



GUIDELINE FOR THE MANAGEMENT OF ACUTE ALLERGIC REACTION

Deepak Doshi; Bernard Foex; Rick Body and
Kevin Mackway-Jones

December 2009

For The College of Emergency Medicine



CONTENTS

1. Executive summary	4
2. Introduction	4
2.1 Responsibility for development	4
2.2 Funding	4
2.3 The Guideline Working Group	4
3. Topic Introduction	5
4. Scope	6
5. Methodology	6
5.1 Levels of evidence and grading of recommendations	6
5.2 Definition of Acute allergic reaction	7
6. Summary of Recommendations	7
6.1 Adrenaline	7
6.1.1 <i>Intravenous or intramuscular adrenaline for anaphylaxis</i>	7
6.1.2 <i>Subcutaneous or intramuscular adrenaline for anaphylaxis</i>	7
6.1.3 <i>Adrenaline self-injection for anaphylaxis in children</i>	7
6.1.4 <i>Adrenaline inhaler: An alternative to intramuscular adrenaline?</i>	7
6.1.5 <i>Sublingual adrenaline tablets: How feasible is this novel approach to treatment of acute allergic reaction?</i>	7
6.1.6 <i>Nebulised adrenaline for wheeze in anaphylaxis</i>	8
6.1.7 <i>Injection of adrenaline in acute allergic reaction: Do the thighs look better than the deltoid? – Read the evidence</i>	8
6.2 Removal of allergen	8
6.2.1 <i>Shaving hair to remove an allergen (hair dye) in acute allergic reaction: Does it help?</i>	8
6.2.2 <i>Does gastric lavage prevent biphasic acute allergic reaction?</i>	8
6.3 Investigation of anaphylaxis	8
6.3.1 <i>Mast cell tryptase and histamine levels in acute allergic reaction</i>	8
6.4 Antihistamines	8
6.4.1 <i>Oral antihistamine on discharge in acute allergic reaction</i>	8
6.5 Corticosteroids	8
6.5.1 <i>Hydrocortisone in acute allergic reaction</i>	8
6.5.2 <i>Oral prednisolone on discharge in acute allergic reaction</i>	8
7. Evidence for Recommendations	9
7.1 Adrenaline	9
7.1.1 <i>Intravenous or intramuscular adrenaline for anaphylaxis</i>	9
7.1.2 <i>Subcutaneous or intramuscular adrenaline for anaphylaxis</i>	10
7.1.3 <i>Adrenaline self-injection for anaphylaxis in children</i>	10
7.1.4 <i>Adrenaline inhaler: An alternative to intramuscular adrenaline?</i>	12
7.1.5 <i>Sublingual adrenaline tablets: How feasible is this novel approach to treatment of acute allergic reaction?</i>	13
7.1.6 <i>Nebulised adrenaline for wheeze in anaphylaxis</i>	14
7.1.7 <i>Adrenaline: site of administration</i>	15
7.2 Removal of allergen	16
7.2.1 <i>Shaving hair to remove an allergen (hair dye) in acute allergic</i>	16

<i>reaction: Does it help?</i>	
7.2.2 <i>Does gastric lavage prevent biphasic acute allergic reaction?</i>	17
7.3 Investigation of anaphylaxis	18
7.3.1 <i>Mast cell tryptase and histamine levels in acute allergic reaction</i>	18
7.4 Antihistamines	19
7.4.1 <i>Oral antihistamine on discharge in acute allergic reaction</i>	19
7.5 Corticosteroids	20
7.5.1 <i>Hydrocortisone in acute allergic reaction</i>	20
7.5.2 <i>Oral prednisolone on discharge in acute allergic reaction</i>	21
Appendix 1: Relevant papers	22
Appendix 2: Search filters	28
Reference List	29

1. EXECUTIVE SUMMARY

- The Guidelines in Emergency Medicine Network (GEMNet) has been created to promote best medical practice in a range of conditions presenting to Emergency Departments (EDs) in the UK
- This guideline presents a summary of the best available evidence to guide the management of adult patients who present to the ED following an acute allergic reaction.
- The document has been developed following discussion amongst Emergency physicians to decide which topics would benefit from the development of clinical guidelines.
- The document is intended as a guideline for use in the ED by Emergency Physicians and is based on the review of the best existing evidence for the diagnostic tools and treatments used in this setting.
- The document is summarized as a Clinical Decision Support Guideline that has been presented as an easy to follow algorithm.
- The intention is for each guideline to be updated and reviewed as further evidence becomes available. The formal revision date has been set at 5 years from publication though the guideline is subject to continuous informal review.

2. INTRODUCTION

2.1 Responsibility for development

This document has been developed in response to a perceived need to improve clinical effectiveness for care in this field. The Emergency Department at the Manchester Royal Infirmary has been undertaking primary and secondary research for a number of years to achieve this aim. The intention is to distil this information into practical advice for clinicians working in the department. The information is presented in the form of Clinical Decision Support Guidelines, available on shop floor in the form of a Clinical Decision Support Manual and on individual A4 sized forms. Departmental Consultants have considered clinical conditions that may benefit from evidence based guidelines and following discussion with other clinical staff have compiled a list of topics that included acute allergic reaction.

2.2 Funding

Funding for the development for this guideline has been received from the College of Emergency Medicine.

2.3 The Guideline Working Group

A Guideline Working Group met to discuss this condition and decide on the clinical questions, consider the evidence available and develop the recommendations. The group process ensured that the working group had access to the relevant information and the required resources in order to develop in a constructive manner.

The guideline has been developed in accordance with the principles described by the National Institute for Health and Clinical Excellence guideline development methods.

3. TOPIC INTRODUCTION

Acute allergic reaction is a common condition presenting to the Emergency Department, with a variety of symptoms ranging from localised rash to life-threatening anaphylaxis. There is no universally accepted definition of anaphylaxis, but it is generally taken to describe a rapidly progressive, potentially life-threatening, acute allergic reaction.¹ Anaphylaxis is caused by the degranulation of mast cells and basophils with subsequent release of inflammatory mediators such as histamine, tryptase, prostaglandins, leukotrienes, cytokines and chemokines.² These inflammatory mediators cause smooth muscle contraction, vasodilation and increased vascular permeability, leading to urticaria, angioedema, bronchoconstriction and hypotension.³

The most common signs and symptoms of anaphylaxis are cutaneous (generalised urticaria, angioedema, flushing and itching), affecting around 90% of patients.⁴ Other features include respiratory symptoms (dyspnoea, wheeze, stridor or hypoxia), affecting 70%, and GI symptoms such as abdominal pain and vomiting, affecting 40%.^{1,4} Hypotension is less common, affecting between 10–30% of patients with anaphylaxis.⁴ The diagnosis is made clinically, on the basis of the patient's symptoms.¹ Anaphylactic reactions can be triggered by virtually any agent capable of activating mast cells and basophils, but the most commonly implicated allergens include:^{2,5}

- Foods (particularly milk, egg, peanuts, tree nuts, fish, shellfish, soy and wheat)
- Drugs
- Stings or venoms
- Latex
- Allergen immunotherapy injections.

In up to one-third of cases, there may be no obvious trigger.

Allergies are among the most common diseases in the UK, affecting around 30% of adults and 40% of children.⁶ The incidence of anaphylaxis is difficult to estimate due to the lack of an accepted definition and the frequent misdiagnosis of the condition. However, in a recent literature review, a working group of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis estimated that anaphylaxis affects between 0.5% and 2% of the population at some point during their lives.⁷ The incidence of severe allergic reactions and anaphylaxis seems to be increasing.⁸

The overall mortality of anaphylaxis has been estimated at <1%.⁹⁻¹¹ Over half of all deaths due to anaphylaxis occur within an hour of allergen exposure, primarily from asphyxia due to upper airway oedema and bronchospasm, or hypotension and circulatory failure.¹² Despite the low mortality rate, the potential for serious consequences and rapid progression of anaphylaxis mean that prompt treatment is essential.

As with all emergencies, the initial management of anaphylaxis involves airway, breathing and circulation assessment, followed by immediate administration of adrenaline.^{1,13} This is followed if necessary by supplementary treatment with oxygen, intravenous fluids and second-line drug therapy with antihistamines or corticosteroids.^{1,13} However, due to the unpredictable and potentially life-threatening nature of anaphylaxis, it is unethical to perform randomised, controlled clinical trials, and these treatment recommendations are therefore based on clinical observations, basic principles of pathophysiology, and some laboratory studies, rather than on clinical evidence.¹⁴ For example, adrenaline is considered the mainstay of anaphylaxis management, but there is little evidence supporting its use in this setting.⁴

The aim of this project is to develop guidelines for the management of acute allergic reaction, in the setting of the Emergency Department. In these guidelines, an attempt has been made to substantiate as much evidence as possible for the suggested recommendations.

4. SCOPE

This guideline encompasses all patients presenting to the ED with a clinical diagnosis of acute allergic reaction. The algorithm is applicable to patients of any age or gender, either with a primary diagnosis of acute allergic reaction or an acute allergic reaction to a medication given in the department.

The guidelines are intended to be used by healthcare professionals working within the Emergency Department. They cover:

- Clinical risk assessment
- Airway management
- Initial drug treatment
- Investigations
- Supportive treatment
- Discharge plan and medication.

Disposition may vary dependent on local resources but the guideline may be adapted as appropriate.

5. METHODOLOGY

This guideline was developed using a novel methodology that has recently been utilised in cardiothoracic surgery⁴. Many guidelines perform a single systematic review of the literature in order to answer all of the relevant clinical questions. In order to maximise sensitivity, a separate systematic review of the literature was performed for each clinical question identified.

Guideline development was structured into several stages. Initially the lead guideline developers met to discuss the scope of the guideline and to identify all clinical questions that may have been relevant. In order to answer the clinical questions identified we performed a series of structured short-cut systematic reviews (Best Evidence Topic Summaries, BETs), the principles of which have been previously described⁵. Where relevant BETs had already been created, the search strategies were checked and updated when necessary. The completed BETs form an appendix of this document.

Having gathered and collated the evidence for each clinical question, the principle guideline developers met to create a series of guideline recommendations, which were used to create an evidence-based flowchart following consultation with the lead guideline developer.

5.1 Levels of evidence and grading of recommendations

Studies included in this guideline were graded for level of evidence according to previously accepted definitions⁶. In summary, level 1 evidence comes from well designed randomised controlled trials (RCT's), level 2 evidence from large cohort studies or poorly designed RCT's, level 3 evidence from small cohort studies or case-control studies and level 4 evidence from experimental studies, case series or case studies. The suffix 'a' implies that evidence at this level is from original research, whereas the suffix 'b' implies that the evidence is from systematic review or meta-analysis.

The recommendations that have been made were graded according to the level of evidence upon which they were based:

Grade A: Based upon multiple level 1a or 1b papers.

Grade B: Based upon individual level 1a or 1b papers or multiple level 2a or 2b papers.

Grade C: Based upon individual level 2a or 2b papers or multiple level 3a or 3b papers.

Grade D: Based upon individual level 3a or 3b papers or level 4 papers.

Grade E: Based on consensus guidelines or studies of expert opinion.

5.2 Definition of Acute allergic reaction

For the purposes of this guideline acute allergic reaction was defined as conglomeration of symptoms and signs consistent with a reaction to an allergen including prescribed medications.

6. SUMMARY OF RECOMMENDATIONS

6.1 Adrenaline

6.1.1 Intravenous or intramuscular adrenaline for anaphylaxis

Intramuscular injection of adrenaline is safe for early progressive to moderate acute allergic reactions (Grade D).

Carefully titrated doses of IV adrenaline should be considered in cases of refractory hypotension or peri-cardiac arrest situations (Grade D).

6.1.2 Subcutaneous or intramuscular adrenaline for anaphylaxis

The intramuscular route is preferred over the subcutaneous route for injection of adrenaline in acute allergic reaction (grade D).

6.1.3 Adrenaline self-injection for anaphylaxis in children

Where available, adrenaline auto-injectors should be utilised in the community at an early stage for severe anaphylactic reactions, although high quality evidence is lacking (Grade C).

To maximise any potential benefit it is important to provide education for patients, parents and carers regarding injection technique and ensuring auto-injector availability at all times (Grade C).

6.1.4 Adrenaline inhaler: An alternative to intramuscular adrenaline?

In view of the lack of evidence and practice supporting beneficial effects, inhaled adrenaline is not recommended used as an alternative to intramuscular adrenaline in patients with acute allergic reactions (Grade D).

6.1.5 Sublingual adrenaline tablets: How feasible is this novel approach to treatment of acute allergic reaction?

Due to a lack of any human studies, sublingual adrenaline can not be recommended for general use in acute allergic reaction.

6.1.6 Nebulised adrenaline for wheeze in anaphylaxis

There is no evidence to support the use of nebulised adrenaline in the management of anaphylaxis (Grade D).

6.1.7 Injection of adrenaline in acute allergic reaction: Do the thighs look better than the deltoid? – Read the evidence

Absorption of adrenaline from the thigh is faster than absorption from the upper arm. The lateral thigh is therefore the preferred site of administration of intramuscular injection of adrenaline (Grade C).

6.2 Removal of allergen

6.2.1 Shaving hair to remove an allergen (hair dye) in acute allergic reaction: Does it help?

There is no published evidence that shaving the hair stops the progression of an acute allergic reaction to hair dye (Grade E).

6.2.2 Does gastric lavage prevent biphasic acute allergic reaction?

There is no published evidence to suggest that gastric lavage prevents biphasic allergic reactions to ingested allergens (Grade E).

6.3 Investigation of anaphylaxis

6.3.1 Mast cell tryptase and histamine levels in acute allergic reaction

Based on the evidence available, tryptase and histamine lack adequate sensitivity as diagnostic markers of acute allergic reaction. However, in the absence of an alternative biomarker, serial monitoring of tryptase levels may be useful and routine monitoring will provide a body of evidence to support or refute its usefulness (Grade B).

6.4 Antihistamines

6.4.1 Oral antihistamine on discharge in acute allergic reaction

There are no randomised controlled trials to support the use of oral antihistamines to reduce the recurrence of allergic reactions, although they may relieve some allergic symptoms (Grade D).

6.5 Corticosteroids

6.5.1 Hydrocortisone in acute allergic reaction

There are no randomised controlled trials supporting the use of hydrocortisone to prevent or treat biphasic or protracted allergic reactions. However, given that corticosteroids are effective in the management of acute asthma, which may be confused with anaphylaxis, their use may be warranted (Grade C).

6.5.2 Oral prednisolone on discharge in acute allergic reaction

There is no evidence to support the prescription of oral prednisolone to prevent recurrence of acute allergic reaction, although corticosteroids may be helpful for symptoms of urticaria (Grade C).

7. EVIDENCE FOR RECOMMENDATIONS

Below are summaries of the evidence of the short cut systematic reviews used to establish the recommendations for this guideline. The three part question and search details are presented with comments and clinical bottom line. The search strategies are summarised and can be found in full in the appendix.

7.1 Adrenaline

7.1.1 Intravenous or intramuscular adrenaline for anaphylaxis

Three part question

In [patients with anaphylaxis] is [intramuscular adrenaline better than intravenous adrenaline] at [treating the anaphylaxis and avoiding toxicity]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

Cochrane database - Nov 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Route filter] limit to humans and English language

Search outcome

A total of 1506 papers or protocol reviews were found, four of which were relevant to the three part question.

Comments

Adrenaline is an alpha- and beta-adrenergic agonist. It causes vasospasm and inotropic effects on the heart. Adrenaline is an effective agent in the management of anaphylaxis, but an inappropriate dose or route of administration can have serious adverse effects. Several case studies report instances of adrenaline induced coronary vasospasm, arrhythmias and pulmonary oedema, which can be fatal.¹⁶⁻¹⁹ Intramuscular adrenaline, however, is rarely associated with adverse events and its benefits in anaphylaxis far outweigh the risks.³

Clinical bottom line

Intramuscular injection of adrenaline is safe for early progressive to moderate acute allergic reactions. Carefully titrated doses of IV adrenaline should be considered in cases of refractory hypotension or peri-cardiac arrest situations.⁴

Recommendation

Intramuscular injection of adrenaline is safe for early progressive to moderate acute allergic reactions (Grade D).

Intravenous adrenaline should be considered for severe acute allergic reactions including refractory hypotension and peri-cardiac arrest situations (Grade D).

7.1.2 Subcutaneous or intramuscular adrenaline for anaphylaxis

Three part question

In [patients with anaphylaxis] is [subcutaneous adrenaline better than intramuscular adrenaline] at [treating the anaphylaxis and avoiding toxicity]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Route filter] limit to humans and English language

Search outcome

A total of 952 papers were identified, two of which were original research papers relevant to the three part question.

Comments

Intramuscular injection of adrenaline provides greater and more rapid systemic absorption of adrenaline than the subcutaneous route.^{20,21} This may be because adrenaline is a strong cutaneous vasoconstrictor, reducing cutaneous blood flow for up to 30 minutes. This may significantly reduce the absorption of adrenaline administered subcutaneously. Self-injectable adrenaline is given intramuscularly into the lateral thigh. However, due to increasing obesity, its site of delivery may, in actual fact, be subcutaneous in many cases. This can lead to failure of treatment in the first stage, and rebound absorption after some time, as a secondary effect. Close monitoring of patients should be maintained to observe the delayed effects of subcutaneous adrenaline.

Clinical bottom line

The intramuscular route is preferred over the subcutaneous route for injection of adrenaline in acute allergic reaction.

Recommendation

Intramuscular injection of adrenaline is preferred over the subcutaneous route in acute allergic reaction (Grade D)

7.1.3 Adrenaline self-injection for anaphylaxis in children

Three part question

In [children with anaphylaxis] does [self-injection of adrenaline] lead to [reduced mortality and morbidity]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Outcome filter] limit to humans and English language

Search outcome

A total of 705 papers were identified. Three papers provided evidence that was relevant to the three part question.

Comments

Adrenaline is the drug of choice for initial treatment of severe anaphylaxis as it blocks mediator release and reverses systemic effects. Many children are now prescribed adrenaline auto-injectors for emergency use in the community.

The survey identified suggests that adrenaline self-injection may reduce subsequent hospital admission and need for adrenaline in hospital. However, it is notable that 76% of parents were not familiar with the correct procedure for using the devices, despite prior instruction.²²

There is evidence that prompt use of adrenaline improves prognosis in severe anaphylactic reactions. Sampson *et al* (1992)²⁴ studied six children and adolescents who died of anaphylactic reactions to foods and seven others who nearly died and required intubation. The six who died had symptoms within 3–30 minutes of allergen ingestion and only two received adrenaline within the first hour. All patients who survived had symptoms within 5 minutes of allergen ingestion and all but one received adrenaline within 30 minutes. Bock *et al* (2001)²⁵ found that only four of 32 fatal anaphylactic reactions identified from a registry had received timely adrenaline.

As 53% of children with reported allergic reactions in the UK and Ireland between 1998 and 2000 have had a previous allergic reaction (9% requiring hospitalisation),²⁶ there is certainly potential to identify children who may be eligible for adrenaline self-treatment in the future. However, the number of patients who may benefit from widespread availability of adrenaline auto-injectors is likely to be small. A significant proportion of children will not have their autoinjector available at the time of the reaction. Others may be unfamiliar with the technique for self-injection, a small number may die despite treatment, and many patients have had no previous reaction (therefore being ineligible for prior adrenaline prescription).

It is known that adrenaline may lead to cardiac arrhythmia. Colver *et al* (2005)²³ reported three cases where excess adrenaline administration in hospital was implicated in clinical deterioration. MacDougall *et al* (2002)²⁶ reported one case in which death was attributed to excess intravenous adrenaline administration. However, the reported search strategy did not reveal any evidence of death or cardiac arrhythmia following self-injection of intramuscular adrenaline.

Although there is no evidence of high quality available to answer the three-part question, there is a sound physiological basis for the early use of adrenaline in severe anaphylaxis. At present it would be unethical to perform a randomized controlled trial. As early adrenaline may be life-saving and in the absence of evidence of harm following self-injection, measures to increase its availability should be encouraged even in the absence of high level evidence.

Clinical bottom line

Where available, adrenaline auto-injectors should be utilised in the community at an early stage for severe anaphylactic reactions, although high quality evidence is

lacking. To maximise any potential benefit it is important to provide education for patients, parents and carers regarding injection technique and ensuring autoinjector availability at all times.

Recommendation

Although high quality evidence is lacking adrenaline auto-injector should be used when available in the community (Grade D).

7.1.4 Adrenaline inhaler: An alternative to intramuscular adrenaline?

Three part question

In [a patient with acute allergic reaction] is [intramuscular adrenaline better than adrenaline inhaler] at [reversing symptoms]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Nebuliser and inhaler filter]
limit to humans and English language

Search outcome

A total of 71 papers were found, of which two were relevant to the three part question.

Comments

Inhalation of adrenaline is perceived as a non-invasive and user friendly approach to the management of anaphylaxis and would be a useful alternative to intramuscular adrenaline in children who refuse injections. However, the dose of inhaled adrenaline needed to achieve therapeutic concentrations is high (estimated to be 20 inhalations in adults), which may limit its usefulness. Volunteer studies suggest that it is difficult for children to inhale an adequate dose of adrenaline promptly enough, either because of poor inhaler technique, adverse effects, or objection to the taste of the inhaled medicine.^{27,28}

Clinical bottom line

In view of the lack of evidence supporting beneficial effects, inhaled adrenaline should not be used as an alternative to intramuscular adrenaline in patients with acute allergic reactions.

Recommendation

Adrenaline inhaler is not recommended as an alternative treatment in acute allergic reaction, due to lack of evidence (Grade D).

7.1.5 Sublingual adrenaline tablets: How feasible is this novel approach to treatment of acute allergic reaction?

Three part question

In [patients with acute allergic reaction] are [sublingual adrenaline tablets better than intramuscular adrenaline injections] at [reversing symptoms and preventing adverse effects of adrenaline?]

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Tablet filter] limit to English language

Search outcome

A total of 147 papers were found, one of which was relevant to the three part question.

Comments

Adrenaline auto-injectors have several disadvantages, including the cost of the injection, the size of the device, inappropriate injection technique, inadequate dosing, and the pain, fear and anxiety surrounding intramuscular injections.

Adrenaline tablets are a novel, rapidly disintegrating formulation suitable for sublingual administration.³⁰ The sublingual route of administration of adrenaline is a promising alternative to intramuscular administration of adrenaline. It is pharmacologically proven that sublingual drugs have fast and reliable effects (for example nitroglycerine tablets in acute coronary syndromes). Sublingual medicines are absorbed directly into the systemic circulation, bypassing the potential problems of metabolic gastrointestinal conversion and hepatic first-pass metabolism.³⁰

In the rabbit model, administration of sublingual adrenaline has been shown to provide a rapid increase in plasma adrenaline that is equivalent to a 0.3mg intramuscular dose.²⁹ As such, it is a potential alternative to intramuscular adrenaline that warrants greater research. Further animal and human studies are required to determine whether sublingual adrenaline is effective in the management of acute allergic reaction.

Clinical bottom line

Due to a lack of any human studies, sublingual adrenaline can not be recommended for general use in acute allergic reaction.

Recommendation

Human studies are awaited for this novel approach (Grade D).

7.1.6 Nebulised adrenaline for wheeze in anaphylaxis

Three part question

In [patients with anaphylaxis] is [nebulised salbutamol better than nebulised adrenaline] at [reducing wheeze]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Nebuliser and inhaler filter]
limit to humans and English language

Search outcome

A total of 36 papers were found but none were relevant to the specific question. However, one Cochrane Library paper was retrieved that studied nebulised adrenaline in severe asthma rather than acute allergic reaction, and one was retrieved that compared injected adrenaline with nebulised salbutamol, again in acute asthma. These are discussed below.

Comments

Nebulised adrenaline has been proposed as a potential alternative to salbutamol in the management of wheeze due to acute allergic reactions. However, there are no studies directly comparing nebulised adrenaline with salbutamol in acute allergic reactions. Some trials of nebulised adrenaline have been performed in acute severe asthmatic patients with symptoms of wheeze and breathing difficulty, who are similar in many ways to patients with acute allergy. These are briefly discussed below.

Zeggwagh *et al* (1998)³¹ concluded from a prospective randomised controlled trial in 44 patients that nebulised adrenaline is as effective as nebulised salbutamol. They also concluded that nebulisation could reduce the systemic side effects of adrenaline.

Turpeinen *et al* (1984)³² compared injected adrenaline with nebulised salbutamol in 46 children with asthma. They concluded that nebulised salbutamol was a more effective bronchodilator than injected adrenaline in children.

Clinical bottom line

There is no evidence to support the use of nebulised adrenaline in the management of anaphylaxis.

Recommendation

There is lack of evidence for the use of adreanline nebuliser in acute allergic reaction (Grade D).

7.1.7 Adrenaline: site of administration

Injection of adrenaline in acute allergic reaction: Do the thighs look better than the deltoid? – Read the evidence

Three part question

In [patients with acute allergic reaction] does [injection of adrenaline into the vastus lateralis or deltoid] produce [faster and better effects]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Site of injection filter] limit to humans and English language

Search outcome

A total of 41 papers were found, one of which was relevant to the three part question.

Comments

There has been some debate over the optimum site of adrenaline administration. Simons *et al* have shown that adrenaline is absorbed more rapidly when administered intramuscularly into the thigh than when administered intramuscularly or subcutaneously into the upper arm.²⁰ However, the plasma and tissue concentration of adrenaline required for successful treatment of acute allergic reaction is unknown so the clinical relevance of this is unclear. Ideally, recommendations for adrenaline administration should be based on prospective, randomised, double blind, placebo-controlled trials in patients actually experiencing acute allergic reaction. However, this type of clinical trial would be unethical and impossible to conduct due to the potentially fatal nature of anaphylaxis.

Clinical bottom line

Absorption of adrenaline from the thigh is faster than absorption from the upper arm. The lateral thigh is therefore the preferred site of administration of intramuscular injection of adrenaline.

Recommendation

Lateral thigh is preferred as compared to deltoid for adrenaline intramuscular injection (Grade C).

7.2 Removal of allergen

7.2.1 Shaving hair to remove an allergen (hair dye) in acute allergic reaction: Does it help?

Three part question

In [patients with acute allergic reaction to hair dye] does [shaving of hair] stop [further progression of reaction]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Hair dye filter] limit to humans and English language

Search outcome

A total of 189 papers were found, none of which was relevant to the three part question.

Comments

The incidence of allergy to hair dye is rising as the use of hair dye increases, particularly among young people.³³ It is predominantly due to aromatic amines, common components of hair dye that are potent contact allergens.³³

In its recent guidelines on the emergency treatment of anaphylactic reactions, the UK's Resuscitation Council recommends the removal of the trigger of anaphylactic reactions where feasible.¹³ However, it is unclear whether shaving the hair to remove allergens present in hair dye effectively prevents progression of the acute allergic reaction.

Clinical bottom line

There is no published evidence that shaving the hair stops the progression of an acute allergic reaction to hair dye. Further studies are required.

Recommendation

There is lack of evidence that shaving the hair stops further progression of reaction (Grade C).

7.2.2 Does gastric lavage prevent biphasic acute allergic reaction?

Three part question

In [patients with acute allergic reaction to food] does [gastric lavage in the early phase] prevent [biphasic reaction]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Gastric lavage filter] limit to humans and English language

Search outcome

A total of 8 papers were found, none of which was relevant to the three part question.

Comments

Allergic reactions to food are common, being estimated to affect approximately 3–7% of children and 1–2% of adults.³⁴ Although any food can cause a reaction in a sensitised individual, eight foods are responsible for 90% of allergic reactions: milk, egg, peanut, tree nuts (e.g. walnuts or cashews), fish, shellfish, soy and wheat.⁵ It is estimated that between 3% and 20% of patients with an anaphylactic reaction that responds to initial treatment go on to develop a biphasic reaction up to 48 hours after the initial episode.³⁵

In its recent guidelines on the emergency treatment of anaphylactic reactions, the UK's Resuscitation Council recommends the removal of the trigger of anaphylactic reactions where feasible.¹³ However, induction of vomiting in patients with food induced anaphylaxis is not recommended. No mention is made of gastric lavage, and there is currently no literature to support or refute that removal of food from the stomach, either by gastric lavage or emesis, would be of benefit to control the immediate allergic reaction or to prevent biphasic reaction.

Clinical bottom line

There is no published evidence to suggest that gastric lavage prevents biphasic allergic reactions to ingested allergens. Further studies are required.

Recommendation

There is lack of evidence to show that the gastric lavage for ingested allergen prevents biphasic reaction.

7.3 Investigation of anaphylaxis

7.3.1 Mast cell tryptase and histamine levels in acute allergic reaction

Three part question

In [patients with acute allergic reaction] do [mast cell tryptase and histamine levels done early in the Emergency Department] lead to [better future care]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Investigation filter] limit to humans and English language

Search outcome

A total of 727 papers were found, two of which were relevant to the three part question.

Comments

A gold standard for the diagnosis for anaphylaxis has not been defined and diagnosis is currently made on the basis of clinical features. However, measurement of immune mediators may be useful in the diagnosis and monitoring of acute allergic reactions.

Tryptase is an immune mediator that is released on mast cell degranulation. In the absence of anaphylaxis, tryptase levels are relatively stable. In cases of anaphylaxis, tryptase peaks approximately 1 hour after the onset of the reaction, and has a half-life of around 2 hours.³⁸ Histamine is a major mediator of anaphylaxis. Its levels peak approximately 15 minutes after the onset of allergic reaction and decline rapidly thereafter.³⁹ Histamine levels can be affected by the method of blood sampling and by haemolysis of the sample, so the timing and handling of blood samples in anaphylaxis are important.

At present, there is insufficient evidence to support the use of tryptase or histamine as sensitive diagnostic markers of anaphylaxis, although serial measurements may be more useful to monitor the subsequent course of the reaction.^{36,37} This is consistent with the UK Resuscitation Council's recommendation to monitor serial tryptase levels in the follow-up of suspected anaphylactic reactions, but not to rely on them for the initial diagnosis.¹³

Clinical bottom line

Based on the evidence available, tryptase and histamine lack adequate sensitivity as diagnostic markers of acute allergic reaction. However, in the absence of an alternative biomarker, serial monitoring of tryptase levels may be useful and routine monitoring will provide a body of evidence to support or refute its usefulness.

Recommendation

Both mast cell tryptase and histamine lack adequate sensitivity as a diagnostic marker of acute allergic reaction. Larger studies are recommended.

7.4 Antihistamines

7.4.1 Oral antihistamine on discharge in acute allergic reaction

Three part question

In [patients with acute allergic reaction] does [oral antihistamine on discharge] lead to [reduction in recurrence of symptoms]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Antihistamines filter] limit to humans and English language

Search outcome

A total of 1117 papers were found, none of which was relevant to the three part question.

Comments

The role of antihistamines in the management of acute allergic reactions is controversial. The UK Resuscitation Council recommends the use of intravenous antihistamines as second line treatment in the initial management of anaphylaxis, and suggests considering a 3 day course of oral antihistamines on discharge to reduce the chance of a recurrence.¹³ Although H1-antihistamines have been shown to be effective in the symptomatic treatment of some localised and less severe allergic reactions (e.g. allergic rhinitis, allergic conjunctivitis and urticaria),⁴⁰ there is no published evidence to suggest that they reduce the risk of a further reaction in patients with anaphylaxis.

Clinical bottom line

There are no randomised controlled trials to support the use of oral antihistamines to reduce the recurrence of allergic reactions, although they may relieve some allergic symptoms.

Recommendation

There are no randomised controlled trials to support the use of oral antihistamines to reduce the recurrence of acute allergic reaction, although they may relieve some allergic symptoms in the early phase.

7.5 Corticosteroids

7.5.1 Hydrocortisone in acute allergic reaction

Three part question

In [patients with acute allergic reaction] does [intravenous hydrocortisone] lead to [reduction in recurrence of symptoms]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Corticosteroid filter] limit to humans and English language

Search outcome

A total of 1064 papers were found, none of which was relevant to the three part question.

Comments

Corticosteroids have a number of theoretical benefits in the management of anaphylaxis, including inhibition of inflammatory mediator release, downregulation of inflammatory cell activation, prevention of neutrophil and platelet aggregation and reduction in IgE expression.¹⁴ Corticosteroids also increase the responsiveness of the airway tissues to β -agonists. However, they are associated with significant adverse effects, such as electrolyte imbalance, myopathies and coronary ischaemia, and even when given intravenously, they may take up to 4–6 hours to reach maximum effectiveness.¹⁴

The role of corticosteroids in anaphylaxis is controversial. It has been suggested that their use might prevent biphasic reactions or shorten prolonged reactions, particularly in patients presenting with bronchospasm.¹⁴ There has also been speculation that corticosteroids may decrease the severity of the reaction. The UK Resuscitation Council recommends the use of intravenous corticosteroids as an adjunct to adrenaline and antihistamine therapy after initial resuscitation, to prevent or shorten protracted anaphylactic reactions.¹³ However, the effectiveness of corticosteroids in this setting has not been determined in placebo controlled trials.

Clinical bottom line

There are no randomised controlled trials supporting the use of hydrocortisone to prevent or treat biphasic or protracted allergic reactions. However, given that corticosteroids are effective in the management of acute asthma, which may be confused with anaphylaxis, their use may be warranted in some cases.

Recommendation

There is lack of evidence that hydrocortisone reduces the symptoms or prevents recurrence in acute allergic reaction.

7.5.2 Oral prednisolone on discharge in acute allergic reaction

Three part question

In [patients with acute allergic reaction] does [oral prednisolone on discharge] lead to [reduction in recurrence of symptoms]?

Search strategy

Ovid medline 1950 to – May week 2 2008

Ovid embase 1980 – June Week 2 2008

[Adrenaline filter] AND [Acute allergic reaction filter] AND [Corticosteroid and discharge filter] limit to humans and English language

Search outcome

A total of 264 papers were found, none of which was relevant to the three part question.

Comments

Corticosteroids have a number of theoretical benefits in the management of anaphylaxis, including inhibition of inflammatory mediator release, downregulation of inflammatory cell activation, prevention of neutrophil and platelet aggregation and reduction in IgE expression.¹⁴ It has been suggested that a short course of oral corticosteroids may be appropriate for patients being discharged after an acute allergic reaction, and there is evidence to suggest that this may reduce the symptoms of acute urticaria.⁴⁶

The UK Resuscitation Council recommends considering a 3 day course of oral corticosteroids on discharge to treat urticaria and reduce the chance of a recurrence.¹³ However, there are no published clinical trials to support the use of oral corticosteroids to prevent recurrence of acute allergic reaction.

Clinical bottom line

There is no evidence to support the prescription of oral prednisolone to prevent recurrence of acute allergic reaction, although corticosteroids may be helpful for symptoms of urticaria. Further studies are required.

Recommendation

There is lack of evidence that oral prednisolone as a discharge medication prevents recurrence of acute allergic reaction.

APPENDIX 1: RELEVANT PAPERS

Table 1: 7.1.1 Intravenous or intramuscular adrenaline for anaphylaxis

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Shaver <i>et al</i> , 2006 ¹⁶ Canada	29 year old woman with anaphylactic reaction to penicillin and no significant past medical history	Single case report Level 4	Treated with 1:10000 dilution IV adrenaline 0.1mg	Patient developed tachycardia, severe chest pain, ST elevation in anterolateral leads with reciprocal changes, and elevated troponin levels CT coronary arteriogram and TOE were unremarkable	Vasospasm rather than acute MI was ultimately diagnosed
Pumphrey, 2000 ¹⁷ UK	164 cases of fatality with anaphylaxis recorded as the cause of death between 1992 and 1998 (148 had records available for further analysis)	Analysis of registry data Level 4	Fatalities due to inappropriate administration of adrenaline	Six patients died after inappropriate adrenaline administration: <ul style="list-style-type: none"> • 2 developed fatal pulmonary oedema after high-dose boluses of IV adrenaline • 1 died from adrenaline overdose and fluid overload after repeated adrenaline injections • 3 died from MI after adrenaline treatment for mild allergic reactions 	Dose and route of adrenaline administration is not recorded for all cases It is not clear whether adrenaline or the underlying allergic reaction was the cause of death in some cases
Anchor <i>et al</i> , ¹⁸ 2004 USA	Two patients treated with IV adrenaline for tongue oedema following presumed allergic reaction	Case reports Level 4	Case 1 Patient was given 1:1000 dilution IV adrenaline 0.3ml	Patient developed dizziness, tunnel vision, mid-sternal chest pain and intermittent VT. Subsequent investigations normal	
			Case 2: Patient was given 1:1000 dilution IV adrenaline 0.2ml	Patient developed transient hypertension with reflective ECG changes but no evidence of myocardial ischaemia	
Brown <i>et al</i> , ¹⁹ 2004 Australia	21 healthy adults with systemic allergic reactions to diagnostic insect sting challenge	Subset of patients from a randomised, double blind, placebo controlled cross over trial Level 2	Requirement for IV adrenaline	19 of 21 subjects required IV adrenaline infusion at a median dose of 590µg over 115 mins	Study involved a small number of volunteers No control group was available for this subset of patients Several other drugs, including atropine, intravenous fluids, antihistamines and steroids, were also administered
			Efficacy of treatment	All subjects recovered rapidly with IV adrenaline treatment with or without volume resuscitation	
			Adverse events	4 of 19 patients developed complications, which were attributed to the allergic reaction, not to adrenaline	

IV = intravenous; MI = myocardial infarction; ECG = electrocardiogram; mins = minutes; TOE = transoesophageal echocardiogram; VT = ventricular tachycardia

Table 2: 7.1.2 Subcutaneous or intramuscular adrenaline for anaphylaxis

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Simons <i>et al</i> , 2001 ²⁰ Canada	13 healthy allergic men 18 to 35 years Injected at different study visits with IM adrenaline from an ampoule in the thigh; IM adrenaline via an EpiPen in the thigh; IM adrenaline in the upper arm; SC adrenaline in the upper arm; IM saline in the upper arm; and SC saline in the upper arm	Prospective, randomised, partially blinded, 6-way crossover study Level 2	Plasma adrenaline levels before and up to 180 mins after injection	Mean maximum plasma adrenaline concentration significantly higher after IM injection into the thigh than IM or SC injection into the arm	Small number of healthy subjects with 3-fold variation in body mass Absorption of IM vs SC adrenaline in the thigh or upper arm not directly compared Clinical significance unclear
			Adverse events	Similar for both routes and sites of injection	
Simons <i>et al</i> , 1998 ²¹ Canada	17 healthy children with a history of anaphylaxis Injected with IM adrenaline via auto-injector (n=9) or SC adrenaline (n=8)	Prospective, randomised, blinded, parallel group study Level 2	Plasma adrenaline levels	C _{max} significantly higher in IM vs SC group T _{max} significantly shorter in IM vs SC group	Small number of healthy subjects Clinical significance unclear
			Serious adverse events	None in either group	

IM = intramuscular; SC = subcutaneous; mins = minutes; C_{max} = peak plasma adrenaline concentration; T_{max} = time to peak plasma adrenaline concentration

Table 3: 7.1.3 Adrenaline self-injection for anaphylaxis in children

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Pumphrey <i>et al</i> , 1999 ¹⁷ UK	164 cases of fatality with anaphylaxis recorded as the cause of death between 1992 and 1998 (148 had records available for further analysis)	Analysis of registry data Level 4	Median time to respiratory or cardiac arrest	30 mins for foods (range 6–360), 15 mins for venom (range 4–120) and 5 mins for iatrogenic reactions (range 1–80)	Registry data, not specifically designed to answer this question Only fatal cases included; cases where adrenaline self-treatment prevented death therefore not included Adults and children included
			Details of patients who had been given adrenaline self-treatment kits	5 did not use the kit (not with patient in 2 cases, out of date in 1 case, may have collapsed too quickly in 1 case, found dead holding unused kit in 1 case (could not assemble it?))	

Table 3 Continued

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Gold <i>et al</i> , 2000 ²² Australia	68 children with a history of anaphylaxis who were prescribed EpiPens by the paediatric allergy service Data collected by telephone interview with parents	Retrospective telephone survey Level 4	Parental recall of method of administration with EpiPen	Only 16 (24%) of parents were able to recall all 4 steps required for the correct use of EpiPens; 5% could not recall any steps	Suboptimal study design to answer this question A prospective observational cohort would be more informative (randomised controlled trial would be ideal but probably unethical) Possible selection bias—the parents of only 80% of the patients identified were interviewed; 19% could not be contacted—their outcome is unknown No standard criteria for initial prescription of EpiPen Time since index reaction not standardised In-hospital adrenaline use apparently assessed by parental interview Severity of episodes not objectively measured
			EpiPen use in anaphylaxis	EpiPen given in 13/45 (29%) anaphylactic reactions Of those not given EpiPen, 15 (45%) were later given adrenaline in hospital Of those given EpiPen, 2/13 (15%) later received adrenaline in hospital (p<0.05)	
			Hospital admission	EpiPen not given: 15/32 (47%) admitted EpiPen given: 2/13 (15%) admitted (p<0.05)	
Colver <i>et al</i> , 2005 ²³ UK	229 cases of children (aged under 16 years) admitted to hospital with food allergic reactions between 1998 and 2000	Prospective survey Level 4	Death	3 children died One received adrenaline via auto-injector at home	Patients only included after reported hospital admission; Emergency Department attendances without admission not included
			Near fatal anaphylaxis	Occurred in 6 children In 3 children excess adrenaline administration (in hospital) was implicated in clinical deterioration	
			Potential reduction in severity by use of adrenaline autoinjectors	6 severe cases and 7 non-severe cases received adrenaline via auto-injector before arriving at hospital Auto-injectors could therefore have reduced the severity of a maximum of 13/229 reactions	
			Potential benefits if adrenaline autoinjectors had been more widely available	Of the 58 severe cases, a maximum of 6 could have benefited had autoinjectors been available to them (the remainder either did not have adrenaline at any point, already had an auto-injector but did not use it, had adrenaline	

				administered by primary care or ambulance staff within 10 mins, had not had a previous allergic reaction to food or were over 12 years old and their only previous reaction had been to allergens as babies)	
--	--	--	--	--	--

Mins = minutes

Table 4: 7.1.4 Adrenaline inhaler: An alternative to intramuscular adrenaline?

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Simons <i>et al</i> , 2000 ²⁷ Canada	19 asymptomatic children with a history of anaphylaxis and EpiPen prescription Treated with 10–20 inhalations of adrenaline (n=11) or placebo (n=8) over 2–4 minutes, depending on weight	Prospective randomized, observer-blind, placebo controlled, parallel group study Level 1	Ability to inhale dose required to achieve adequate plasma adrenaline concentration	2 of 11 children in the adrenaline group; 2 of 8 children in the placebo group	Small study in healthy individuals Adequate plasma adrenaline concentration difficult to define Assessed plasma concentrations but not clinical efficacy
			Percent of precalculated dose inhaled	74% adrenaline group; 89% placebo group	
			Plasma adrenaline levels	No significant difference between groups at any time point	
			Adverse effects	Unpleasant taste (10/11 adrenaline group; 4/8 placebo group) Cough (2/11 adrenaline group; 4/8 placebo group) Dizziness (3/11 adrenaline group; 3/8 placebo group) Nausea, pallor and muscle twitching (1/11 adrenaline group)	
Dahlof <i>et al</i> , 1987 ²⁸	Healthy volunteers given adrenaline by SC injection, nasal or oral inhalation, or eye drops	Prospective, crossover study Level 2	Plasma adrenaline levels	Significant increase within 5 minutes of SC administration; No increase after 10 inhalations; Significant increase after 20 inhalations; No significant increase after eye drops	Healthy volunteer study only Did not assess clinical efficacy
			Maximum cardiovascular effects	Within 15 mins of SC administration; After 20 inhalations but less pronounced than SC administration; No significant effect after eye drops	
			Duration of action	90 mins after SC administration; Shorter-acting after inhalation; No significant effect after eye drops	

SC = subcutaneous; mins = minutes

Table 5: 7.1.5 Sublingual adrenaline tablets: How feasible is this novel approach to treatment of acute allergic reaction?

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Rawas-Qalaji <i>et al</i> , 2006 ²⁹ Canada	5 New Zealand white rabbits Administered SL adrenaline 0mg, 10mg, 20mg and 40mg; and IM adrenaline 0.3mg on different days	Preclinical study	Plasma adrenaline levels	AUC, C _{max} and T _{max} not significantly different between SL adrenaline 40mg and IM adrenaline 0.3mg	Animal study; cannot be extrapolated to humans Clinical parameters not assessed

SL = sublingual; IM = intramuscular; AUC = area under the concentration–time curve; C_{max}= peak plasma concentration; T_{max} = time to peak plasma concentration

Table 6: 7.1.7 Adrenaline: site of administration

Injection of adrenaline in acute allergic reaction: Do the thighs look better than the deltoid? – Read the evidence

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Simons <i>et al</i> , 2001 ²⁰ Canada	13 healthy allergic men 18 to 35 years Injected at different study visits with IM adrenaline from an ampoule in the thigh; IM adrenaline via an EpiPen in the thigh; IM adrenaline in the upper arm; SC adrenaline in the upper arm; IM saline in the upper arm; and SC saline in the upper arm	Prospective, randomised, partially blinded, 6-way crossover study Level 2	Plasma adrenaline levels before and up to 180 mins after injection Adverse events	Mean maximum plasma adrenaline concentration significantly higher after IM injection into the thigh than IM or SC injection into the arm Similar for both routes and sites of injection	Small number of healthy subjects with 3-fold variation in body mass Absorption of adrenaline in the arm included results of SC as well as IM administration Clinical significance unclear

IM = intramuscular; SC = subcutaneous; mins = minutes

Table 7: 7.3.1 Mast cell tryptase and histamine levels in acute allergic reaction

Author, date and country	Patient group	Study type and level of evidence	Outcomes	Key results	Study weaknesses
Lin <i>et al</i> , 2000 ³⁶ USA	97 adult patients with symptoms of acute allergic reaction of <12 hours' duration	Prospective cohort study Level 2	Elevated plasma histamine (>10nmol/l)	42 of 89 patients	Small study Many patients had mild symptoms and did not have true anaphylaxis 9 patients had symptoms persisting >12 hours prior to blood sampling, which may have affected the results Timings of blood samples varied between patients
			Elevated serum total tryptase (>15ng/ml)	20 of 97 patients	
			Detectable β-tryptase (>1ng/ml)	23 of 96 patients	
			Correlations	No significant correlation between histamine and tryptase levels High correlation between histamine level and urticaria, erythema and initial heart rate (p≤0.001) Correlation between tryptase level and urticaria	
Brown <i>et al</i> , 2004 ³⁷ Australia	64 adults with a history of anaphylactic reactions to jack jumper ant sting Underwent sting challenge	Cohort of patients from a randomised, placebo controlled, venom immunotherapy trial Level 2	Severe systemic reaction	11 of 64 patients	Small number of patients included in analysis Wide confidence intervals Dispute over diagnostic cut-off levels for serum tryptase and histamine
			Diagnostic performance of peak tryptase levels in patients with severe reaction	Sensitivity 0.36 Specificity 0.89	
			Diagnostic performance of serial tryptase levels in patients with severe reaction	Sensitivity 0.73 Specificity 0.98	
			Diagnostic performance of peak histamine levels in patients with severe reaction	Sensitivity 0.70 Specificity 0.69	
			Diagnostic performance of serial histamine levels in patients with severe reaction	Sensitivity 0.60 Specificity 0.94	

APPENDIX 2: SEARCH FILTERS

Adrenaline filter

ADRENALIN\$.MP OR EPINEPHRIN\$.MP OR EPIPEN.MP
EPIPEN.MP OR EPI-PEN.MP OR "EPI-EZ PEN".MP OR "EPI EZ PEN".OR ANAKIT.MP OR EXP
EPINEPHRINE/ OR ADRENALINE.MP

Acute allergic reaction filter

ANAPHYLA\$.MP OR ALLERG\$.MP OR ACUTE ADJ ALLERGIC ADJ REACTION OR
HYPERSENSITIVITY
EXP ANAPHYLAXIS/ OR ANAPHYLA\$.MP OR EXP HYPERSENSITIVITY/ OR ALLERG\$.MP

Route filter

ROUTE OR INTRAMUSCULAR OR INTRAVENOUS OR SUBCUTANEOUS

Nebuliser and Inhaler filter

NEBULIS\$.MP OR INHAL\$.MP OR METERED ADJ DOSE OR PRESSURIZED ADJ METERED ADJ
DOSE

Site of injection filter

LATERAL ADJ THIGH OR VASTUS ADJ LATERALIS OR DELTOID OR UPPER ADJ ARM OR ARM

Outcome filter

EXP HOME CARE SERVICES/ OR OUTPATIENTS/ OR COMMUNITY.MP OR OUT-PATIENT\$.MP
OR SELF-ADMINISTR\$.MP OR HOME.MP OR EXP FIRST AID/ OR FIRST AID.MP) OR (EXP
INFANT MORTALITY/ OR EXP CHILD MORTALITY/ OR MORTALITY.MP OR EXP HOSPITAL
MORTALITY/ OR EXP MORTALITY/ OR EXP DEATH/ OR EXP "CAUSE OF DEATH"/ OR EXP
DEATH, SUDDEN/ OR DEATH.MP

Tablet filter

TABLET\$.MP OR SUBLINGUAL\$.MP

Hair dye filter

HAIR ADJ DYE AND HAIR OR SHAV\$.MP OR REOV\$.MP

Gastric lavage filter

GASTRIC ADJ LAVAGE

Investigation filter

MAST ADJ CELL ADJ TRYPTASE OR HISTAMINE ADJ LEVEL OR TRYPTASE ADJ LEVEL

Antihistamine filter

ANTIISTAMIN\$.MP OR HISTAMINE ADJ ANTAGONIST OR H1 ADJ BLOCKER

Discharge filter

ORAL OR ENTERAL OR PER ADJ ORAL OR DISCHARGE OR PRESCRIPTION

Corticosteroid filter

HYDROXORTISON\$.MP OR CORTICOSTEROIDS\$.MP OR PREDISOLON\$.MP OR
PREDNISON\$.MP

Cochrane Library search terms

(MeSH heading ANAPHYLAXIS) OR ANAPHYLA*
AND

(MeSH heading EPINEPHRINE) OR ADRENALINE OR EPINEPHRINE OR EPIPEN

REFERENCE LIST

- (1) Sampson H, Munoz-Furlong A, Campbell R, Adkinson N, Bock S, Branum A, Brown S, Camargo C, Cydulka R, Galli S, Gidudu J, Gruchalla R, Harlor A, Hepner D, Lewis L, Lieberman P, Metcalfe D, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons F, Thomas S, Wood J, Decker W. Second symposium on the definition and management of anaphylaxis - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *Ann Emerg Med* 2006; 47(4): 373-380.
- (2) Kemp S, Lockey R. Anaphylaxis: a review of causes and mechanisms. *J Allergy Clin Immunol* 2002; 110(3): 341-348.
- (3) McLean-Tooke A, *et al.* Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003; 327: 1332-1335.
- (4) Sheikh A, Shehata Y, Simons F. Adrenaline for the treatment of anaphylaxis with or without shock. *Cochrane Database of Systematic Reviews* 2006; Issue 4: CD006312. DOI:10.1002/14651858.CD006312.
- (5) The Food Allergy and Anaphylaxis Network. Common food allergens: FAAN, 2007. Available at: <http://www.foodallergy.org/allergens/index.html> [Accessed 23rd June, 2008].
- (6) Corrigan C. Allergy: the unmet need - A blueprint for better care. Royal College of Physicians; 2003.
- (7) Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Annals of Allergy, Asthma and Immunology* 2006; 97(5): 596-602.
- (8) Winberry S, Lieberman P. Histamines and antihistamines in anaphylaxis. *Clin Allergy Immunol* 2002; 17: 287.
- (9) Bohlke K, Davis R, DeStefano F, Marcy S, Braun M, Thompson R. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004; 113(3): 536-542.
- (10) Brown A, McKinnon D, Chu K. Emergency department anaphylaxis: A review of 142 patients in a single year. *J Allergy Clin Immunol* 2000; 108(5): 861-866.
- (11) Yocum M, Butterfield J, Klein J, Volcheck G, Schroeder D, Silverstein M. Epidemiology of anaphylaxis in Olmsted County: A population-based study. *J Allergy Clin Immunol* 1999; 104(2 Pt 1): 452-456.
- (12) Sadana A, O'Donnell C, Hunt M, Gavalas M. Managing acute anaphylaxis: Intravenous adrenaline should be considered because of the urgency of the condition. *BMJ* 2000; 320(7239): 937.
- (13) Working Group of the Resuscitation Council (UK). Emergency treatment of anaphylactic reactions: Guidelines for healthcare providers: Resuscitation Council, 2008. Available at: <http://www.resus.org.uk/pages/reaction.pdf> [Accessed 2nd June, 2008].
- (14) Brown A. Therapeutic controversies in the management of acute anaphylaxis. *J Accid Emerg Med* 1998; 15: 89-95.

- (15) Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. Levels of evidence and grades of recommendation: Oxford Centre for Evidence-Based Medicine, 2001. Available at: <http://www.cebm.net/index.aspx?o=1047> [Accessed 25th April, 2008].
- (16) Shaver K, Adams C, Weiss S. Acute myocardial infarction after administration of low dose intravenous epinephrine for anaphylaxis. *J Can Ass Emerg Phys* 2006; 8(4): 289-294.
- (17) Pumphrey R. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exper All* 2000; 30: 1144-1150.
- (18) Anchor J, Settignano R. Appropriate use of epinephrine in anaphylaxis. *Am J Emerg Med* 2004; 22: 488-490.
- (19) Brown S, *et al.* Insect sting anaphylaxis: prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J* 2004; 21: 149-154.
- (20) Simons F, Xioachen G, Simons K. Epinephrine absorption in adults: Intramuscular versus subcutaneous injection. *J Allergy Clin Immunol* 2001; 108: 871-873.
- (21) Simons F, Roberts J, Gu X, Simons K. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998; 101(1): 33-37.
- (22) Gold M, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). *J Allergy Clin Immunol* 2000; 106: 171-176.
- (23) Colver A, Nevantaus H, MacDougall C, *et al.* Severe food-allergic reactions in children across the UK and Ireland, 1998-2000. *Acta Paediatr* 2005; 94: 689-695.
- (24) Sampson H, Mendelson L, Rosen J. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380-384.
- (25) Bock S, Munoz-Furlong A, Sampson H. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001; 107: 191-193.
- (26) MacDougall C, Cant A, Colver A. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002; 86: 236-239.
- (27) Simons F, Gu X, Johnston L, Simons K. Can epinephrine inhalations be substituted for epinephrine injection in children at risk for systemic anaphylaxis. *Pediatrics* 2000; 106: 1040-1044.
- (28) Dahlof C, Mellstrand T, Svedmyr N. Systemic absorption of adrenaline after aerosol, eye-drop and subcutaneous administration to healthy volunteers. *Eur J All Clin Immunol* 1987; 42(3): 215-221.
- (29) Rawas-Qalaji M, Simons F, Simons K. Sublingual epinephrine tablets versus intramuscular injection of epinephrine: Dose equivalence for potential treatment of anaphylaxis. *J Allergy Clin Immunol* 2006; 117(2): 398-403.
- (30) Rawas-Qalaji M, Simons F, Simons K. Fast-disintegrating sublingual tablets: Effect of epinephrine load on tablet characteristics. *AAPS PharmSciTech* 2006; 7(2): E1-E7.

- (31) Zeggwagh A, Abougal R, Madani N, Abidi K, Moussaoui R, Zekraoui A, Kerkeb O. Comparative efficiency of nebulized adrenaline and salbutamol in severe acute asthma - A randomized controlled prospective study. *Annales Francaises d'Anesthesie et de Reanimation* 2002; 21: 703-709.
- (32) Turpeinen M, Kuokkanen J, Backman A. Adrenaline and nebulized salbutamol in acute asthma. *Arch Dis Child* 1984; 59: 666-668.
- (33) McFadden J, White I, Frosch P, Sosted H, Johansen J, Menne T. Allergy to hair dye. *BMJ* 2007; 334: 220.
- (34) European Food Information Council. Food allergy and food intolerance: EUFIC, 2006. Available at: <http://www.eufic.org/article/en/page/BARCHIVE/expid/basics-food-allergyintolerance/> [Accessed 23rd June, 2008].
- (35) Smit D, Cameron P, Rainer T. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med* 2004; 28(4): 381-388.
- (36) Lin R, Schwartz L, Curry A, Pesola G, Knight R, Lee H-S, Bakalchuk L, Tenenbaum C, Westfal R. Histamine and tryptase levels in patients with acute allergic reactions: An emergency department-based study. *J Allergy Clin Immunol* 2000; 106(1): 65-71.
- (37) Brown S, Blackman K, Heddle R. Can serum mast cell tryptase help diagnose anaphylaxis? *Emerg Med Aust* 2004; 16: 120-124.
- (38) Schwartz L, Yunginger J, Miller J, Bokhari R, Dull D. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989; 83: 1551-1555.
- (39) Laroche D, Vergnaud M-C, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. *Anesthesiol* 1991; 75: 945-949.
- (40) Sheikh A, VM ten Broek, Brown S, Simons F. H1-antihistamines for the treatment of anaphylaxis with or without shock. *Cochrane Database of Systematic Reviews* 2007; Issue 1: CD006160. DOI:10.1002/14651858.CD006160.pub2.
- (41) Moscati R, Moore G. Comparison of cimetidine and diphenhydramine in the treatment of acute urticaria. *Ann Emerg Med* 1990; 19(1): 12-15.
- (42) Runge J, Martinez J, Caravati E, *et al.* Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med* 1992; 21(3): 237-242.
- (43) Lin R, Curry A, Pesola G, *et al.* Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med* 2000; 36(5): 462-468.
- (44) Watson N, Weiss E, Harter P. Famotidine in the treatment of acute urticaria. *Clin Exp Dermatol* 2000; 25: 186-189.
- (45) Lieberman P. The use of antihistamines in the prevention and treatment of anaphylaxis and anaphylactoid reactions. *J Allergy Clin Immunol* 1990; 86(4 pt 2): 684-686.
- (46) Poon M, Reid C. Best evidence topic reports. Oral corticosteroids in acute urticaria. *Emerg Med J* 2004; 21(1): 76-77.

SUMMARY OF RECOMMENDATIONS

