Diagnosing, managing and preventing anaphylaxis: systematic review

Debra de Silva[1], Chris Singh[2], Antonella Muraro[3], Margitta Worm[4], Cherry Alviani[5], Victoria Cardona[6,7], Audrey DunnGalvin[8], Lene Garvey[9], CARMEN RIGGIONI[10], Elisabeth Angier[5], Stefania Arasi[11], Abdelouahab Bellou[12], Kirsten Beyer[13], Diola Bijlhout[14], M Beatrice Bilo[15], Knut Brockow[16], Montserrat Fernandez-Rivas[17], Susanne Halken[18], Britt Jensen[19], Ekaterina Khaleva[5], Louise Michaelis[20], Hanneke Oude Elberink[21], Lynne Regent[22], Berber Vlieg - Boerstra[23], Angel Sanchez San[24], and Graham Roberts[5]

[1]The Evidence Centre
[2]The Evidence Centre
[3]Padua General University Hospital
[4]Charité - Universitätsmedizin Berlin
[5]University of Southampton
[6]Vall d'Hebron Institut de Recerca
[7]Hospital Universitari Vall d'Hebron
[8]University College Cork (UCC)
[9]Copenhagen University Hospital Gentofte
[10]Hospital Sant Joan de Déu
[11]Universita degli Studi di Messina
[12]European Society for Emergency Medicine
[13]Charité Universitätsmedizin Berlin
[14]Association for Teacher Education in Europe (ATEE)
[15]University Hospital of Ancona Umberto I G M Lancisi G Salesi
[16]Technical University of Munich
[17]Hospital Clinico San Carlos
[18]University of Southern Denmark, Odense
[19]Odense University Hospital, University of Southern Denmark
[20]Great North Children's Hospital
[21]University Medical Center Groningen
[22]The Anaphylaxis Campaign
[23]Onze Lieve Vrouwe Gasthuis
[24]Asociación Española de Personas con Alergia a Alimentos y Látex

June 17, 2020

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.

i. Title

Diagnosing, managing and preventing anaphylaxis: systematic review

ii. Short running title

Anaphylaxis: systematic review

iii. Full names of authors

Debra de Silva,* Chris Singh,* Antonella Muraro, Margitta Worm, Cherry Alviani, Victoria Cardona, Audrey DunnGalvin, Lene Heise Garvey, Carmen Riggioni, Elizabeth Angier, Stefania Arasi, Abdelouahab Bellou, Kirsten Beyer, Diola Bijlhout, M Beatrice Bilo, Knut Brockow, Montserrat Fernandez-Rivas, Susanne Halken, Britt Jensen, Ekaterina Khaleva, Louise J Michaelis, Hanneke Oude Elberink, Lynne Regent, Angel Sanchez, Berber Vlieg-Boerstra, Graham Roberts on behalf of European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group.

* joint first author

iv. Author institutional affiliations

Debra de Silva: The Evidence Centre Ltd, London, UK.

Chris Singh: The Evidence Centre Ltd, London, UK.

Antonella Muraro: Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University Hospital, Padua, Italy.

Margitta Worm: Division of Allergy and Immunology, Department of Dermatology, Venerology and Allergy, Charité Universitätsmedizin Berlin, Germany.

Cherry Alviani: Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, UK.

Victoria Cardona: Allergy Section, Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain & ARADyAL Research Network.

Audrey DunnGalvin: University College Cork, Ireland. Sechnov University Moscow, Ireland.

Lene Heise Garvey: Allergy Clinic, Department of Dermatology and Allergy, Gentofte Hospital, Denmark and Department of Clinical Medicine, University of Copenhagen, Denmark.

Carmen Riggioni: Paediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Deu and Sant Joan de Deu Research Foundation, Barcelona, Spain.

Elizabeth Angier: Primary Care and Population Sciences, University of Southampton, Southampton, UK.

Stefania Arasi: Pediatric Allergology Unit, Bambino Gesù Hospital (IRCCS), Rome, Italy.

Abdelouahab Bellou: European Society for Emergency Medicine, Brussels, Belgium.

Kirsten Beyer: Department of Pediatric Pulmonology, Immunology and Intensive Care Medicine, Charite Universitatsmedizin Berlin, Berlin, Germany.

Diola Bijlhout: Association for Teacher Education in Europe (ATEE), Brussels, Belgium.

M Beatrice Bilo: Allergy Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Department of Internal Medicine, University Hospital of Ancona - Italy.

Knut Brockow: Department of Dermatology and Allergy Biederstein, Technical University of Munich, Munich, Germany.

Montserrat Fernandez-Rivas: Allergy Department, Hospital Clinico San Carlos, Facultad Medicina Universidad Complutense, IdISSC, ARADyAL, Madrid, Spain.

Susanne Halken: Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark.

Britt Jensen: Department of Dermatology and Allergy Centre, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital, Odense, Denmark.

Ekaterina Khaleva: Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, Southampton, UK.

Louise J Michaelis: Paediatric Allergy Research, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK.

Hanneke Oude Elberink: Department of Allergology, University Medical Center Groningen, University of Groningen, and Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands.

Lynne Regent: Anaphylaxis Campaign, Farnborough, UK.

Angel Sanchez: AEPNAA Spanish Association for People with Food and Latex Allergy, Spain.

Berber Vlieg-Boerstra: OLVG, Department of Paediatrics, Amsterdam; Hanze University of Applied Sciences, dept Nutrition & Dietetics, Groningen. The Netherlands.

Graham Roberts: NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton; Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, Southampton; and The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK.

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.

The following authors declared no potential interests: AB, CA, CR, CS, DB, DdS, EK, SA.

The following authors declared interests as follows:

ADG: Research: Aimmune Therapeutics, National Children's Research Centre Ireland, DBV Technologoes, 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: Norvatis;

BV-B: Consultant: Marfo Food Goups. 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;

HOE: Speaker: ALK-Abelló, Meda. Consultant: ALK-Abello; Advisory Board of PIMS Epinephrine. Research: Novartis, MEDA Pharma, ALK-Abello.

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;

MFR: Research: ISCIII (Ministry of Science, Spanish Government), Aimmune. Consultant: Aimmune, DBV, Novartis, Schreiber Foods. Speaker: Aimmune, Allergy Therapeutics, Diater, GSK, HAL Allergy, Thermofisher Scientific;

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;

VC: Consultant: ALK, Allergopharma, Allergy Therapeutics, Diater, LETI, Thermofisher. Other: SLAAI chair anaphylaxis committee, WAO chair anaphylaxis committee.

v. Acknowledgements

The European Academy of Allergy and Clinical Immunology (EAACI) funded the systematic review to support the development of an anaphylaxis guideline. The funder had no role in the development of the protocol, conduct or write up of the review or decision to publish.

The EAACI anaphylaxis task force was chaired by Antonella Muraro, Graham Roberts and Margitta Worm. The systematic review was managed by Debra de Silva.

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

Anaphylaxis is a severe and potentially life-threatening allergic reaction that all professionals working in healthcare and education should be able to help recognise, manage and prevent. In Europe, about one in 300 people will experience anaphylaxis at some time in their lives.11Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilò MB, Cardona V, Dubois AE, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ, Sheikh A.. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013;68(11):1353-1361. The number of emergency department visits and hospitalisations associated with anaphylaxis is increasing.22Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, Pumphrey R, Boyle RJ. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015;135(4):956-963.e1.

Rapid and effective care has an important role in keeping the rate of deaths low,33Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P, Warner JO, Boyle RJ. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clin Exp Allergy 2013;43(12):1333-1341. but delayed or ineffective diagnosis and treatment is associated with unnecessary social, psychological and health burden as well as extra costs.44Lindor RA, McMahon EM, Wood JP, Sadosty AT, Boie ET, Campbell RL. Anaphylaxis-related malpractice lawsuits. West J Emerg Med 2018;19(4):693-700. It is essential that patients, families, health professionals and teachers remain up-to-date with ways to diagnose, manage and prevent anaphylaxis, particularly as potential triggers such as food allergy and medication use rise.55Anagnostou K. Anaphylaxis in children: epidemiology, risk factors and management. Curr Pediatr Rev 2018;14(3):180-186.

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released guidelines for managing anaphylaxis.66Muraro 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.

A number of other systematic reviews have examined anaphylaxis.77Liyanage CK, Galappatthy P, Seneviratne SL. Corticosteroids in management of anaphylaxis; a systematic review of evidence. Eur Ann Allergy Clin Immunol 2017;49(5):196-207.'88Nurmatov UB, Rhatigan E, Simons FE, Sheikh A.H2-antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. Ann Allergy Asthma Immunol 2014;112(2):126-131.'99Dhami S, Sheikh A, Muraro A, Roberts G, Halken S, Fernandez Rivas M, Worm M, Sheikh A. Quality indicators for the acute and long-term management of anaphylaxis: a systematic review. Clin Transl Allergy 2017;7:15.'1010Tomasiak-Łozowska MM, Klimek M, Lis A, Moniuszko M, Bodzenta-Łukaszyk A. Markers of anaphylaxis - a systematic review. Adv Med Sci 2018;63(2):265-277.'1111Chipps BE. Update in pediatric anaphylaxis: a systematic review. Clin Pediatr 2013;52(5):451-461.'1212Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2010;65(10):1205-1211.'1313Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2007;62(8):830-837.'1414Nurmatov U, Worth A, Sheikh A. Anaphylaxis management plans for the acute and long-term management of anaphylaxis: a systematic review. J Allergy Clin Immunol 2008;122(2):353-61, 361.e1-3. However, none provide the broad, up to date review that is required to inform and update the EAACI guideline. A recent systematic review for an American Practice Parameter contains useful information about the risk factors for biphasic anaphylaxis and the prophylactic use of glucocorticoids and antihistamine premedication.1515Shaker 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. However EAACI's guideline will cover a much wider range of interventions to diagnose, treat and manage anaphylaxis, and as such available reviews alone are not sufficient to inform the new 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.

The review protocol is registered with the International Prospective Register of Systematic Reviews so the methods are only briefly described here (PROSPERO registration: CRD42019159739).11de Silva D, Roberts G, Worm M, Muraro A. EAACI anaphylaxis guidelines: systematic review protocol. Clin Trans Allergy 2020;10(14). https://ctajournal.biomedcentral.com/articles/10.1186/s13601-020-00320-3.

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.
- *Intervention* : any intervention to immediately diagnose at emergency presentation, manage or prevent anaphylaxis in the community or hospital. Studies related to immunotherapy were excluded as these are covered in other EAACI guidelines.11Muraro A, Roberts G, Halken S, Agache I, Angier E, Fernandez-Rivas M, Gerth van Wijk R, Jutel M, Lau S, Pajno G, Pfaar O, Ryan D, Sturm GJ, van Ree R, Varga EM, Bachert C, Calderon M, Canonica GW, Durham SR, Malling HJ, Wahn U, Sheikh A. EAACI guidelines on allergen immunotherapy: Executive statement. Allergy 2018;73(4):739-743.
- *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.

Previous reviews have identified limited trials about interventions to prevent and manage anaphylaxis22Armstrong N, Wolff R, van Mastrigt G, Martinez N, Hernandez AV, Misso K, Kleijnen J. A systematic review and cost-effectiveness analysis of specialist services and adrenaline auto- injectors in anaphylaxis. Health Technol Assess 2013;17(17):1-117, v-vi.,33El Turki A, Smith H, Llewellyn C, Jones CJ. A systematic review of patients', parents' and healthcare professionals' adrenaline auto-injector administration techniques. Emerg Med J 2017;34(6):403-416.,44Tejedor-Alonso MA, Farias-Aquino E, Pérez-Fernández E, Grifol-Clar E, Moro-Moro M, Rosado-Ingelmo A. Relationship between anaphylaxis and use of beta-blockers and angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis of observational studies. J Allergy Clin Immunol Pract 2019;7(3):879-897.e5. so we included other comparative designs. Consecutive case series were eligible when studying diagnostic tests and adrenaline because expert advice suggested that it is difficult and potentially unethical to implement more robust designs in these areas. Registry studies, cohort studies and uncontrolled before-and-after studies were excluded in order to focus on the most robust comparative evidence.

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, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC. The Cochrane

Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed) 2011;343:d5928. was used for trials, ROBINS-I22Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016;355:i4919. for observational studies and QUADAS 233Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(8):529-536. for diagnostic studies. Arbitration was available from two senior clinicians (GR, MW) but there was 100% agreement in the risk of bias assessments.

Synthesis of results

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.11Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-394.

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).22Santesso 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 (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).11Fleming 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).22Liu 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.

We identified two randomised trials and two non-randomised trials about adrenaline inhalation as the primary route of administration; three in adults and one in children. Most studies found that inhalation did not deliver a therapeutically appropriate dose of adrenaline or reduce adverse effects compared to intramuscular or subcutaneous injection or placebo (very low certainty, supplement S5c).11Breuer C, Wachall B, Gerbeth K, Abdel-Tawab M, Fuhr U. Pharmacokinetics and pharmacodynamics of moist inhalation epinephrine using a mobile inhaler. Eur J Clin Pharmacol 2013;69(6):1303-1310.'22Foucard T, Cederblad F, Dannaeus A, Swenne I, Niklasson F. Anaphylaxis in severe food allergy. Adrenaline injection is safer than inhalation. Lakartidningen 1997;94(16):1478, 1483.'33Heilborn H, Hjemdahl P, Daleskog M, Adamsson U. Comparison of subcutaneous injection and high-dose inhalation of epinephrine–implications for self-treatment to prevent anaphylaxis. J Allergy Clin Immunol 1986;78(6):1174-1179.'44Simons FE, Gu X, Johnston LM, Simons KJ. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis? Pediatrics 2000;106(5):1040-1044.

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).55Campbell 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.

Two trials compared intramuscular versus subcutaneous injection of adrenaline in children and young adults. Intramuscular adrenaline was associated with an absolute increase of mean plasma adrenaline concentration (very low certainty, supplement S5e).66Simons FE, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. J Allergy Clin Immunol 2001;108(5):871-873.'77Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol 1998;101(1 Pt 1):33-37. However these studies may be confounded by using different injection sites (thigh versus arm), in addition to different depth of injection.

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 prefilled 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).88Suwan 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.

In a non-randomised trial, health professionals tested an autoinjector or a syringe (not pre-filled). Using

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).99Asch 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.

Some studies explored modifying autoinjectors, such as changing the colour of the safety cap, having an arrow pointing to the injection tip or using voice prompts to guide people through their use. Such modifications may slightly increase the proportion of people correctly using the devices (low certainty)11Arga M, Bakirtas A, Topal E, Yilmaz O, Hacer Ertoy Karagol I, Demirsoy MS, Turktas I. Effect of epinephrine autoinjector design on unintentional injection injury. Allergy Asthma Proc 2012;33(6):488-492.›22Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turktas I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. Pediatr Allergy Immunol 2011;22(7):729-733.›33Umasunthar 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.›44Robinson MN, Dharmage SC, Tang ML. Comparison of adrenaline auto-injector devices: ease of use and ability to recall use. Pediatr Allergy Immunol 2014;25(5):462-467.›55Guerlain S, Hugine A, Wang L. A comparison of 4 epinephrine autoinjector delivery systems: usability and patient preference. Ann Allergy Asthma Immunol 2010;104(2):172-177. and decrease the time taken to administer adrenaline (low certainty).66Arga M, Bakirtas A, Topal E, Yilmaz O, Hacer Ertoy Karagol I, Demirsoy MS, Turktas I. Effect of epinephrine autoinjector design on unintentional injection injury. Allergy Asthma Proc 2012;33(6):488-492.›77Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turktas I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. Pediatr Allergy Immunol 2011;22(7):729-733.

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).88Arga M, Bakirtas A, Topal E, Yilmaz O, Hacer Ertoy Karagol I, Demirsoy MS, Turktas I. Effect of epinephrine autoinjector design on unintentional injection injury. Allergy Asthma Proc 2012;33(6):488-492.›99Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turktas 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).1010Umasunthar 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).11Song TT, Nelson MR, Chang JH, Engler RJ, 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.›22Tsai 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 15kg may be at risk of having an autoinjector injected into bone with a needle length of 12.7mm (very low certainty, CI not reported).33Kim 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 11White 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).11Wheeler 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 1;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).11Brockow 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, Schnadt 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 training22Brockow 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, Schnadt 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. and another compared it to video training.33Fernandez-Mendez F, Saez-Gallego NM Barcala-Furelos R, Abelairas-Gomez C(2)(3)(5), Padron-Cabo A, Perez-Ferreiros A, Garcia-Magan C, Moure-Gonzalez J, Contreras-Jordan O, Rodriguez-Nuñez A. Learning and treatment of anaphylaxis by laypeople: a simulation study using pupilar technology. Biomed Res Int2017;2017:9837508.

Practising self-injection

It is unclear whether practising injecting adrenaline using an empty syringe at clinic appointments has any effect on outcomes for people at risk of anaphylaxis because the certainty of evidence is very low. One trial found that adolescents who practised felt more comfortable self-injecting than those who did not practise (very low certainty, supplement S6b).11Shemesh E, D'Urso C, Knight C, Rubes M, Picerno KM, Posillico AM, Atal Z, Annunziato RA, Sicherer SH. Food-Allergic Adolescents at Risk for Anaphylaxis: A Randomized Controlled Study of Supervised Injection to Improve Comfort with Epinephrine Self-Injection. J Allergy Clin Immunol Pract 2017;5(2):391-397.e4.

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).11Hernandez-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

It is unclear whether prompts or visual aids help health professionals manage anaphylaxis more effectively because the certainty of evidence is very low (supplement S6d). One trial found that hospital residents who received training on the use of a wallet sized prompt sheet did not improve their knowledge more than controls in nine out of ten topic areas (very low certainty).11Hernandez-Trujillo V, Simons FE. Prospective evaluation of an anaphylaxis education mini-handout: the AAAAI Anaphylaxis Wallet Card. J Allergy Clin Immunol Pract 2013;1(2):181-185. Another trial found that a visual prompt about the Brighton Collaboration case definition did not improve the accuracy of anaphylaxis diagnosis compared to a journal article containing the full definition (very low certainty).22Joshi D, Alsentzer E, Edwards K, Norton A, Williams SE. An algorithm developed using the Brighton Collaboration case definitions is more efficient for determining diagnostic certainty. Vaccine 2014;32(28):3469-3472. A non-randomised trial found that a flowchart did not reduce administration errors in a simulation about reactions to contrast media.33Gardner JB, Rashid S, Staib L, Asch D, Cavallo J, Arango J, Kirsch J, Pahade J. Benefit of a Visual Aid in the Management of Moderate-Severity Contrast Media Reactions. AJR Am J Roentgenol 2018;211(4):717-723.

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). 22McCoy CE, Menchine M, Anderson C, Kollen R, Langdorf MI, Lotfipour 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).11Premawardhena AP, de Silva CE, Fonseka MM, Gunatilake SB, de Silva HJ. Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. BMJ 1999;318(7190):1041-1043.,22de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwatthage W, Aronson JK, Armitage JM, Lalloo DG, de Silva HJ. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011;8(5):e1000435.

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).33de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwatthage W, Aronson JK, Armitage JM, Lalloo DG, de Silva HJ. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011;8(5):e1000435.,44Gawarammana IB, Kularatne SA, Dissanayake WP, Kumarasiri RP, Senanayake N, Ariyasena H. Parallel infusion of hydrocortisone +/- chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. Med J Aust 2004;180(1):20-23.

Two trials in children and adults found that the antihistamine promethazine did not reduce the incidence of anaphylaxis within 24 to 48 hours of antivenom (very low certainty, supplement S7c)55de Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, Kalupahana R, Ratnatilaka GA, Uluwatthage W, Aronson JK, Armitage JM, Lalloo DG, de Silva HJ. Low-dose adrenaline, promethazine, and hydrocortisone in the prevention of acute adverse reactions to antivenom following snakebite: a randomised, double-blind, placebo-controlled trial. PLoS Med 2011;8(5):e1000435.,66Fan HW, Marcopito LF, Cardoso JL, França FO, Malaque CM, Ferrari RA, Theakston RD, Warrell DA. Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. BMJ 1999;318(7196):1451-1452.

Antihistamine for plasma-substitute and experimental histamine-induced reactions

It is unclear whether prophylactic antihistamine reduces plasma substitute and histamine-induced anaphylaxis because the certainty of evidence is very low (supplement S7d). One trial about prophylactic antihistamine prior to plasma substitute haemaccel found a 24% reduction in the incidence of anaphylaxis (statistically significant, CI not reported, very low certainty).11Lorenz W, Doenicke A, Dittmann I, Hug P, Schwarz B. Anaphylactoid reactions following administration of plasma substitutes in man. Prevention of this side-effect of haemaccel by premedication with H1- and H2-receptor antagonists. Anaesthesist 1977;26(12):644-648. 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).22Tryba M, Zevounou F, Zenz M. Prevention of anaphylactoid reactions using intramuscular promethazine and cimetidine. Studies of a histamine infusion model. Anaesthesist 1984;33(5):218-223.

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, Kounaves 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 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 MASNRN 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, Dunngalvin 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.,22Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015;8:32.,33Chipps BE. Update in pediatric anaphylaxis: a systematic review. Clin Pediatr 2013;52(5):451-461.

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

Certainty of evidence	Size of effect	Size of effect	Size of effect	Size of effect
	None / minor / not clinically meaningful (0% to 39% relative change)	Small (40% to 60% relative change)	Medium (61% to 80% relative change)	Large (81%+ relative change)

Certainty of evidence	Size of effect	Size of effect	Size of effect	Size of effect
High	X does not reduce / increase outcome	X reduces / increases outcome slightly	X reduces / increases outcome	X results in a large reduction / increase in outcome
Moderate	X probably does not reduce / increase outcome	X probably reduces / increases outcome slightly	X probably reduces / increases outcome	X probably results in a large reduction / increase in outcome
Low	X may not reduce / increase outcome	X may reduce / increase outcome slightly	X may reduce / increase outcome	X may result in a large reduction / increase in outcome
Very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low

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

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

Intervention	Population	Sensitivity (95% CI)	Specificity (95% CI)	Certainty of evidence	Overall conclusion	Studies (participants)
Brighton Collaboration case definition	Adults and children in emergency department	0.68 (0.54 to 0.80)	0.91 (0.80 to 0.96)	Very low	Unknown accuracy	1 case control (n = 128) Erlewyn-Lajeunesse 2010

Note: CI = confidence interval.

Table 3: Impact of adrenaline in the acute management of anaphylaxis

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Biphasic reactions associated with adrenaline	Children	Range 9% (p>0.05) to 18% (p<0.05) reduction	OR 0.08 from one study (0.014 to 0.43)	Very low	Unknown impact	2 case control (n = 269) (Manuyakorn 2015, Mehr 2009)
Biphasic reactions associated with adrenaline administered within 30 minutes of onset	Adults and children	23% reduction (p<0.05)	OR 3.39 (1.13 to 10.18)	Very Low	Unknown impact	1 case control (n = 430) (Liu 2020)
Hospital admissions associated with adrenaline administered before vs at ED	Children	26% reduction if administered before ED (p<0.05)	OR 0.25 (0.10 to 0.62)	Very Low	Unknown impact	1 case control (n = 384) (Fleming 2015)
Admission to ICU associated with adrenaline administered before vs at ED	Children	0%	-	Very low	Unknown impact	1 case control (n = 384) (Fleming 2015)

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Overdose associated with intravenous bolus compared to intramuscular adrenaline	Adults and children	13% increase (p<0.05)	OR 61.3 (7.5 to infinity)	Very low	Unknown impact	1 case series (n = 301) (Campbell 2015)
Cardiovascular events associated with intravenous bolus compared to intramuscular adrenaline	Adults and children	8% increase (p<0.05)	OR 7.5 (1.6 to 35.3)	Very low	Unknown impact	1 case series (n = 301) (Campbell 2015)

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

Table 4: Impact of medications to prevent anaphylaxis

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Severe reactions within 1 hour of prophylactic adrenaline for snake bite anti-venom	Children and adults	43% reduction (p<0.05)	OR 0.57 (0.43 to 0.75)	Very Low	Unknown impact	1 trial (n = 1007) (de Silva 2011)
Severe reactions within 48 hours of prophylactic adrenaline for snake bite anti-venom	Children and adults	Range 8% to 38% reduction (p<0.05)	RR in one study 0 (0 to 1.3) OR in another study 0.62 (0.51 to 0.74)	Low	May reduce	2 trials (n = 1112) (Premawardhena 1999, de Silva 2011)

Outcomes	Population	Absolute effect	Relative effect (95% CI)	Certainty of effect	Overall conclusion	Studies (participants)
Severe reactions within 1 hour of prophylactic hydrocortisone for snake bite anti-venom	Children and adults	0.5% increase (p>0.05)	OR 0.86 (0.60 to 1.24)	Very low	Unknown impact	1 trial (n = 1007) (de Silva 2011)
Moderate and severe reactions within 48 hours of prophylactic hydrocortisone for snake bite anti-venom	Children and adults	23% reduction (p>0.05)	Not reported	Very Low	Unknown impact	1 trial (n = 52) (Gawarammana 2004)
Moderate and severe reactions within 48 hours of prophylactic hydrocortisone plus chlorpheniramine for snake bite anti-venom	Children and adults	23% reduction (p>0.05)	Not reported	Very low	Unknown impact	1 trial (n = 52) (Gawarammana 2004)
Severe reactions within 1 hour of prophylactic promethazine (antihistamine) for snake bite anti-venom	Children and adults	2.9% reduction (p>0.05)	OR 0.81 (0.51 to 1.30)	Very low	Unknown impact	1 trial (n = 1007) (de Silva 2011)
Anaphylactic reactions within 24 hours of prophylactic promethazine (antihistamine) for snake bite anti-venom	Children and adults	1% reduction (p>0.05)	Not reported	Very low	Unknown impact	1 trial (n = 101) (Fan 1999)

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