis (see online supplement S2). There was 100% inter-rater agreement about the studies included.

Data about study characteristics and outcomes were extracted into a template independently by two methodologists (CS, DdS) and by task force members divided into small topic groups (all authors).

**Risk of bias in individual studies**

Two methodologists independently assessed the risk of bias in individual studies (CS, DdS) as did small groups of task force members (all authors). The Cochrane Risk of Bias tool 2 (ROB2)11Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC. The Cochrane

**Synthesis of results**


Small groups of clinicians and methodologists reviewed studies about each intervention and created evidence profiles (all authors). Authors were not involved in decisions about topics where they had a potential conflict. All taskforce members decided on the conclusions by consensus.

Results were summarised using narrative synthesis. We did not undertake meta-analysis because the minimum criteria for meta-analysis set out in the review protocol were not met.

We used standardised GRADE statements to narratively indicate the effect size and the certainty of the evidence (Table 1).\textsuperscript{22} Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, Kuijpers T, Meerpohl J, Morgan R, Mustafa R, Skoetz N, Sultan S, Wiysonge C, Guyatt G, Schünemann HJ. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-135. For example, if the certainty of evidence was very low, regardless of effect size, the following terminology was used: ‘It is unclear whether [intervention] affects [outcomes] because the evidence is very uncertain.”

**RESULTS**

**Study characteristics**

Figure 1 summarises the number of studies screened and selected. Fifty studies with 18,449 participants were included: 29 randomised trials (58%), seven non-randomised controlled trials (14%), seven consecutive case series (14%) and seven case-control studies (14%). Three studies focused on diagnosis, 26 on the acute management of anaphylaxis or the characteristics of adrenaline administration, 9 on education to improve emergency management and 12 on long-term management and prevention.

Overall, 50% of the studies were from North America, 28% from Europe, 12% from Asia, 4% from Australia and 6% from elsewhere. Two thirds (66%) of the studies were published between 2010 and 2020, 18% from 2000 to 2009 and 16% prior to 2000. The online supplement summarises the individual studies and their risk of bias assessments (see supplement S3).

More than half of the studies (56%) were at high risk of bias, 40% at moderate risk and 4% at low risk. The GRADE certainty of evidence was generally low or very low (online supplements S4-8) and was often downgraded due to risk of bias, indirectness and imprecision.

The studies contained multiple outcomes, measured in a range of ways and at a variety of time points. Space does not permit a description of every outcome so only a selection are described here and not all numerical findings and confidence intervals are listed. The online supplements describe the outcomes in more detail.

**Diagnosis of anaphylaxis at presentation**\textsuperscript{(Table 2)}

We included three studies with 516 participants about the immediate diagnosis of people presenting with anaphylaxis (as opposed to retrospectively confirming a suspected diagnosis). Other approaches such as serum
tryptase are not summarised here because they help with subsequent confirmation rather than immediate diagnosis.

The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria aim to define anaphylaxis for research and clinical purposes. It is unclear whether these criteria help to diagnose anaphylaxis because the certainty of evidence is very low, but there are positive trends (supplement S4a and Table 2).

Sensitivity is an important indicator of the accuracy of criteria for the immediate diagnosis of anaphylaxis. The NIAID/FAAN criteria may be highly sensitive, but less specific. There were three eligible studies in adults and children. One consecutive case series found that the NIAID/FAAN criteria had sensitivity of 0.95 (95% confidence interval (CI) 0.85 to 0.99) and specificity of 0.71 (95% CI 0.61 to 0.79, very low certainty).11Loprinzi Brauer CE, Motosue MS, Li JT, Hagan JB, Bellolio MF, Lee S, Campbell RL. Prospective validation of the NIAID/FAAN criteria for emergency department diagnosis of anaphylaxis. J Allergy Clin Immunol Pract 2016;4(6):1220-1226. A case-control study found sensitivity of 97% (95% CI 89% to 99%) and specificity of 82% (95% CI 76% to 88%, very low certainty).22Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, Smith VD, Li JT. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. J Allergy Clin Immunol 2012;129(3):748-52. Another case control study found sensitivity of 0.67 (95% CI 0.46 to 0.75) and specificity of 0.70 (0.59 to 0.80, very low certainty)33Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O, Benger JR. Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. Drug Saf 2010;33(1):57-64.

The Brighton Collaboration case definition is designed for standardising adverse events following immunisations. It includes many different adverse effects to vaccines, not solely anaphylaxis. It is unclear whether this definition helps to diagnose anaphylaxis because the certainty of evidence is very low (supplement S4b). One case control study found that this definition had sensitivity of 0.68 (95% CI 0.54 to 0.80) and specificity of 0.91 (95% CI 0.80 to 0.96) in children and adults (very low certainty).44Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O, Benger JR. Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. Drug Saf 2010;33(1):57-64.

Acute management of anaphylaxis (Table 3)

We identified 26 studies with 3,645 participants about the emergency management of anaphylaxis or adrenaline administration.

Adrenaline

Adrenaline is the cornerstone of acute pharmacotherapy for anaphylaxis and has been used for more than 100 years. A number of reviews have examined the benefits of adrenaline,11Ring J, Klimek L, Worm M. Adrenaline in the acute treatment of anaphylaxis. Dtsch Arztebl Int 2018;115(31-32):528–534. but these mainly reported studies at high risk of bias. Our review only included comparative studies or consecutive case series with at least 20 participants, but robust studies comparing adrenaline versus no adrenaline are unrealistic because it is not ethical to withhold adrenaline in an emergency.

We identified no eligible studies comparing adrenaline versus no adrenaline in terms of mortality or most other outcomes. Two case-control studies reported on biphasic reactions in children, but it is unclear whether adrenaline prevents biphasic anaphylactic reactions because the certainty of evidence is very low. One study found a non-statistically significant reduction of 9% and the other a significant reduction of 18% (odds ratio (OR) 0.08, 95% CI 0.014 to 0.43, see Table 3 and supplement S5a).22Manuyakorn W, Benjaponpitak S, Kamchaisatian W, Vilaiyuk S, Sasisakulporn C, Jotikasthira W. Pediatric anaphylaxis: triggers, clinical features, and treatment in a tertiary-care hospital. Asian Pac J Allergy Immunol 2015;33(4):281-8.33Mehr S, Liew WK, Tey D, Tang ML. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009;39(9):1390-1396.
Timing of adrenaline administration

The most effective timing of adrenaline administration is unknown because the certainty of evidence is very low (supplement S5b). One case control study in children found that administering adrenaline before hospital arrival reduced admissions by 26% compared to administration in the emergency department. There was no reduction in ICU admissions (very low certainty, see Table 3).11 Fleming JT, Clark S, Camargo CA Jr, Rudders SA. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. J Allergy Clin Immunol Pract 2015;3(1):57-62. One consecutive case series in children and adults found that administering adrenaline within 30 minutes of symptom onset reduced the incidence of biphasic reactions by 23% (OR 3.39, 95% CI 1.13 to 10.18, very low certainty).22 Liu X, Lee S, Lohse CM, Hardy CT, Campbell RL. Biphasic reactions in emergency department anaphylaxis patients: a prospective cohort study. J Allergy Clin Immunol Pract 2020;8(4):1230-1238. Studies did not report on mortality.

Adrenaline administration route

It is unclear whether different adrenaline administration routes affect outcomes because the certainty of evidence is very low.


One consecutive case series in children and adults found that intravenous bolus administration was associated with a 13% increase in the incidence of adrenaline overdose (OR 61.3, 95% CI 7.5 to infinity) and an 8% increase in the incidence of cardiovascular events compared with intramuscular administration (OR 7.5, 95% CI 1.6 to 35.3, very low certainty, supplement S5d and Table 3).55 Campbell RL, Bellolio MF, Knutson BD, Bellamkonda VR, Fedko MG, Nestler DM, Hess EP. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. J Allergy Clin Immunol Pract 2015;3(1):76-80.


Adrenaline autoinjectors are not readily available everywhere so alternatives have been tested. One trial with caregivers of children at risk of anaphylaxis tested an adrenaline autoinjector versus a pre-filled syringe. 61% more people using a pre-filled syringe administered adrenaline without errors compared to those using an autoinjector (OR 4.07, 95% CI 1.29 to 12.86, low certainty, supplement S5f).88 Suwan P, Praphaiphin P, Chatchatee P. Randomized comparison of caregivers’ ability to use epinephrine autoinjectors and prefilled syringes for anaphylaxis. Asian Pac J Allergy Immunol 2018;36(4):248-256.
an autoinjector reduced the time to administration by an average of 70 seconds compared to a syringe and resulted in fewer administration errors (statistically significant, confidence intervals not reported, very low certainty, supplement S5g).99 Asch D, Pfeifer KE, Arango J, Staib L, Cavallo J, Kirsch JD, Arici M, Pahade J. Benefit of Epinephrine Autoinjector for Treatment of Contrast Reactions: Comparison of Errors, Administration Times, and Provider Preferences. AJR Am J Roentgenol 2017;209(2):W363-W369.

**Autoinjector models**

We identified seven randomised trials, two non-randomised controlled trials and one consecutive case series examining the usability of autoinjectors (supplement S5h). These encompassed heterogeneous types of autoinjectors and testers, including those at risk of anaphylaxis, healthy volunteers and healthcare professionals.


It is unclear whether specific autoinjector models reduce the risk of unintentional injuries because the certainty of evidence is very low. Two trials in adults found that a modified EpiPen was associated with a 18% or 40% reduction in unintentional injuries compared to the ‘old’ EpiPen (very low certainty, statistically significant, confidence intervals not reported).88 Arga M, Bakirtas A, Topal E, Yilmaz O, Hacer Ertuy Karagol I, Demirsoy MS, Turkats I. Effect of epinephrine autoinjector design on unintentional injection injury. Allergy Asthma Proc 2012;33(6):488-492. 99 Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turkats I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. Pediatr Allergy Immunol 2011;22(7):729-733. Another trial in mothers of children at risk of anaphylaxis found that Anapen was associated with a 14% decrease in unintentional injuries compared to EpiPen (very low certainty, statistically significant, CI not reported).1010 Umasunthar T, Procktor A, Hodes M, Smith JG, Gore C, Cox HE, Marrs T, Hanna H, Phillips K, Pinto C, Turner PJ, Warner JO, Boyle RJ. Patients’ ability to treat anaphylaxis using adrenaline autoinjectors: a randomized controlled trial. Allergy 2015;70(7):855-863.

**Autoinjector needle length**

The most effective autoinjector needle length to administer adrenaline is unknown because the certainty of evidence is very low (supplement S5i). Studies measured the distance between skin and muscle rather than measuring the resulting serum plasma adrenaline concentration or speed of delivery.

Two consecutive case series in adults found that needle length of 14.3mm or 15.2mm may be too short to reach the muscle for one to two fifths of women (very low certainty, confidence intervals not reported).11 Song TT, Nelson MR, Chang JH, Engler R, Chowdhury BA. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy Asthma Immunol 2005;94(5):539-542. 22 Tsai G, Kim L, Nevis IF, Dominic A, Potts R, Chiu J, Kim HL. Auto-injector needle length may be
inadequate to deliver epinephrine intramuscularly in women with confirmed food allergy. Allergy, Asthma & Clinical Immunology 2014;10(1):39.

Another consecutive case series found that 29% of children under 15 kg may be at risk of having an autoinjector injected into bone with a needle length of 12.7 mm (very low certainty, CI not reported).33 Kim L, Nevis IF, Tsai G, Dominic A, Potts R, Chiu J, Kim HL. Children under 15 kg with food allergy may be at risk of having epinephrine auto-injectors administered into bone. Allergy, Asthma & Clinical Immunology 2014;10(1):40.

Adrenaline dose for people taking beta-blockers

We did not identify robust comparative studies exploring the most effective adrenaline dose. It is unclear whether taking beta-blockers influences the number of adrenaline doses needed because the certainty of evidence is very low (supplement S5j). A case control study in adults found that beta-blockers were associated with a 3% increase in the likelihood of requiring more than one adrenaline dose (OR 1.26, 95% CI 0.58 to 2.75, very low certainty). This was non-significant, even after adjusting for age, sex, allergen and other conditions.11 White JL, Greger KC, Lee S, Kahoud RJ, Li JT, Lohse CM, Campbell RL. Patients taking β-blockers do not require increased doses of epinephrine for anaphylaxis. J Allergy Clin Immunol Pract 2018;6(5):1553-1558.e1.

Adrenaline dose labelling

It is unclear whether the way adrenaline doses are labelled influences outcomes because the certainty of evidence is very low (supplement S5k). One trial with hospital professionals in a simulated environment found that professionals using ratio labels (1 mL of a 1:1000 solution) had a greater risk of dose errors compared with mass concentration labels (1 mg in 1 mL) (OR 13.4, 95% CI 2.2 to 81.7) and took longer to administer adrenaline (adjusted mean increase 91 seconds, 95% CI 61 to 122 seconds, very low certainty).11 Wheeler DW, Carter JJ, Murray LJ, Degnan BA, Dunling CP, Salvador R, Menon DK, Gupta AK. The effect of drug concentration expression on epinephrine dosing errors: a randomized trial. Ann Intern Med 2008;148(1):11-14.

Education to improve acute management

We identified nine studies with 574 participants about various types of educational interventions to support acute management for people at risk of anaphylaxis, their family, teachers and clinicians.

Face-to-face training for laypeople

Face-to-face training can take various forms and durations so it is difficult to generalise. Based on the evidence available, a series of face-to-face sessions probably improves knowledge about anaphylaxis in people at risk of anaphylaxis or their carers. One trial found that two three-hour training sessions improved knowledge amongst adults at risk of anaphylaxis and the caregivers of children at risk. This effect remained after three months (moderate certainty, supplement S6a).11 Brockow K, Schallmayer S, Beyer K, Biedermann T, Fischer J, Gebert N, Grosber M, Jakob T, Klimek L, Kugler C, Lange L, Pfaar O, Przybilla B, Rietschel E, Rueff F, Schmidt S, Szczepanski R, Worm M, Kupfer J, Gieler U, Ring J; working group on anaphylaxis training and education (AGATE). Effects of a structured educational intervention on knowledge and emergency management in patients at risk for anaphylaxis. Allergy 2015;70(2):227-235.

Face-to-face training may slightly improve laypeople’s competence in administering adrenaline autoinjectors, but it is difficult to estimate the exact size of the effect due to differences in measurement approaches (supplement S6a, low certainty). One trial compared face-to-face training with no training.22 Brockow K, Schallmayer S, Beyer K, Biedermann T, Fischer J, Gebert N, Grosber M, Jakob T, Klimek L, Kugler C, Lange L, Pfaar O, Przybilla B, Rietschel E, Rueff F, Schmidt S, Szczepanski R, Worm M, Kupfer J, Gieler U, Ring J; working group on anaphylaxis training and education (AGATE). Effects of a structured

Practising self-injection


Smartphone app for laypeople

It is unclear whether smartphone educational apps for people at risk of anaphylaxis affect outcomes because the certainty of evidence is very low. In one trial 38% more laypeople who used a smartphone app to guide them through using an autoinjector undertook all steps correctly compared to those who received standard autoinjector instruction (CI not reported, statistically significant, very low certainty, supplement S6c). Hernandez-Munoz LU, Woolley SI, Luyt D, Stiefel G, Kirk K, Makwana N, Melchior C, Dawson TC, Wong G, Collins T, Diwakar L. Evaluation of AllergiSense Smartphone Tools for Adrenaline Injection Training. IEEE J Biomed Health Inform 2017;21(1):272-282.

Educational aids for health professionals


Simulation training

It is unclear whether simulation training for health professionals has any effect on anaphylaxis management because the certainty of evidence is very low. We identified two trials, each using a different approach to simulation with medical students (supplement S6e). In one trial simulation-based training did not increase the proportion of medical students who correctly managed anaphylaxis11Tan GM, Ti LK, Tan K, Lee T. A comparison of screen-based simulation and conventional lectures for undergraduate teaching of crisis management. Anaesth Intensive Care 2008;36(4):565-569. and in the other trial there was a mean improvement of 22% compared to those taught without simulation (very low certainty, CI not reported). McCoy CE, Menchine M, Anderson C, Kollen R, Langdorf MI, Lotfpour S. Prospective randomized crossover study of simulation vs. didactics for teaching medical students the assessment and management of critically ill patients. J Emerg Med 2011;40(4):448-455. Other studies of simulation training are available but these did not meet the inclusion criteria.
Medications to prevent anaphylaxis (Table 4)

We identified seven studies with 13,383 participants about adrenaline, corticosteroids and antihistamine to prevent anaphylaxis as a result of reactions to snake bite anti-venom or other medications.

Prophylactic medications for anti-venom anaphylaxis

Adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis and not be associated with significant adverse effects, though it is difficult to generalise as there are a variety of anti-venoms and only a small amount of evidence was identified. Two trials in children and adults in Asia found that low dose prophylactic adrenaline 0.25ml (1:1000) injected subcutaneously reduced the absolute risk of severe reactions to anti-venom without significant adverse effects (see Table 4, low certainty, supplement S7a).


It is unclear whether prophylactic intravenous corticosteroids or histamine receptor blockers reduce anaphylaxis resulting from anti-venom for snake bite because the certainty of evidence is very low. Two trials in children and adults in Asia found that hydrocortisone alone or with chlorpheniramine did not reduce the incidence of moderate to severe reactions. (low certainty, supplement S7b).


Another trial of prophylactic antihistamine prior to intravenous histamine infusion found that intramuscular H1+H2 receptor-antagonist pre-treatment reduced reactions (numbers not reported, very low certainty).

Long-term management approaches

We identified five studies with 331 participants about long-term management approaches for anaphylaxis.

Carrying an autoinjector

It is unclear whether carrying an adrenaline autoinjector impacts on the perceived burden of care amongst people at risk of anaphylaxis because the certainty of evidence is very low (supplement S8a). One trial with people allergic to yellow jacket venom found that carrying an adrenaline autoinjector was associated with a 44% increase in the perceived burden of treatment compared to venom immunotherapy (statistically significant, CI not reported, very low certainty).11Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006;118(3):699-704.

We did not identify any eligible studies assessing the most effective number of autoinjectors to prescribe.

Financial incentives to carry autoinjectors

It is unclear whether providing people at risk of anaphylaxis with financial incentives increases how often they carry autoinjectors because the certainty of evidence is very low (supplement S8b). One trial in people aged 18 to 30 years found that financial incentives were associated with a 27% mean increase in the proportion of people carrying their autoinjector (statistically significant, CI not reported, very low certainty).11Cannuscio CC, Dupuis R, Graves A, Seymour JW, Konnaves S, Strupp E, Leri D, Frasso R, Grande D, Meisel ZF. A behavioral economics intervention to encourage epinephrine-carrying among food-allergic adults: a randomized controlled trial. Ann Allergy Asthma Immunol 2015;115(3):234-240.e1.

School nurse checks of carrying autoinjectors

It is unclear whether regular checking by school nurses encourages school students to carry their adrenaline autoinjectors because the certainty of evidence is very low (supplement S8c). In one non-randomised trial checks by school nurses were associated with an absolute decrease (not improvement) of 15% in the proportion of students carrying autoinjectors (not statistically significant, CI not reported, very low certainty).11Spina JL, McIntyre CL, Pulcini JA. An intervention to increase high school students’ compliance with carrying auto-injectable epinephrine: a MASRN study. J Sch Nurs 2012;28(3):230-237.

Legislation about school management plans

It is unclear whether legislation requiring schools to have anaphylaxis management plans affects outcomes because the certainty of evidence is very low (supplement S8d). A case control study found that legislation improved the consistency of school policies with best practice guidelines (very low certainty) and was associated with a 13% increase in the proportion of school staff scoring 4 out of 4 on observed autoinjector technique (statistically significant, CI not reported, very low certainty).11Cicutto L, Julien B, Li NY, Nguyen-Luu NU, Butler J, Clarke A, Elliott SJ, Harada L, Mcghan S, Stark D, Vander Leek TK, Waserman S. Comparing school environments with and without legislation for the prevention and management of anaphylaxis. Allergy 2012;67(1):131-137.

Helpline

It is unclear whether telephone helplines improve outcomes for those at risk of anaphylaxis because the certainty of evidence is very low (supplement S8e). One trial with children and their families found that a telephone helpline was associated with a clinically important improvement on a validated food allergy quality of life scale at 12 months. There was no statistically significant difference in use of health services for allergic events or anaphylaxis (very low certainty).11Kelleher MM, Dunganvin A, Sheikh A, Cullinane C, Fitzsimons J, Hourihane JO. Twenty four-hour helpline access to expert management advice for food-allergy-triggered anaphylaxis in infants, children and young people: a pragmatic, randomized controlled trial. Allergy 2013;68(12):1598-1604.

DISCUSSION
**Summary of evidence**

We found little robust evidence about the most effective strategies to diagnose, manage or prevent anaphylaxis. There were only three areas where the certainty of evidence was not ‘very low’. Firstly, newer / modified models of adrenaline autoinjectors may slightly increase the proportion of people correctly using the devices and reduce the time taken to administer adrenaline. Secondly, face-to-face training probably improves knowledge about anaphylaxis in people at risk of anaphylaxis and their family and may slightly improve laypeople’s competence in administering adrenaline autoinjectors. Face-to-face training can be of varying duration and content, but there is little evidence about the most effective type of training. Thirdly, adrenaline prophylaxis prior to snake bite anti-venom may reduce anaphylaxis. However, this evidence comes largely from Asia and may relate to types of anti-venoms that are not commonly used in other parts of the world.

For all other diagnostic and management interventions, the evidence was of too low certainty to draw conclusions. We searched for but found no eligible studies examining treatments that have been considered as adjuncts to adrenaline such as fluid replacement, oxygen, glucocorticosteroids (apart from for antivenom), methylxanthines and bronchodilators.

**Comparison with previous research**

This review differs from previous reviews because it excluded non-consecutive case series, registry and cohort studies and other observational methods at high risk of bias. The rationale was to focus on research designs of higher quality to best inform the EAACI guideline. This means that there are some differences in our findings compared to past reviews. In particular, we found little evidence about the effectiveness of adrenaline or any other acute management approaches, whereas reviews that have included observational study designs have found trends towards improved health outcomes and fewer hospital admissions when adrenaline is used as first-line treatment.11Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Greenhawt M, Khan DA, Lang DM, Lang ES, Lieberman JA, Portnoy J, Rank MA, Stukus DR, Wang J. Anaphylaxis - a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145(4):1082-1123.

Our review differs from the 2020 American Practice Parameter44Shaker MS, Wallace DV, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, Dinakar C, Ellis A, Greenhawt M, Khan DA, Lang DM, Lang ES, Lieberman JA, Portnoy J, Rank MA, Stukus DR, Wang J. Anaphylaxis - a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145(4):1082-1123. which focused primarily on prophylactic use of glucocorticoids and antihistamine premedication. Our narrower study design inclusion criteria were designed to collate the most robust research. This meant that we found few eligible studies about premedication compared to the Practice Parameter. Furthermore immunotherapy studies were not eligible for our review. Another difference is that we included only studies of clear and explicit anaphylaxis and excluded studies which explored ‘reactions’ whereas the American Practice Parameter included a broader range of reactions. On the other hand, the wider scope of our review means we have explored educational initiatives and non-pharmacological long-term management approaches, which were not covered in the Practice Parameter. Thus, our review complements that undertaken for the Practice Parameter as each had a different focus.

**Implications for research**

This review highlights the need for further research. With regards to diagnosis, robust studies are needed to test the feasibility of various criteria against gold standard expert review and the value of other approaches such as tryptase measurements to help confirm the diagnosis.
In terms of acute management, there is a paucity of robust evidence about adrenaline, but a lack of evidence is not the same as a lack of effect. It is unlikely that randomised comparative studies of adrenaline versus no adrenaline would be undertaken as it would be considered unethical to withhold a potentially life-saving treatment. However much remains left to learn about adrenaline, such as the ideal dosage and delivery mechanism required for adults and children, including those weighing less than 15kgs. Robust studies comparing the most effective number of autoinjectors to prescribe would also inform practice.

Long-term management and prevention may help people to identify triggers, minimise the risk of further reactions, learn skills and address psychological consequences. Various educational programmes, smartphone apps and leaflets have been developed, and anaphylaxis management plans and legislation have been implemented in some areas. Randomised trials or quasi-randomised studies would help to understand whether such approaches are worth expanding.

**Strengths and limitations**

This review was conducted by a task force of diverse clinicians, allied health professionals, public representatives, teachers and researchers. This was a strength because it meant that interventions and outcomes were considered on clinical and methodological grounds, with robust checks by multiple experts.

The review provides an up-to-date summary of research, with two thirds of the included studies being published in the past decade. However, it has several limitations. The available evidence is heterogeneous and mostly at moderate or high risk of bias. Meta-analysis was not appropriate because the interventions and outcomes varied greatly and there were too few studies with similar outcomes. A number of studies examined outcomes that may not be the most helpful when seeking to assess effectiveness, such as whether people carry autoinjectors or short-term changes in quality of life. Very few studies reported in detail on mortality, admissions, preferences or resource use. There was also a lack of evidence about emergency management outside hospital.

Not all available interventions are included in the review because data from registry studies, cohort studies and similar were not included. These designs have often been used to explore educational interventions or to track the value of preventive approaches.

**Conclusions**

There is low certainty of evidence upon which to suggest the most effective strategies for diagnosing, managing and preventing anaphylaxis. Adrenaline is generally regarded as a life-saving intervention, but due to ethical concerns, there is a lack of robust studies backing up expert opinion about the efficacy and optimal way to administer adrenaline. EAACI’s forthcoming anaphylaxis guidelines will combine the findings from this review with expert opinion and other evidence to suggest practical implications for health professionals, teachers and families.

**Word count:** 7546

**ix. Tables**

Table 1: Wording conventions used in this article to summarise effect size

<table>
<thead>
<tr>
<th>Certainty of evidence</th>
<th>Size of effect</th>
<th>Size of effect</th>
<th>Size of effect</th>
<th>Size of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>None / minor / not clinically meaningful (0% to 39% relative change)</td>
<td>Small (40% to 60% relative change)</td>
<td>Medium (61% to 80% relative change)</td>
<td>Large (81%+ relative change)</td>
<td></td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>Size of effect</td>
<td>Size of effect</td>
<td>Size of effect</td>
<td>Size of effect</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>High</td>
<td>X does not reduce / increase outcome</td>
<td>X reduces / increases outcome slightly</td>
<td>X reduces / increases outcome</td>
<td>X results in a large reduction / increase in outcome</td>
</tr>
<tr>
<td>Moderate</td>
<td>X probably does not reduce / increase outcome</td>
<td>X probably reduces / increases outcome slightly</td>
<td>X probably reduces / increases outcome</td>
<td>X probably results in a large reduction / increase in outcome</td>
</tr>
<tr>
<td>Low</td>
<td>X may not reduce / increase outcome</td>
<td>X may reduce / increase outcome slightly</td>
<td>X may reduce / increase outcome</td>
<td>X may result in a large reduction / increase in outcome</td>
</tr>
<tr>
<td>Very low</td>
<td>It is unclear whether [intervention] has any impact because the certainty of the evidence is very low</td>
<td>It is unclear whether [intervention] has any impact because the certainty of the evidence is very low</td>
<td>It is unclear whether [intervention] has any impact because the certainty of the evidence is very low</td>
<td>It is unclear whether [intervention] has any impact because the certainty of the evidence is very low</td>
</tr>
</tbody>
</table>

Editing note: the author citations will be replaced by endnotes in final editing. They are kept as is at present to keep the correct order when making changes following peer review.

Table 2: Summary of accuracy of approaches to diagnose anaphylaxis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Certainty of evidence</th>
<th>Overall conclusion</th>
<th>Studies (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second</td>
<td>Adults and children in emergency department</td>
<td>0.67 (0.46 to 0.75)</td>
<td>0.70 (0.59 to 0.80)</td>
<td>Very low</td>
<td>Unknown accuracy</td>
<td>1 case control study (n = 128) Erlewyn-Lajeunesse 2010</td>
</tr>
<tr>
<td>Symposium on the Definition and Management of Anaphylaxis NIAID / FAAN definition</td>
<td>0.97 (0.89 to 0.99)</td>
<td>0.82 (0.76 to 0.88)</td>
<td>Very low</td>
<td>Unknown accuracy</td>
<td>1 case control study (n = 214) Campbell 2012</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.95 (0.85 to 0.99)</td>
<td>0.71 (0.61 to 0.79)</td>
<td>Very low</td>
<td>Unknown accuracy</td>
<td>1 case series (n = 174) Loprinzi Brauer 2016</td>
</tr>
</tbody>
</table>
### Table 3: Impact of adrenaline in the acute management of anaphylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Population</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of effect</th>
<th>Overall conclusion</th>
<th>Studies (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic reactions associated with adrenaline</td>
<td>Children</td>
<td>Range 9% (p &gt; 0.05) to 18% (p &lt; 0.05) reduction</td>
<td>OR 0.08 from one study (0.014 to 0.43)</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>2 case control (n = 269) (Manuyakorn 2015, Mehr 2009)</td>
</tr>
<tr>
<td>Biphasic reactions associated with adrenaline</td>
<td>Adults and children</td>
<td>23% reduction (p &lt; 0.05)</td>
<td>OR 3.39 (1.13 to 10.18)</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 case control (n = 430) (Liu 2020)</td>
</tr>
<tr>
<td>Hospital admissions associated with adrenaline administered before vs at ED</td>
<td>Children</td>
<td>26% reduction if administered before ED (p &lt; 0.05)</td>
<td>OR 0.25 (0.10 to 0.62)</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 case control (n = 384) (Fleming 2015)</td>
</tr>
<tr>
<td>Admission to ICU associated with adrenaline administered before vs at ED</td>
<td>Children</td>
<td>0%</td>
<td>-</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>1 case control (n = 384) (Fleming 2015)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Population</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of effect</th>
<th>Overall conclusion</th>
<th>Studies (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose associated with intravenous bolus compared to intramuscular adrenaline</td>
<td>Adults and children</td>
<td>13% increase ($p&lt;0.05$)</td>
<td>OR 61.3 (7.5 to infinity)</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>1 case series (n = 301) (Campbell 2015)</td>
</tr>
<tr>
<td>Cardiovascular events associated with intravenous bolus compared to intramuscular adrenaline</td>
<td>Adults and children</td>
<td>8% increase ($p&lt;0.05$)</td>
<td>OR 7.5 (1.6 to 35.3)</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>1 case series (n = 301) (Campbell 2015)</td>
</tr>
</tbody>
</table>

Note: OR = odds ratio. CI = confidence interval. ED = emergency department.

Table 4: Impact of medications to prevent anaphylaxis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Population</th>
<th>Absolute effect</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of effect</th>
<th>Overall conclusion</th>
<th>Studies (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe reactions within 1 hour of prophylactic adrenaline for snake bite anti-venom</td>
<td>Children and adults</td>
<td>43% reduction ($p&lt;0.05$)</td>
<td>OR 0.57 (0.43 to 0.75)</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 trial (n = 1007) (de Silva 2011)</td>
</tr>
<tr>
<td>Severe reactions within 48 hours of prophylactic adrenaline for snake bite anti-venom</td>
<td>Children and adults</td>
<td>Range 8% to 38% reduction ($p&lt;0.05$)</td>
<td>RR in one study 0 (0 to 1.3) OR in another study 0.62 (0.51 to 0.74)</td>
<td>Low</td>
<td>May reduce</td>
<td>2 trials (n = 1112) (Premawardhena 1999, de Silva 2011)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Population</td>
<td>Absolute effect</td>
<td>Relative effect (95% CI)</td>
<td>Certainty of effect</td>
<td>Overall conclusion</td>
<td>Studies (participants)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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<td>-----------------------------------------</td>
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</tr>
<tr>
<td>Severe reactions within 1 hour of prophylactic hydrocortisone for snake bite anti-venom</td>
<td>Children and adults</td>
<td>0.5% increase (p&gt;0.05)</td>
<td>OR 0.86 (0.60 to 1.24)</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>1 trial (n = 1007) (de Silva 2011)</td>
</tr>
<tr>
<td>Moderate and severe reactions within 48 hours of prophylactic hydrocortisone for snake bite anti-venom</td>
<td>Children and adults</td>
<td>23% reduction (p&gt;0.05)</td>
<td>Not reported</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 trial (n = 52) (Gawarammana 2004)</td>
</tr>
<tr>
<td>Moderate and severe reactions within 48 hours of prophylactic hydrocortisone plus chlorpheniramine for snake bite anti-venom</td>
<td>Children and adults</td>
<td>23% reduction (p&gt;0.05)</td>
<td>Not reported</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 trial (n = 52) (Gawarammana 2004)</td>
</tr>
<tr>
<td>Severe reactions within 1 hour of prophylactic promethazine (antihistamine) for snake bite anti-venom</td>
<td>Children and adults</td>
<td>2.9% reduction (p&gt;0.05)</td>
<td>OR 0.81 (0.51 to 1.30)</td>
<td>Very low</td>
<td>Unknown impact</td>
<td>1 trial (n = 1007) (de Silva 2011)</td>
</tr>
<tr>
<td>Anaphylactic reactions within 24 hours of prophylactic promethazine (antihistamine) for snake bite anti-venom</td>
<td>Children and adults</td>
<td>1% reduction (p&gt;0.05)</td>
<td>Not reported</td>
<td>Very Low</td>
<td>Unknown impact</td>
<td>1 trial (n = 101) (Fan 1999)</td>
</tr>
</tbody>
</table>
Note: OR = odds ratio. CI = confidence interval. RR= relative risk.

x. Figure legends

Figure 1: PRISMA diagram showing study selection

xi. References

Editing note: duplicates have been retained in the reference list and will be removed in the final edit to keep the correct order in changes made following peer review.

Hosted file

Figure 1.doc available at https://authorea.com/users/333888/articles/459985-diagnosing-managing-and-preventing-anaphylaxis-systematic-review