Emergency action plans for people at risk of anaphylaxis (major allergy) (Protocol)

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[Intervention Protocol]

Emergency action plans for people at risk of anaphylaxis (major allergy)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of emergency action plans for people at risk of anaphylaxis in improving health, service use and other outcomes.

BACKGROUND

Description of the condition

Anaphylaxis is a severe, potentially life-threatening allergic reaction, in which the immune system responds to otherwise harmless substances from the environment. The onset of anaphylaxis is typically very rapid, usually within minutes and can involve multiple body systems simultaneously.

Anaphylaxis is a severe, potentially life-threatening generalised or systemic hypersensitivity allergic reaction. In most cases, these reactions arise as a result of the immune system responding to otherwise harmless substances in the environment. Anaphylaxis can affect multiple systems in the body simultaneously. Symptom onset can be rapid, usually within minutes, although occasionally symptoms may develop over a few hours after allergen exposure. It is characterised by rapidly developing, airway and/or breathing and/or circulatory problems, which are, in the majority of cases, accompanied by skin and mucosal changes (Resuscitation Council 2008; Simons 2011). Although a century has elapsed since anaphylaxis was first described, there is still no universally-accepted definition (Sampson 2006). Nor is there a diagnostic test in routine clinical use. The diagnosis of anaphylaxis therefore rests on the identification of an array of symptoms and signs in the context of a history suggestive of exposure to an allergic trigger (Lieberman 2005).

Anaphylaxis can affect any number of organs either individually or in combination. Skin signs are the most common, with up to 90% of affected people experiencing symptoms ranging from a localised rash, itch, or wheals, to swelling of the lips. The airways are the next most affected; up to 70% of people with anaphylaxis experience breathlessness and cough. Up to 40% will have gut or bowel involvement manifesting with diarrhoea, abdominal pain, nausea and/or vomiting. The cardiovascular system is only affected in 10 to 30% of sufferers, with symptoms such as dizziness, collapse or loss of consciousness (Lieberman 2009).

In children, food such as cow's milk, eggs, peanuts and tree nuts are often the cause of anaphylaxis. In adults, foods can also be implicated, but medications, either prescribed or over-the-counter, are more often the culprit agents (Alves 2001). Other commonly-reported triggers of anaphylaxis include latex rubber, insect venom, exercise and vaccination. It is important to note that in up to a third of all cases of anaphylaxis, no obvious triggers can be identified.

In recent years there has been a rapid upward trend in hospital admissions for anaphylaxis in the UK (Sheikh 2000; Gupta 2003; Gupta 2004; Gupta 2007). Anaphylaxis admission rates increased by 700% from 5 per million people in 1990/1 to 36 per million people in 2003/4 (Gupta 2007). As few people with anaphylaxis are admitted to hospital, the actual numbers of people experiencing anaphylaxis are likely to be considerably higher than hospital admission rates suggest (Stewart 1996; Sheikh 2008; Anandan 2009). Studies show that the lifetime risk of anaphylaxis may be as high as 2% in the general population (Neugut 2001; Lieberman 2006; Lieberman 2009). People who have had at least one previous anaphylaxis attack are at risk of it occurring again. That recurrence risk has been estimated as 1 in 12 per year (Mullins 2003). Population-based studies show that the overall prognosis of anaphylaxis is good, with a low case fatality rate of around 1% (Yocum 1999; Brown 2001; Bohlke 2004).

Current guidelines for the management of anaphylaxis include prompt administration of adrenaline (also known as epinephrine) at the onset of symptoms (Resuscitation Council 2008; Simons 2011). In the community setting, adrenaline is usually administered in the form of an auto-injector. Studies have shown that there are serious gaps of knowledge in the use of an auto-injector by all parties - healthcare professionals, patients, parents and care givers (Grouhi 1999; Sicherer 2000; Simons 2000; Hayman 2003; Levy 2004; Gallagher 2011). Given that anaphylaxis has a high risk of recurrence, progresses rapidly and may result in death, guidelines and clinical pathways emphasise the importance of people at risk of anaphylaxis learning strategies to recognise anaphylactic reactions and manage them effectively (see Appendix 1 for examples of educational resources) (Pumphrey 2000; Holgate 2003; Kemp 2008; Resuscitation Council 2008; Clark 2011). These management strategies should include methods for identifying trigger agents, ways to avoid these triggers and an emergency action plan should accidental exposure occur to the trigger, or a reaction spontaneously occur. This review focuses on assessing evidence for the effectiveness of these emergency action plans.

Description of the intervention

The concept of patient self-management in chronic disease was first made popular in the 1970s by Kate Lorig, who pioneered the use of self-management plans in patients with arthritis. Lorig's work has led to the development of self-management plans (e.g. Expert Patients Programme in the UK) for chronic diseases such as rheumatoid arthritis, asthma and diabetes (Clark 1991; Superio-Cabuslay 1996; Lorig 2005). For example, studies on self-management education for asthma have shown that such knowledge can significantly improve quality of life and other health outcomes (Gibson 2002; Boyd 2009). These plans can focus on different facets of living with a long-term condition, including emergency self-management of acute reactions.

This review assesses the effects of emergency action plans that aim to support individuals to self-manage an anaphylactic reaction. We are interested in the following three components of such plans:

- a plan for managing further reactions should accidental exposure occur; this includes recognition of the symptoms and sign of an anaphylaxis event and the severity of the reaction,
- information to help patients be aware of the indicators for emergency treatment strategies, and the timing and method of delivery of adrenaline, and
- advice to seek further help from healthcare professionals, either in the community or hospital setting.

The detailed content of the action plan is usually tailored to the individual and it may contain all or only some of the components detailed above (Worth 2010). For the purpose of this review, we will only include studies in which the emergency action plans have all three components as detailed above.

As most anaphylaxis events happen in the community, in the absence of healthcare professionals, education on these action plans are usually aimed at people who have experienced anaphylaxis in the past or are deemed to be at high risk of experiencing anaphylaxis in the future (but who may not necessarily already had an anaphylactic reaction). The type of patient or patient groups that could benefit from an action plan includes patients themselves, their primary carers and other caregivers, for example school teachers and school nurses (Rankin 2006; Shehata 2006; Kemp 2008).

How the intervention might work

People who have had previous anaphylaxis events are at risk of a relapse, with most events usually occurring in the community setting. Emergency action plans that are developed in partnership between patients and their healthcare providers aim to empower patients with the knowledge and skills to manage their day-to-day risk of anaphylaxis. By providing insight into anaphylaxis itself, the plans may instil confidence, develop skills and promote self-efficacy in managing an anaphylaxis event (Lorig 2003; Akeson 2007; Gallagher 2011). The idea is that patients will be more willing and able to take responsibility in managing their anaphylaxis in the future. Studies in the context of other long-term conditions such as asthma and arthritis have shown that self-management plans are, when coupled with regular reviews, effective in changing clinical outcomes such as improving physiological function, decreasing morbidity, promoting self-perception and diminishing healthcare utilisation. (Bodenheimer 2002; Gibson 2002; Wolf 2003; Lorig 2005).The use of self-management plans in people

with chronic conditions can, for example, reduce the risk of exacerbations and associated hospital admissions (Deakin 2005; Effing 2007; Lindsay 2010) More generally, they have also been shown to empower patients and improve quality of life and treatment satisfaction (Deakin 2005).

Why it is important to do this review

For selected patient groups with long-term conditions such as diabetes, arthritis, epilepsy, asthma and chronic obstructive pulmonary disease (COPD), self-management plans have been found to be beneficial (Gibson 2002; Powell 2002; Deakin 2005; Effing 2007; Foster 2007; Garcio-Alamino 2010; Lindsay 2010). Although self-management plans are increasingly being advocated for routine use in anaphylaxis (Moneret-Vautrin 2001; Walker 2003; Ewan 2005; Simons 2006), very few patients have such plans in place (Ewan 2001). Any widespread roll-out of this approach will require a secure underlying evidence-base (Choo 2007; Nurmatov 2008). To inform these deliberations, we seek to evaluate the effects of emergency action plans for improving health, service use and other outcomes in patients at risk of anaphylaxis.

OBJECTIVES

To assess the effects of emergency action plans for people at risk of anaphylaxis in improving health, service use and other outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

For this review, we are particularly interested in including randomised controlled trials (RCTs). However, as we anticipate identifying few, if any RCTs, we will also include quasi-randomised controlled trials, controlled before-and-after studies, and interrupted time series studies. The criteria for including studies employing these designs are detailed below (Ryan 2009):

1. RCT: Participants (or other units) definitely assigned prospectively to one or more alternative forms of health care using a process of random allocation (i.e. random number generation, coin flips).

2. Quasi-RCT: Participants (or other units) were:

(a) definitely assigned prospectively to one or more alternative forms of health care using a quasi-random allocation method (i.e. alternation, date of birth, patient identifier); or

(b) possibly assigned prospectively to one or more alternative forms of health care using a process of random or quasi-random allocation.

3. Controlled before-and-after (CBA) study: Involvement of intervention and control groups other than by random process and inclusion of baseline period of assessment of main outcomes; there are three minimum criteria for inclusion of controlled before-and-after studies:

(a)There must be at least two intervention and two control sites,

(b) Contemporaneous data collection, and

(c) The intervention and control sites must be comparable on key characteristics.

4. Interrupted time series (ITS): A study design that collects observations at multiple time points before and then after an intervention (i.e. the intervention 'interrupts' the collection of data). To be included in this review, ITS studies must have:

(a) a clearly defined point in time at which the intervention occurred, and this should be specified by the researchers, and

(b) at least three data points before and three data points after the intervention was introduced.

Types of participants

We will include studies of people of all ages (i.e. children and adults) who had previously experienced anaphylaxis or who have been deemed by health professionals to be at an increased risk of anaphylaxis (but who have not necessarily experienced an anaphylactic event). Examples of people who are at an increased risk of anaphylaxis are:

- those who have experienced reaction to trace allergen exposure with respiratory or cardiovascular involvement;
- people known to be allergic to specific triggers that are known to be associated with severe/fatal reactions such as bee stings and nuts;
- people with other medical conditions such as asthma;
- those in whom a significant allergic event occurred that was not definitively diagnosed as anaphylaxis, and
- those living in remote areas who are likely to re-encounter a trigger.

We define anaphylaxis as any serious systemic allergic reaction that is rapid in onset with potentially fatal manifestations. Often such reactions involve more than one body system (e.g. skin, respiratory, gastrointestinal, or cardiovascular) (Soar 2008; Simons 2011). We will include all anaphylaxis events, regardless of mechanism or trigger, including idiopathic causes.

Types of interventions

We will include studies that involve an emergency action plan for anaphylaxis, whether it is intervention versus usual care or comparing different types of intervention. These emergency action plans can be oral, written or electronic, targeted at the patient and/

or carer. They can be provided by the health professional or lay person and developed in partnership with the patient.
We define emergency action plans as any interventions that offer the following strategies for emergency self-management of anaphylactic reactions:

- a plan for managing further reactions should accidental exposure occur; this includes recognition of the symptoms and sign of an anaphylaxis event and the severity of the reaction,
- information to help patients be aware of the indicators for emergency treatment strategies, and the timing and method of delivery of adrenaline, and
- advice to seek further help from healthcare professionals, either in the community or hospital setting.

Types of outcome measures

Primary outcomes

- Hospitalisation rate: emergency department attendance, admission & readmission
- Mortality rate

Secondary outcomes

Morbidity

- Clinical improvement by any objective measures e.g. number of exposure to trigger events, number of anaphylaxis events
- Presence of and severity of symptoms as detailed below (Brown 2004):

Mild reactions: Reactions limited to the skin (localised rash, wheals and swelling of the lips)
Moderate reactions: Excessive sweating, vomiting, dizziness, breathlessness, difficulty with and/or noisy breathing, wheeze, chest/throat tightness, nausea, vomiting, and abdominal pain
Severe reactions: Confusion, collapse, unconsciousness, incontinence, low blood pressure and low blood oxygen level

- Use of rescue medications
- Quality of life, functional health status
- Days off work/school

Health service use

- Length of hospital stay
- Primary care practitioner visits
- Cost in terms of health service use and medication

Other outcomes

- Patient or carer's knowledge of, confidence in, or adherence to the self-management plan
- Patient or carer's knowledge of trigger factors, anaphylaxis symptoms and technique of adrenaline auto-injector administration

Search methods for identification of studies

For published evidence we will search the following databases:

- MEDLINE (Ovid SP)
- The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*)
- ERIC
- EMBASE (Ovid SP)

For MEDLINE we will use the search strategy as detailed in Appendix 2. Modified versions of this strategy will be used for other databases and registers.
We will search all databases from their start date to the present.
We will also search the reference lists of relevant studies and handsearch key journals.
In an attempt to locate additional relevant published data, grey literature, unpublished data and research in progress we will contact international anaphylaxis experts and relevant pharmaceutical companies (see Appendix 3). We will search online databases that list ongoing trials (www.clinicaltrials.gov, www.controlledtrials.com) to identify any work in progress.
No language restrictions will be employed.

Data collection and analysis

Three authors will be conducting this review (KC, UN and AS), KC being the main co-ordinator.

Selection of studies

KC and UN will run the searches as specified by the search method and will independently review titles and abstracts from literature searches to identify potentially relevant trials for full review. KC will retrieve the full-text paper of all potentially eligible studies and both authors will subject the papers to independent review using the inclusion criteria detailed above. KC will also write to authors of papers for additional information if the paper cannot be determinatively included or excluded based on the full text.
Potentially relevant studies that were excluded after the full-text version has been examined will be listed in the table 'Characteristics of Excluded Studies' with the reason for exclusion given.
We will resolve any disagreements by discussion between the authors with AS arbitrating, if necessary.

Data extraction and management

Two authors (KC and UN) will independently extract data using a suitably adapted version of the data extraction form developed by the Cochrane Consumers and Communication Review Group. We will resolve any disagreements by discussion between the authors. Both authors will enter data into RevMan software (RevMan 5.1).

Assessment of risk of bias in included studies

We will assess the risk of bias of included RCTs following the Cochrane approach using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and the guidelines of the Cochrane Consumers and Communication Review Group (Ryan 2011), which recommends the explicit reporting of the following individual elements for RCTs:

- random sequence generation,
- allocation sequence concealment,
- blinding of participants and personnel
- blinding of outcome assessment
- completeness of outcome data,
- selective outcome reporting, and
- other potential threats to validity

We will grade each parameter as

- Low risk of bias;
- High risk of bias; and
- Unclear

Quasi-RCTs, CBA and ITS studies will be assessed for risk of bias using appropriate adaptations of the above criteria.

We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will incorporate the results of the risk of bias assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment the risk of bias of included studies and a judgement about the internal validity of the review's results. We will summarise the risk of bias for important outcomes within and across studies using the methods detailed in section eight of the Cochrane Handbook (Higgins 2011). We will perform this analysis for all primary outcomes as listed above.

In all cases, two authors will independently assess the risk of bias of included studies, with any disagreements resolved by discussion and consensus; in the event of agreement not being reached AS will arbitrate.

Measures of treatment effect

KC and UN will both analyse the data. We will use Review Manager (RevMan 5.1) for data analysis and quantitative data synthesis. For dichotomous data, we will calculate individual and pooled statistics as relative risks (RR) with 95% confidence intervals (95% CI). For continuous data, we will calculate individual and pooled statistics as mean differences (MD) and/or standardised means differences (SMDs) with 95% CI.

Unit of analysis issues

Both parallel group and cluster design trials will be eligible for inclusion and appropriate consideration for unit of allocation/analysis issues will be undertaken to ensure appropriate analysis of trial data.

When there is missing information on the intra-cluster correlation, we will, where appropriate, initially try to contact the research team to see if we can obtain the findings from a more appropriate analysis that takes clustering into account. If these data are not forthcoming, we will descriptively report data making clear that there are concerns about the precision of the summary effect measures as clustering has not been taken into account. These data will therefore not be entered into any meta-analysis.

Dealing with missing data

Whenever possible, KC will contact the lead trial investigator for missing data. Failing that, sensitivity analyses will be performed to assess how sensitive results are to reasonable assumptions that are made to replace the missing data.

Assessment of heterogeneity

We will give consideration to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We will quantify inconsistency between included studies using the I^2 statistic as described in section nine of the Cochrane Handbook (Higgins 2011).

Assessment of reporting biases

We will evaluate reporting biases by using a funnel plot as described in section ten of the Cochrane Handbook (Higgins 2011). We will conduct tests for funnel plot asymmetry if there are 10 or more studies included in the meta-analysis of the primary outcomes (clinical improvement by any objective measures, hospitalisation rate and mortality rate).

Data synthesis

Quantitative analyses of outcomes will be, wherever possible, on an intention to treat basis. We will, where appropriate and if data allow, undertake random effects meta-analysis in which we will combine data from different studies. If meta-analysis is however not considered appropriate and/or is not feasible, we will undertake a descriptive and narrative synthesis of the data as described in section nine of the Cochrane Handbook (Higgins 2011).

We will assess for evidence of publication bias graphically using funnel plots and statistically using Begg and Egger tests (Begg 1994; Egger 1997).

Subgroup analysis and investigation of heterogeneity

In the event of identifying significant heterogeneity, we will investigate this by undertaking subgroup analyses. Our subgroups of interest are different patient groups (i.e. children < 16 years or adults, aged > 17 years).

Sensitivity analysis

We will conduct sensitivity analysis by focusing on studies with low risk of bias, with the risk of bias judged based on section eight of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Consumer involvement

We will work with members of the Edinburgh Allergy and Respiratory Research Group's Consumer Involvement Group to advice on the preliminary draft of the review and seek their comments on the review's results and our plans for reporting findings.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Educational Resources on Anaphylaxis

The Food Allergy and Anaphylaxis Network (FAAN) www.foodallergy.org
Australasian Society of Clinical Immunology and Allergy www.allergy.org.au
World Allergy Organization (www.worldallergy.org)
Resuscitation Council (www.resus.org.uk/siteindx.htm)
American Academy of Allergy, Asthma, and Immunology (AAAAI) (www.aaaai.org)
American College of Allergy, Asthma, and Immunology (www.acaai.org)
Anaphylaxis Campaign (www.anaphylaxis.org.uk)
Allergy UK (www.allergyuk.org)
Anaphylaxis Canada (www.anaphylaxis.org)

Appendix 2. MEDLINE (OvidSP) search strategy

1. anaphylaxis/
2. (anaphylax* or anaphylact*).tw.
3. ((acute or severe or major or serious or life threatening or fatal*) and (allerg* or hypersensitivity)).tw.
4. hypersensitivity immediate/
5. exp food hypersensitivity/
6. respiratory hypersensitivity/
7. exp drug hypersensitivity/
8. ((nut* or peanut* or sting* or venom*) and (allerg* or hypersensitivity)).tw.
9. ((allerg* or hypersensitivity) and reaction*).tw.
10. or/1-9

11. exp teaching materials/
12. (plan or plans or written procedure* or guide*).tw.
13. clinical protocols/
14. practice guidelines as topic/
15. (manag* and (program* or material* or procedure*)).tw.
16. exp health education/
17. health knowledge attitudes practice/
18. (educat* or instruct* or teach* or learn* or coach* or train* or counsel* or advis* or advice*).tw.
19. exp health promotion/
20. exp self care/
21. (self adj (care or manag* or administ*)).tw.
22. patient cent?red.tw.
23. or/11-22
24. 10 and 23
25. randomized controlled trial.pt.
26. controlled clinical trial.pt.
27. clinical trial.pt.
28. evaluation studies.pt.
29. comparative study.pt.
30. random*.tw.
31. placebo*.tw.
32. trial.tw.
33. research design/
34. follow up studies/
35. prospective studies/
36. cross over studies/
37. (experiment* or intervention*).tw.
38. (pre test or pretest or post test or posttest).tw.
39. (preintervention or postintervention).tw.
40. time series.tw.
41. (cross over or crossover or factorial* or latin square).tw.
42. (assign* or allocat* or volunteer*).tw.
43. (control* or compar* or prospectiv*).tw.
44. (impact* or effect? or chang* or evaluat*).tw.
45. or/25-44
46. exp animals/ not humans.sh.
47. 45 not 46
48. 24 and 47

Appendix 3. Experts and pharmaceutical companies to be contacted

Panel of Experts
Sampson HA
Brown AF
Lieberman PL
Ewan PW
Pumphrey RS
Helbling A

(*Continued*)

Negro-Alvarez JM Moneret-Vautrin DA Muller U Fisher M Lin RY Clark S Golden D Lockey R Bock A Kemp S Ring J Camargo C
Pharmaceutical Companies
Allerbio Ltd (Ana-pen) ALK-Abello Ltd (Epi-pen)

HISTORY

Protocol first published: Issue 4, 2012

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Aziz Sheikh (AS)

Co-ordinating the review: Karen Choo (KC)

Undertaking searches: KC and Ulugbek Nurmatov (UN)

Screening search results: KC and UN

Organising retrieval of papers: KC and UN

Screening retrieved papers against inclusion criteria: KC, UN and AS

Appraising quality of papers: UN and AS

Extracting data from papers: UN and AS

Writing to authors of papers for additional information: KC

Providing additional data about papers: UN and AS

Obtaining and screening data on unpublished studies: KC, UN and AS

Data management for the review: KC, UN and AS

Entering data into Review Manager (RevMan 5.1): KC and UN

RevMan statistical data: KC, UN and AS

Other statistical analysis not using RevMan: UN and AS

Double entry of data: (data entered by person one KC ; data entered by person two: UN)

Interpretation of data: KC, UN and AS

Statistical inferences: KC, UN and AS

Writing the review: KC, UN and AS

Securing funding for the review: AS

Performing previous work that was the foundation of the present study: AS

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: AS

DECLARATIONS OF INTEREST

AS has provided consultancy advice to ALK Abello, Meda and Phadia on various aspects of anaphylaxis management.