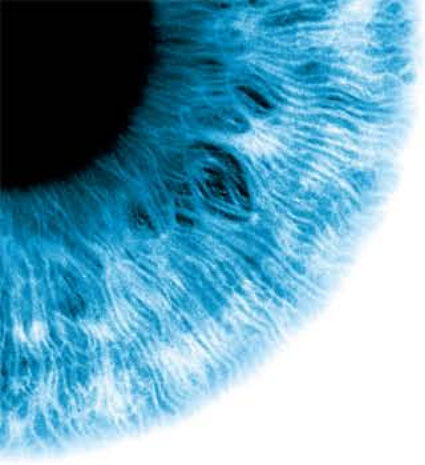

Anaphylaxis
Evidence Update March 2013

A summary of selected new evidence relevant to NICE clinical guideline 134 'Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode' (2011)

Evidence Update 36

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline available from the NHS Evidence topic page for anaphylaxis.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

National Institute for Health and Clinical Excellence

Level 1A
City Tower
Piccadilly Plaza
Manchester M1 4BT
www.nice.org.uk

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Contents

Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode. NICE clinical guideline 134 (2011).**

A search was conducted for new evidence from 23 August 2010 to 19 October 2012. A total of 8542 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 13 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Introduction		
• Across the UK during the period 2005–09, anaphylaxis accounted for an estimated 0.1% of admissions to paediatric critical care units and 0.3% of admissions to adult critical care units, with little difference in the proportions admitted from operating theatres and emergency departments.		✓
Assessment and the decision to refer after a suspected anaphylactic reaction		
• Introduction of a departmental protocol to aid clinical implementation of guidelines may result in improved care of children with anaphylaxis, including increased prescription of adrenaline, longer observation periods and better clinical follow-up.		✓
• Older adults (50 years and above) may be more likely than younger adults to present with cardiovascular symptoms of anaphylaxis.		✓
• Access to specialist allergy services for allergy testing for adults following a suspected anaphylactic reaction may be limited.		✓
• Evidence on the clinical effectiveness of adrenaline autoinjectors in emergency situations is limited, most probably by practical and ethical difficulties.		✓
Patient information after a suspected anaphylactic reaction		
• Healthcare professionals may need further training and support to ensure appropriate use of adrenaline autoinjectors.		✓
• Patients may have an ongoing need for information about anaphylaxis including the signs and symptoms of an anaphylactic reaction, what to do if an anaphylactic reaction occurs and the correct and appropriate use of adrenaline autoinjectors. Patients may also need training in the use of autoinjectors, which should incorporate psychological and emotional barriers to delivery as well as practical aspects.		✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

Introduction

NICE clinical guideline 134 (CG134) provides guidance on initial assessment and referral following emergency treatment for an anaphylactic episode. The guideline notes that there is no overall figure for the frequency of anaphylaxis from all causes in the UK, with patients presenting in both accident and emergency departments and in outpatient settings. Anaphylaxis may not be recorded, may be misdiagnosed (for example, as asthma) or recorded by cause (for example, food allergy). NICE CG134 recommended further research to establish the prevalence of anaphylactic reactions and related outcomes.

Frequency of admissions for anaphylaxis

Gibbison et al. (2012) analysed the frequency of admissions for anaphylaxis from critical care units in the UK over the period 2005–09. Referral pathways and outcomes were also studied. Information was taken from three national audits, available from the Intensive Care National Audit and Research Centre (covering 65–70% of the 230 adult general critical care units in England, Wales and Northern Ireland), the Scottish Intensive Care Society Audit Group (covering all 24 critical care units in Scotland) and the Paediatric Intensive Care Audit Network (collecting data from all 33 NHS paediatric critical care units in all areas of the UK). All physician-diagnosed cases of anaphylaxis during the study period were analysed, after the removal of duplicate data (arising from children treated in both adult and paediatric critical care units) and 1 case that appeared to be erroneously coded as anaphylaxis.

During the study period, on average each UK critical care unit saw at least 1 anaphylaxis case per year. There were 81 paediatric admissions with anaphylaxis (0.1% of the 77,392 admissions) and 1269 adult admissions with anaphylaxis (0.3% of the 460,213 adult admissions at the units covered by the audits). The number of adult admissions showed a significant increase from 2005 (183 out of 84,115 admissions, 0.2%) to 2009 (331 out of 95,196 admissions, 0.3%, $p<0.001$). Similar proportions of female (47%) and male (53%) children were admitted (rate ratio [RR]=0.88; 95% confidence interval [CI] 0.64 to 1.20) but there were significantly more adult female admissions than male (65% vs 35%, RR=1.83, 95% confidence interval [CI] 1.68 to 1.99).

Although many paediatric and adult anaphylaxis admissions were from emergency departments (42.0% and 37.3%, respectively), the study indicated that life-threatening anaphylaxis may originate in operating theatres almost as frequently (32.1% and 38.0% of admissions for children and adults, respectively). Admissions from wards (14.8% and 22.9%, respectively) and other routes (11.1% and 1.6%, respectively) accounted for the balance of admissions. Survival to discharge from the critical care unit was 95% (77 of 81) for children and survival to hospital discharge was 92% (1166 of 1269) for adults.

The authors noted some limitations in the analysis: incomplete coverage of general critical care units, potential inaccuracies in physician-recorded diagnosis at discharge and lack of information on investigations to confirm diagnosis. Nevertheless, this evidence provides national data from comprehensive, robust and validated sources. It is also likely to include patient admissions for anaphylaxis that were not previously reported, because earlier work relied on data from hospital episode statistics, which record only the primary reason for

hospital admission. Consequently, this evidence may provide context for NICE CG134. Although current guidance does not exclude anaphylaxis originating in hospital, it largely focuses on anaphylaxis originating in the community.

Key reference

Gibbison B, Sheikh A, McShane P et al. (2012) Anaphylaxis admissions to UK critical care units between 2005 and 2009. Anaesthesia 67: 833–8

1.1 Use and timing of mast cell tryptase testing in the anaphylaxis diagnostic pathway

No new key evidence was found for this section.

1.2 Duration of observation after a suspected anaphylactic reaction

No new key evidence was found for this section.

1.3 Assessment and the decision to refer after a suspected anaphylactic reaction

After assessment of the circumstances of the reaction, its clinical features and emergency treatment for suspected anaphylaxis, NICE CG134 recommends referral to a specialist (age-appropriate) allergy service. This should be provided by healthcare professionals with the skills and competencies necessary to investigate, diagnose, monitor and manage patients with suspected anaphylaxis. NICE CG134 also recommends that patients are offered an appropriate adrenaline injector as an interim measure while awaiting the specialist allergy service appointment.

Emergency department assessment and referral of anaphylaxis

Arroabarren et al. (2011) reported a retrospective study to compare the diagnosis, treatment and subsequent follow-up of children attending a paediatric emergency unit in a tertiary hospital in Spain, before and after the introduction of an anaphylaxis protocol. Discharge summaries for children attending the unit with anaphylaxis during the period 2006–07 (before the protocol was introduced) were compared with those for children attending with anaphylaxis during the 2 years (2008–09) after introduction of the protocol.

The records of children attending the unit with a discharge diagnosis of anaphylactic shock, urticaria, angioneurotic oedema, angioedema, and unspecified allergy were examined by three reviewers, and those providing sufficient written information to meet criteria for anaphylaxis were included in the study if identified by all reviewers. A total of 31 children (median age 3 years, range 0.2 to 13 years) met inclusion criteria for the period before protocol introduction and were compared with the 33 children (median age 4 years, range 0.5 to 13 years, p=0.1) who met the inclusion criteria for the period following introduction of the protocol.

Following the introduction of the protocol, the proportion of children treated with adrenaline increased from 27% to 58% (p=0.012). The number of children admitted to the paediatric emergency observation area increased significantly from 15 (49%) to 28 (85%, p=0.003). The median length of observation increased from 2.5 hours (range 0.5 to 72 hours) to 9 hours (range 0.5 to 12 hours, p=0.003). This fell somewhat short of the recommended duration of observation stated in the protocol (12 hours), but the authors considered that this covered the risk period for a biphasic reaction. Other significant changes in care included the increased prescription of self-administered adrenaline devices (from 7% of patients to 58% after

introduction of the protocol, p<0.0005) and reduced discharge without follow-up instructions (from 69% to 22%, p=0.001).

The authors acknowledged limitations relating to the observational design of the study and to the definition of anaphylaxis, which was based on criteria that have not been universally accepted. However, although the study setting and specific recommendations in the protocol used differed in detail from those in NICE CG134, the evidence shows the improvement in patient care that may occur when guidelines are implemented.

Key reference

Arroabarren E, Lasa EM, Olaciregui I et al. (2011) Improving anaphylaxis management in a pediatric emergency department. Pediatric Allergy and Immunology 22: 708–14

Assessment and referral of adults aged 50 years and above

Campbell et al. (2011) conducted a retrospective cohort study of patients to investigate assessment, management and referral of older adults following presentation at a hospital emergency department. The study was conducted in a tertiary referral hospital (approximately 80,000 visits per year) in Minnesota, USA during the period April 2008 to June 2010. Records of patients diagnosed with anaphylaxis, allergic reactions, insect stings and related diagnoses were examined, and patients meeting national criteria for the diagnosis of anaphylaxis were invited to participate in the study. Of 224 patients identified, 220 agreed to participate in the study. Most patients (90.5%) were white, and 58.2% were female. The median age of patients was 33.6 years (interquartile range [IQR] 18.8 to 49.6 years). A total of 54 patients (24.5%) included in the study were aged 50 years or older, with 28 of these patients (12.7% of the total sample) aged 65 years or older.

Compared with younger patients, those aged 50 years or older were less likely to have a history of asthma (11.1% vs 27.7%, p=0.02), and the suspected cause of the reaction was less likely to be food (14.8% vs 42.2%, p<0.001) and more likely to be contrast medium (14.8% vs 3.0%, p=0.001). Similar findings were reported for patients aged 65 years and above compared with younger patients (asthma history 7.1% vs 26.0%, p=0.03; food as suspected cause 14.3% vs 38.5%, p=0.01; contrast medium as suspected cause 21.4% vs 3.6%, p=0.002). The likelihood of most presenting symptoms was not significantly different across the age groups studied. However, older patients were more likely to present with cardiovascular symptoms (55.6% of patients aged 50 years and above vs 30.1% of younger patients, p<0.001; 64.3% of patients aged 65 years and above vs 32.3% of younger patients, p=0.001). Of the individual cardiovascular symptoms considered, hypotension showed the only age-related difference in occurrence in patients aged 65 years and above (21.4%) compared with younger patients (6.8%, p=0.02).

Patients aged 65 years and above were more likely than younger patients to be discharged from the emergency department to an intensive care unit (21.4% vs 8.3%, p=0.04) or a general medical department (21.4% vs 6.3%, p=0.02). Both groups of older adults were significantly less likely to be discharged directly to home (35.2% of patients aged 50 years and above vs 56.6% for younger patients, p=0.006; 32.1% of patients aged 65 years and above vs 54.2% for younger patients, p=0.023). There was no age-related difference in the proportion of patients referred for specialist allergy follow-up (p value not reported).

With regard to treatment, patients aged 50 years and above, and aged 65 years and above were significantly less likely than younger patients to have self-injected adrenaline prescribed (40.7% vs 63.3%, p=0.004; 32.1% vs 61.5%, p=0.003, respectively), and were significantly less likely to have been prescribed self-injected adrenaline previously (9.3% vs 30.7%, p=0.002; 3.6% vs 28.7%, p=0.04, respectively).

Limitations of this evidence include the lack of ethnic mix in the included population, the US care setting, and the inherent difficulties with studies of this design that depend on the quality

of information in patient records. Nevertheless, this study provides useful information relating to the causes of anaphylaxis and presenting symptoms in older adults. The use of self-injected adrenaline may appear lower in these patients than expected from recommendations in NICE CG134. However, such prescribing may be appropriate given the limited risk for future exposure to hospital-related triggers (contrast medium), which the study showed were a frequent cause of anaphylaxis in older patients in this population.

Key reference

Campbell RL, Hagan JB, Li JTC et al. (2011) Anaphylaxis in emergency department patients 50 or 65 years or older. Annals of Allergy, Asthma & Immunology 106: 401–6

Access to specialist allergy services

Burton et al. (2010) conducted a qualitative study of patients who had or perceived themselves to have serious allergies, to investigate the experience of obtaining allergen testing. The study was conducted in the Lothian region of Scotland. The patients included in the study were recruited through 7 general practices, a paediatric allergy clinic and via the Anaphylaxis Campaign, which emailed local membership with details of the study. Patients who responded to the initial invitation to participate, which included a short questionnaire designed to enable selection of a maximum variation sample, were followed up by telephone to answer any further questions, and if appropriate, to arrange an interview. Of the 20 in-depth interviews conducted, 13 were with adult patients (6 with a history of anaphylaxis and 7 with a range of allergic or possibly allergic conditions) and 7 were parents of children with a history of anaphylaxis (or at high risk of anaphylaxis).

Among children who developed anaphylaxis with no previous signs of severe allergy, allergen testing was conducted as part of the initial evaluation in hospital or shortly afterwards. These tests were seen as part of the routine process of care, giving results that confirmed the apparent trigger. For the children who had indicators of severe food allergy before the first episode of anaphylaxis, the accounts were characterised by reports of prior parental concern being dismissed. Test results were described as unhelpful or perplexing, although interpretation by a specialist was seen as a useful source of information. In contrast to the children (who had all been assessed and tested in a specialist clinic), adults with anaphylaxis reported difficulty obtaining allergy tests. Most adults had not been tested. Adults with anaphylaxis reported that their GPs were supportive but unable to help because there was no specialist service for referral of patients. None of the adults classified as at low risk of anaphylaxis had received allergen testing.

The study has a number of limitations. Despite efforts to obtain a broad socioeconomic spread, the authors reported that all but 1 participant was of white British origin and most had professional or skilled occupational backgrounds. It is therefore not possible to generalise the findings from this urban area of Scotland to other areas of the UK. Furthermore, there is an inherent risk of bias in selecting patients for studies of this type. Despite these caveats, the study indicates that access to allergy testing may be limited, at least in Lothian. The study also highlights the importance of specialist interpretation of test results, as part of an expert package of care for patients with, or at high risk of, anaphylaxis, which is consistent with the recommendations of NICE CG134 for referral to specialist allergy services.

Key reference

Burton C, Irshad T, Sheikh A (2010) Understanding the experiences of allergy testing: a qualitative study of people with perceived serious allergic disorders. Postgraduate Medical Journal 86: 591–6

Adrenaline injectors

A Cochrane review by **Sheikh et al. (2012)** considered the effectiveness of adrenaline autoinjectors for the community-based treatment of anaphylaxis, with or without cardiovascular collapse. After removal of duplicates, 1328 publications were identified.

However, no publications met the inclusion criteria (randomised and quasi-randomised controlled trials comparing adrenaline autoinjector use with placebo, no intervention or other adrenergic treatments). Therefore, no conclusions regarding the effectiveness of adrenaline autoinjectors could be drawn based on this evidence, with no impact on NICE CG134. The lack of studies for inclusion in the review highlights the practical and ethical difficulties of obtaining data on the effectiveness of adrenaline autoinjectors for the emergency treatment of anaphylaxis.

Key references

Sheikh A, Simons FER, Barbour V et al. (2012) Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. Cochrane Database of Systematic Reviews issue 8: CD008935

1.4 Patient information after a suspected anaphylactic reaction

Before discharge, NICE CG134 recommends that a healthcare professional with the appropriate skills and competencies should offer patients (or their parents or carer) information on anaphylaxis, including the correct use of the adrenaline injector device.

Healthcare professional skills and competencies

Johnson et al. (2012) evaluated the prescription of adrenaline autoinjectors by paediatric allergists and general paediatricians. The study consisted of an online survey conducted from February 2009 until October 2010 that presented 10 paediatric allergy case histories. Although only 1 case specifically mentioned anaphylaxis, all described severe allergic reactions in children aged from 10 months to 15 years. Respondents (54 paediatric allergists and 27 general paediatricians) were asked about any relevant guidelines they had read. For each case, respondents were asked whether or not they would prescribe an adrenaline autoinjector and about factors influencing their prescribing decision. Considered against the guidelines from the European Academy of Allergology and Clinical Immunology, an adrenaline autoinjector should have been prescribed in 5 of the cases, considered in 1 case and not prescribed in 4 cases.

There was significant variability in prescribing practices. Although all allergists and generalists prescribed an autoinjector (94.4% and 92.6%, respectively) or would offer the patient a choice about autoinjectors (5.6% and 7.4%, respectively) in the case specifically mentioning anaphylaxis, many cases had almost no consensus on prescription of adrenaline autoinjector. The prescribing patterns of allergists and generalists showed no significant differences for 9 of the cases. For the remaining case, which described a child with oral allergy syndrome, all specialists (n=54, 100%) reported that they would not prescribe an autoinjector (in line with guidelines) compared with only 20 (74.1%) of generalists ($p<0.001$).

Allergists were significantly more likely than generalists to have read at least one relevant guideline (51 of 54, 94.4% vs 19 of 27, 70.4%, $p=0.005$). Most respondents prescribed according to the guidelines for some cases but not for others. Guidelines did not have a significant effect on prescribing decisions in any of the cases, although other case-dependent factors (for example, history of previous reaction to nuts, distance from medical facilities and parental anxiety) did significantly affect prescribing decisions.

This evidence, based on hypothetical prescribing decisions surveyed before NICE CG134 was published, has limitations inherent in the study design and the self-selection of respondents. Nevertheless, it suggests a need for further training and support of healthcare professionals to ensure guideline implementation and appropriate use of adrenaline autoinjectors. Two further studies, by **Arga et al. (2011)** and **Lowe et al. (2010)**, were identified that also support this view, although limitations restrict the relevance of the evidence.

Arga et al. (2011) studied the ability of physicians to use adrenaline autoinjectors in four tertiary hospitals in Ankara, Turkey. All physicians in general paediatric departments were included, but specialists in allergy were excluded from the study. Assessment was with a questionnaire and a practical session using an adrenaline autoinjector training device. The assessments were carried out before and 6 months after a lecture on anaphylaxis with demonstration of autoinjector use. Of 196 participants, 151 (77%) completed all assessments. Correct use of the autoinjector improved from 23.3% of participants to 74.2%, with a reduction in the mean time taken for administration from 28.01±6.22 seconds to 19.62±5.01 seconds ($p<0.001$ for each comparison). Although conducted in a non-UK setting, the study supports the importance of providing healthcare professionals with an educational programme to ensure the correct use of autoinjectors, and highlights the importance of repeating training to reinforce learning.

Lowe et al. (2010) surveyed all GPs in Scotland using a questionnaire to find out how patients with potentially life-threatening allergies are managed. The survey found that 90% of the 613 respondents had prescribed adrenaline autoinjectors. However, only 49% of respondents were confident in use of these devices, and only 17% had access to a trainer pen for demonstration to patients. If called upon in an anaphylactic emergency (experienced by 36% of respondents), only 50% of respondents would use the appropriate dose and 14% would use an inappropriate route of administration (subcutaneous or intravenous).

The survey also covered referral to specialist centres. Although 31% of respondents reported ready access to secondary care for investigation and advice about anaphylaxis, 17% reported access but with prolonged waiting times and 24 respondents noted that specialist referral was only available for paediatric cases. Access to secondary care support was not readily available according to 40% of respondents, and 12% did not answer this question. In open comments about anaphylaxis and the provision of allergy care, 153 respondents emphasised the need for specialist advice or clinics, 61 thought that provision of care was poor, 50 felt ill-prepared and required training, 19 respondents stated that allergy was under-recognised or under-resourced, and 17 found anaphylaxis management scary and stressful.

Limitations of the study include the restricted sampling area (Scotland) and low response rate (16.6%), so that findings cannot be extrapolated to the UK as whole. However, the evidence highlights shortcomings in the skill levels of non-specialist healthcare professionals who may be involved in anaphylaxis management, given the difficulties of access to specialist allergy services.

The studies by Arga et al. (2011) and Lowe et al. (2010) support the need for training of healthcare professionals in the use of adrenaline autoinjectors, as recommended in NICE CG134.

Key references

Arga M, Bakirtas A, Catal F et al. (2011) Training of trainers on epinephrine autoinjector use. Pediatric Allergy and Immunology 22: 590–3

Johnson MJ, Foote KD, Moyses HE et al. (2012) Practices in the prescription of adrenaline autoinjectors. Pediatric Allergy and Immunology 23: 124–7

Lowe G, Kirkwood E, Harkness S (2010) Survey of anaphylaxis management by general practitioners in Scotland. Scottish Medical Journal 55: 11–4

Patient education on anaphylaxis and autoinjector use

Noimark et al. (2011) conducted a prospective, questionnaire-based study to assess the use of adrenaline autoinjectors during anaphylactic reactions, and to determine why they were not used in situations in which they were clinically indicated. The questionnaire to ask respondents about allergic reactions experienced in the previous year was developed by a team of paediatric allergists, and refined following feedback from the Paediatric Allergy Group

e-forum and piloting with 368 patients. Participants were children and young people up to the age of 18 years who attended 14 paediatric allergy clinics throughout the UK and had been prescribed an adrenaline autoinjector for at least a year. There were no specific exclusion criteria. A total of 969 patients (mean age 8.6 years, 58.7% males, 63.5% white) were identified who satisfied the inclusion criteria and all agreed to participate in the survey.

A total of 466 participants experienced an allergic reaction in the previous year (48.1%, 95% CI 37.9 to 58.2%). Of these patients, 245 (52.6%, 95% CI 43.1 to 62.1%) experienced anaphylaxis (defined as loss of consciousness, difficulty swallowing, feeling of impending doom, difficulty breathing, wheeze, throat tightness, change in voice, or dizziness). Only 41 of these patients (16.7%, 95% CI 11.7 to 21.3%) used their adrenaline autoinjector.

Multivariate analysis showed that symptoms most likely to result in autoinjector use were loss of consciousness (odds ratio [OR]=5.51, 95% CI 1.31 to 22.51), difficulty swallowing (OR=3.07, 95% CI 1.36 to 6.33), feeling of impending doom (OR=3.52, 95% CI 1.18 to 11.40), difficulty breathing (OR=2.59, 95% CI 1.15 to 4.82), and swelling (OR=3.44, 95% CI 1.74 to 7.63). Adrenaline was administered by parents (n=26, 55%), healthcare professionals (n=18, 38%) or the patient (n=2, 4%). Of the 41 patients with anaphylaxis in the previous year who had used their autoinjector, 13 (32%, 95% CI 10.2 to 55.0) received more than 1 dose.

The 204 participants who experienced anaphylaxis in the previous year but did not use their autoinjector reported that this was primarily because they thought it was unnecessary (54.4%) or were unsure if it were unnecessary (19.1%). Other reasons given were that they had called an ambulance (7.8%), the device was not available (5.4%), they were too scared to use it (2.5%), they were not trained in its use (2.5%), they attended an emergency department (1.5%) or the device was out of date (1.0%).

Limitations of the study acknowledged by the authors included the lack of data on socioeconomic status. Other limitations include the self-reported nature of the study design and the potential variability in diagnosis of patients from different centres. Furthermore, information was not collected on whether the use of a second dose of adrenaline was clinically appropriate, or on the symptoms prompting the use of additional adrenaline. However, the low level of autoinjector use in children and young people experiencing anaphylaxis in the UK, even when clinically indicated during an anaphylactic episode, highlights the importance of education on when and how to use these devices.

Gallagher et al. (2011) undertook a qualitative study in Scotland to explore the attitudes of young people with a history of anaphylaxis (and their parents) towards adrenaline autoinjectors. Potential participants were recruited from locations across Scotland via school nurses, allergy specialists, primary care, a patient support group and a press release. Patients included in the study were defined as adolescents who had experienced anaphylaxis in the last 5 years or with an earlier reaction or testing indicating high risk of anaphylaxis. Those who had experienced only mild reactions or reactions in early childhood were excluded.

Of 45 young people identified as potential participants, 29 were deemed eligible for inclusion and 26 patients agreed to participate (age range 13–19 years, 54% male, all but one prescribed an autoinjector). These patients, and their parents (n=28), were included in the study. Individual, in-depth, semi-structured interviews (approximate duration 1 hour) were carried out with all participants, predominantly face-to-face. Following preliminary analysis of the interview data, participants were invited to focus groups to discuss possible interventions including improvements to autoinjector design and training. A total of 8 patients and 10 parents participated in focus groups.

Of the 25 young people prescribed an autoinjector, 18 had anaphylaxis when autoinjectors were close to hand but 11 reported not using their autoinjector. Barriers were identified at all

stages required for the appropriate use of an autoinjector: training in its use, carrying and storing the device, correct identification of an anaphylactic reaction, making the decision to administer adrenaline, and correct administration technique. Overall, there appeared to be a tendency for patients and their parents to focus on ensuring autoinjectors are carried at all times, while neglecting other barriers that precluded appropriate and effective use.

As noted by the authors, the small number of participants in qualitative studies such as this precludes generalisation of the findings to other patients or settings. There may also be some methodological concerns regarding the role of the researcher and how the analysis was conducted. Nevertheless, the study enhances understanding of the multiple and complex barriers to use of autoinjector devices appropriately and effectively in young people.

Taken together, the evidence from these studies highlights the ongoing need that patients have for information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction, what to do if an anaphylactic reaction occurs, and the correct and appropriate use of adrenaline autoinjectors, consistent with the recommendations of NICE CG134. The evidence also suggests that autoinjector training should be comprehensive, addressing psychological and emotional barriers to the use of emergency medication as well as practical aspects. Three further studies, by **DeMuth and Fitzpatrick (2011)**, **Amirzadeh et al. (2010)** and **Segal et al. (2012)**, were identified that were consistent with these findings, although limitations preclude drawing firm conclusions from this evidence.

DeMuth and Fitzpatrick (2011) determined the proportion of children with food allergy having their adrenaline autoinjector readily available, and factors associated with carrying it at all times. The study was conducted at a paediatric allergy centre in the USA and included consecutive children presenting to the centre with a history of physician-diagnosed food-allergy who had previously been prescribed an adrenaline autoinjector. Exclusion criteria included no evidence of food allergy and children or parents unwilling to participate in the study. A total of 63 children (mean age 6.4 years, 68% male) were included.

Parents of the children completed a questionnaire on preparedness to treat a food allergy, including availability of the child's autoinjector and training of the parents and school in its use. Staff also recorded whether the child had the autoinjector available during the clinic visit. Only 59% of children had their autoinjector with them at the clinic, but this was significantly more likely among children of the 79% of parents who reported being trained in adrenaline autoinjector use (adjusted OR=8.74, 95% CI 1.69 to 45.04). However, only 33% of parents reported that children had their autoinjector with them at lunchtime (42% for children under 5 years compared with 25% for school-age children, p=0.002). Limitations of the study identified by the authors include the presence of the autoinjector at the clinic visit as an outcome measure, misclassification bias due to the definition of food allergy used, recall bias that may affect questionnaire answers, lack of questionnaire validation and the small number of participants.

Amirzadeh et al. (2010) assessed the proportion of adults regularly carrying their adrenaline autoinjector, and knowledge about its use. The study was conducted at an allergy centre in the USA and included adults presenting at the centre during January to July 2009 who had been prescribed an adrenaline autoinjector. A total of 66 patients (mean age 50 years, 66.7% male) completed a questionnaire. Patients were diagnosed with food allergy (n=23, 35%), drug allergy (n=19, 29%, including 9 patients given adrenaline autoinjectors prophylactically for omalizumab injections), idiopathic or autoimmune angioedema (n=16, 24%), stinging insect reactions (n=3, 5%) and other diagnoses (n=5, 8%). Most patients (88%) had never used their autoinjector, although 92% stated that they knew how to use it. However, only 58% of participants carried their device at all times, but these patients were significantly more likely to refill their prescription than patients not regularly carrying the autoinjector (95% vs 59%, $p<0.05$). Limitations of the study identified by the authors include a possible overestimate of

ability to use the autoinjector because participants did not need to demonstrate use, a risk of bias in that the questionnaire was conducted over the telephone by the physician rather than anonymously, and the inclusion of patients receiving omalizumab automatically given an autoinjector.

Segal et al. (2012) determined the benefit of an instruction session on the use of an adrenaline autoinjector, with follow-up instruction. The study was conducted in a paediatric allergy centre in Israel and included patients who had been referred by a hospital ward or primary care physician and subsequently received a confirmed diagnosis of anaphylactic reaction. According to the protocol at the centre, all such patients and their parents received an individualised written emergency plan and instructions for use of an adrenaline autoinjector, with training in its use provided in the clinic by a physician. At the next clinic visit, children (aged over 12 years) or their parents (for children younger than 12 years) were asked to complete a questionnaire and demonstrate autoinjector use with a training device.

The study population was recruited from patients attending the clinic during June 2006 to June 2009. A total of 141 children were included in the study (median age 5.8 years, range 22 months to 23.4 years, 66% male, 83% with anaphylaxis caused by food allergy, 12 children >12 years). Most of the patients or parents (77%) were able to cite at least 2 symptoms of systemic allergic reaction, 75% knew what to do in an emergency and all (100%) reported that the autoinjector was carried at all times. However, only 47% of participants had the autoinjector with them at the clinic visit and in 21% of these cases, the device had passed its expiry date, so only 37% of participants carried a valid autoinjector at the time of the survey.

During the demonstration of use, 38% of participants did not remove the cap, 34% did not hold the device correctly, 31% did not position and activate the device correctly, 62% did not hold the device in place for 10 seconds, and 87% did not massage the injection site. A subgroup of participants (n=41, 29%) who were evaluated again at a second follow-up visit after a mean of 1 year showed improved questionnaire scores (from a mean of 4.7 to 6.7, $p<0.001$) and reduced failure to remove the training device cap (15%). The authors concluded that repeated training in the use of autoinjectors is needed. Lack of detail about the selection of participants and potential confounders limit the strength of the evidence.

Taken together, the studies by DeMuth and Fitzpatrick (2011), Amirzadeh et al. (2010) and Segal et al. (2012) are consistent with other evidence confirming the need for patient education on autoinjectors, as noted in NICE CG134.

Key references

Amirzadeh A, Verma P, Lee S et al. (2010) Epinephrine auto-injector use and demographics in a Veterans Administration population. Allergy and Asthma Proceedings 31: 304–7

DeMuth KA, Fitzpatrick AM (2011) Epinephrine autoinjector availability among children with food allergy. Allergy and Asthma Proceedings 32: 295–300

Gallagher M, Worth A, Cunningham-Burley S et al. (2011) Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. Clinical & Experimental Allergy 41: 869–77

Noimark L, Wales J, Du Toit G et al. (2011) The use of adrenaline autoinjectors by children and teenagers. Clinical & Experimental Allergy 42: 284–92

Segal N, Garty B-Z, Hoffer V et al. (2012) Effect of instruction on the ability to use a self-administered epinephrine injector. Israel Medical Association Journal 14: 14–7

1.5 Models of care for the diagnosis of anaphylaxis

No new key evidence was found for this section.

New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Assessment and the decision to refer after a suspected anaphylactic reaction

- Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community

Further evidence uncertainties for anaphylaxis can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Anaphylaxis. NICE clinical guideline 134 (2011).

Searches

The literature was searched to identify systematic reviews and studies (RCTs, observational and qualitative) relevant to the scope. Searches were conducted of the following databases, covering the dates 23 August 2010 (the week after the end of the search period for NICE clinical guideline 134) to 19 October 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PreMEDLINE
- PsycINFO

The original guideline search had a number of separate strategies to answer specific clinical questions. The search for evidence for the Evidence Update was based on search terms for anaphylaxis taken from the reference guidance search. Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above.

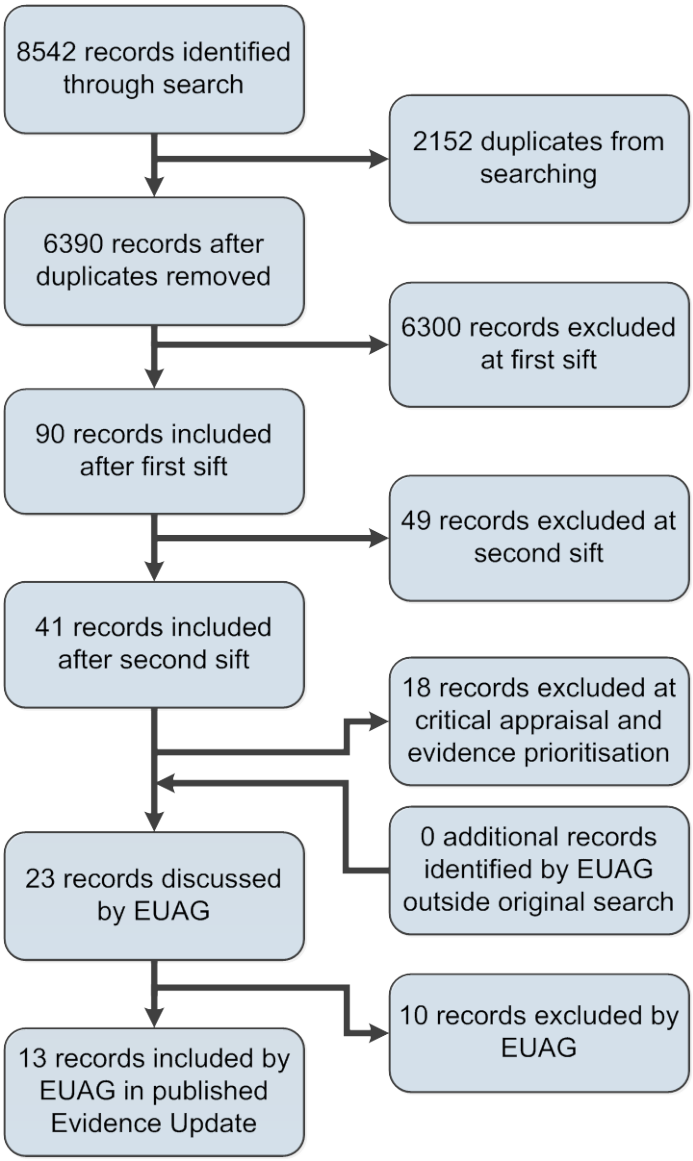
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Anaphylaxis/
2	Anaphylactic shock/
3	Anaphyla*.ti,ab.
4	(severe* or immediate* or acute*) adj3 (allerg* or hypersensitiv*)
5	Or/1-4

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

Professor Peter Howdle – Chair

Emeritus Professor of Clinical Medicine, University of Leeds

Dr Trevor Brown

Consultant Paediatric Allergist, The Ulster Hospital, Belfast

Sue Clarke

Nurse Advisor, Anaphylaxis Campaign

Dr Matthew Doyle

GP, Cromwell Place Surgery, St Ives, Cambridgeshire

Dr Pamela Ewan

Consultant Allergist, Cambridge University Hospitals NHS Foundation Trust

Dr Nigel Harper

Consultant Anaesthetist, Central Manchester University Hospitals NHS Foundation Trust

Dr Prashant Kumar

Consultant Paediatrician, City Hospital Sunderland NHS Trust

Lynette Williams

Paediatric Respiratory and Allergy Nurse Specialist, Shrewsbury and Telford Hospitals NHS Trust

Evidence Update project team

Marion Spring
Associate Director

Tom Quinn
Clinical Lead

Cath White
Programme Manager

Fran Wilkie
Project manager

Wesley Hubbard
Information specialist

Diane Storey
Medical Writer