Anaphylaxis: assessment and referral after emergency treatment (2016) NICE guideline CG134

Summary of new evidence from surveillance

Recommendations

134–01 What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

Recommendations derived from this question

1.1.1 Document the acute clinical features of the suspected anaphylactic reaction (rapidly developing, life-threatening problems involving the airway [pharyngeal or laryngeal oedema] and/or breathing [bronchospasm with tachypnoea] and/or circulation [hypotension and/or tachycardia] and, in most cases, associated skin and mucosal changes).

1.1.2 Record the time of onset of the reaction.

1.1.3 Record the circumstances immediately before the onset of symptoms to help to identify the possible trigger.

Surveillance decision

This review question should not be updated.

2-year evidence update

One retrospective cohort study[1] investigated the assessment, management and referral of patients aged 50 years and above after presenting at the emergency department of a tertiary referral hospital. Authors reported that 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). Hypotension occurred in significantly more patients who were 65 years and above (21.4%) compared with younger patients (6.8%, p=0.02).

The evidence update highlighted that limitations of the evidence included a lack of ethnic diversity in the study sample and the fact that the study was conducted in a US care setting.

A qualitative study[2] explored the experience of obtaining allergen testing in patients who had or perceived themselves to have serious allergies. 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.

It was considered that the study highlighted 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. This was considered to be consistent with recommendations in CG134 for referral to specialist allergy services.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The 2-year evidence update highlighted 2 studies. One study compared the assessment, management and referral of patients in different age groups; however, the study population and location were not applicable to a UK context. The second study highlighted the importance of specialist interpretation of test results, as part of an expert package of care. This was consistent with guideline recommendations.

No additional evidence or topic expert feedback was identified at the 4-year surveillance review that would change these conclusions.

New evidence is unlikely to change guideline recommendations.

134–02 Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?

Recommendations derived from this question

1.1.4 After a suspected anaphylactic reaction in adults or young people aged 16 years or older, take timed blood samples for mast cell tryptase testing as follows:

- a sample as soon as possible after emergency treatment has started.
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

1.1.5 After a suspected anaphylactic reaction in children younger than 16 years, consider taking blood samples for mast cell tryptase testing as follows if the cause is thought to be venom-related, drug-related or idiopathic:

- a sample as soon as possible after emergency treatment has started.
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

1.1.6 Inform the person (or, as appropriate, their parent and/or carer) that a blood sample may be required at follow-up with the specialist allergy service to measure baseline mast cell tryptase.

Surveillance decision

This review question should not be updated.

2-year evidence update
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback

Topic experts highlighted studies that supported the use of mast cell tryptase.

One prospective observational study[3] assessed mast cell tryptase levels in children during an anaphylactic reaction and at 9-month follow-up. A total of 203 children had serum tryptase levels measured; of these, 39 children (19.2%) had elevated levels. Severe cases were associated with reaction levels of 11.4µg/L or more (Odds ratio [OR], 6.5; 95% Confidence Interval [CI], 2.2 to 19.0). Anaphylaxis, triggered by ingestion of milk, was associated with increased tryptase levels (OR, 4.0; (95% CI, 0.95 to 7.0). Authors stated that "reaction levels exceeding the threshold of 2n/mL + 1.2 x (postreaction tryptase level) detected most of the anaphylactic reactions, particularly if baseline levels were taken within 2 months of the reaction".

A cohort study[4] examined mast cell tryptase levels in 102 patients presenting with acute anaphylaxis. Serum tryptase was measured at baseline, and 1 to 2 hours, 4 to 6 hours and 12 to 24 hours following onset of the anaphylactic episode. Tryptase concentrations 1 to 2 hours post-onset were significantly higher than levels at baseline, 4 to 6 hours and 12 to 24 hours. Tryptase was not raised in in 36.3% of cases. Additionally, no changes between baseline levels and levels measured 1 to 2 hours post-onset were observed in 60.6% of patients. Authors report that tryptase levels were significantly higher in more severe anaphylaxis and there was a positive correlation with the grades of severity. Anaphylaxis was significantly more severe and tryptase levels were significantly higher when the anaphylactic trigger was a drug compared to food, at baseline and 1 to 2 hours post-onset. Age and coronary risk factors were also significantly associated with more severe anaphylaxis.

In another prospective observational study[5] serum tryptase levels were measured in 39 patients with shrimp allergy who underwent shrimp challenges. Of the 39 patients, 12 patients had anaphylactic reactions, 20 had mild allergic reactions and 7 had no symptoms (control group). The peak tryptase levels were significantly higher than baseline in patients who had anaphylactic reactions. Furthermore, delta-tryptase (peak tryptase levels minus baseline values) and tryptase ratios were higher in the anaphylaxis group compared to the mild reaction and control groups. The manufacturer's cut-off for peak tryptase was >11.4 µg/L with 17% sensitivity, 100% specificity. Authors stated that the optimum cut-off for peak tryptase to confirm anaphylaxis was 2.99 µg/L with 50% sensitivity and 85% specificity.

In 1 prospective observational study[6] histamine and tryptase levels were measured in patients who had a reaction suggestive of hypersensitivity during general anaesthesia. Measurements were taken at baseline, at the time of the reaction and 2 hours later. Allergy tests were performed 4 to 8 weeks after the reaction to confirm allergic triggers. In total 37 patients who exhibited hypersensitivity and completed allergy tests were included. Elevated plasma histamine was recorded in 92% (34/37) of patients whereas tryptase exceeded twice the basal values in 31% (10/37) of patients. Authors stated that the median tryptase level for IgE-mediated reactions was 9.0 µg/L (2-70 µg/L) and 4.0 µg/L (3-13 µg/L) in non-IgE-mediated reactions. Median tryptase levels were found to be higher in more severe reactions. The best serum tryptase ratio (during reaction/baseline) to distinguish IgE and non-IgE reactions was 2.0.

One prospective observational study[7] used receiver operated characteristic (ROC) curves to evaluate the diagnostic performance of tryptase in 55 patients who experienced anaphylactic reactions during anaesthesia. Authors reported that a positive predictive value for predicting IgE-mediated anaphylaxis was 80% if the absolute tryptase value was greater than 15.7mg/L and the percentage change from baseline was greater than 141%.

One topic expert suggested that the optimal timing of mast cell tryptase testing is changing in drug allergy guidelines. Another topic expert confirmed that a large amount of new evidence has become available since the guideline was published but most support guideline recommendations.

Impact statement

No randomised controlled trials or systematic reviews were identified in the evidence update and during this 4-year surveillance review. Topic experts proffered a number of studies which indicate some benefit of measuring mast cell tryptase in patients with anaphylactic reactions. These are mainly in line with guideline recommendations which recommend

that blood samples should be taken for mast cell tryptase testing in people with suspected anaphylaxis. One topic expert suggested that most of the new literature published since the guideline was published was supportive of guideline recommendations. It was suggested that the timings for mast cell tryptase tests have changed in drug allergy guidelines; however, no additional information was provided to support this suggestion.

New evidence is unlikely to change guideline recommendations.

134–03 Should people be observed after an anaphylactic reaction? And if so, for how long?

Recommendations derived from this question

1.1.7 Adults and young people aged 16 years or older who have had emergency treatment for suspected anaphylaxis should be observed for 6–12 hours from the onset of symptoms, depending on their response to emergency treatment. In people with reactions that are controlled promptly and easily, a shorter observation period may be considered provided that they receive appropriate post-reaction care prior to discharge.

1.1.8 Children younger than 16 years who have had emergency treatment for suspected anaphylaxis should be admitted to hospital under the care of a paediatric medical team.

Surveillance decision

This review question should not be updated.

2-year evidence update
One retrospective study[8] compared 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. After introduction of the anaphylaxis protocol 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).

The evidence showed potential improvements in patient care that may occur when guidelines are implemented; however it was not considered that this would affect guideline recommendations.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
One study was identified in the 2-year evidence update. It highlighted improvements in patient care associated with the introduction of treatment protocols. It was considered that the evidence was unlikely to affect guideline recommendations.

No additional evidence or topic expert feedback was identified at the 4-year surveillance review that would change this conclusion.

New evidence is unlikely to change guideline recommendations.

134–04 Who should be referred, when, and to where or whom?

Recommendations derived from this question

1.1.9 After emergency treatment for suspected anaphylaxis, offer people a referral to a specialist allergy service (age-appropriate where possible) consisting of healthcare professionals with the skills and competencies necessary to accurately investigate, diagnose, monitor and provide ongoing management of, and patient education about, suspected anaphylaxis.

Surveillance decision

This review question should not be updated.

2-year evidence update

One retrospective study[8] compared 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. 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). 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 evidence showed potential improvements in patient care that may occur when guidelines are implemented; however it was not considered in the evidence update that this would affect guideline recommendations.

One retrospective cohort study [1] investigated the assessment, management and referral of patients aged 50 years and above after presentation at the emergency department of a tertiary referral hospital. 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).

It was considered that this study would not affect guideline recommendations because the study population and location were not applicable to a UK context.

A survey[9] of GPs in Scotland explored how patients with potentially life-threatening allergies were managed in relation to referrals 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.

The evidence update considered that the restricted sampling area and low response rate (16.6%) were considerable limitations and the findings would not have been generalisable to a UK setting.

4-year surveillance summary

One systematic review[10] of 5 observational studies, including 1725 patients, reported that the risk of anaphylaxis recurrence (over a lifetime) ranged between 30% and 42.8% (duration until recurrence was not reported). In children less than 12 years, the recurrence rate was 27%: food was found to be the most frequent allergen. Cost-effectiveness analysis comparing specialist services with standard care revealed that standard care using adrenaline auto-injectors was dominated by specialist services with or without injectors. Analysis revealed that specialist services without the use of adrenaline injectors would be cost-effective if the threshold for a QALY was greater than 740, whereas specialist services with injectors would be cost-effective if the threshold was greater than 1800.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

One of the studies identified in the 2-year evidence update highlighted improvements in patient care after introduction of treatment protocols in a tertiary hospital; however, nothing was identified that would affect guideline recommendations. The other 2 studies identified in the evidence update explored referral rates but it was considered that the study populations were not generalisable to a UK setting.

During the 4-year surveillance, one systematic review highlighted that that standard care using adrenaline auto-injectors was dominated by specialist services with or without injectors. No new evidence was identified on who should be referred, when, and to whom. As a result, additional evidence is needed to establish whether the guideline should be updated.

New evidence is unlikely to change guideline recommendations.

134–05 Who should be given an emergency treatment plan and when should that include an adrenaline injector?

Recommendations derived from this question

1.1.9 After emergency treatment for suspected anaphylaxis, offer people a referral to a specialist allergy service (age-appropriate where possible) consisting of healthcare professionals with the skills and competencies necessary to accurately investigate, diagnose, monitor and provide ongoing management of, and patient education about, suspected anaphylaxis.

1.1.10 After emergency treatment for suspected anaphylaxis, offer people (or, as appropriate, their parent and/or carer) an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment.

Surveillance decision

This review question should not be updated.

2-year evidence update

One retrospective cohort study [1] investigated the assessment, management and referral of patients aged 50 years and above after presentation at the emergency department of a tertiary referral hospital. 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).

It was considered that the use of self-injected adrenaline appeared lower in these patients than expected from recommendations in NICE

guideline CG134. However, such prescribing may be appropriate given the limited risk of future exposure to hospital-related triggers (contrast medium), which the study showed were a frequent cause of anaphylaxis in older patients in this population.

A Cochrane systematic review[11] considered the effectiveness of adrenaline auto-injectors for the community-based treatment of anaphylaxis, with or without cardiovascular collapse. After removal of duplicates, 1328 potentially relevant publications were identified; however, no publications met the inclusion criteria (randomised and quasi-randomised controlled trials comparing adrenaline auto-injector use with placebo, no intervention or other adrenergic treatments). As a result, no conclusions regarding the effectiveness of adrenaline auto-injectors could be drawn based on this evidence.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The 2-year evidence update identified a cohort study which reported that older patients were less likely to be prescribed an adrenaline injector than patients. It was considered that the study population and location were not applicable to a UK context.

No additional evidence or topic expert feedback was identified at the 4-year surveillance review that would change this conclusion.

New evidence is unlikely to change guideline recommendations.

134–06 What information do people need after an anaphylactic reaction, and before referral?

Recommendations derived from this question

1.1.11 Before discharge a healthcare professional with the appropriate skills and competencies should offer people (or, as appropriate, their parent and/or carer) the following:

- information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction.
- information about the risk of a biphasic reaction.
- information on what to do if an anaphylactic reaction occurs (use the adrenaline injector and call emergency services).
- a demonstration of the correct use of the adrenaline injector and when to use it.
- advice about how to avoid the suspected trigger (if known).
- information about the need for referral to a specialist allergy service and the referral process.
- information about patient support groups.

Surveillance decision

This review question should not be updated.

2-year evidence update

Healthcare professional skills and competencies

A cross-sectional study[12] evaluated the prescription of adrenaline auto-injectors by paediatric allergists and general paediatricians using an online survey which described 10 hypothetical cases of severe allergy or anaphylaxis. All allergists and generalists prescribed an auto-injector (94.4% and 92.6%, respectively) or would offer the patient a choice about auto-injectors (5.6% and 7.4%,

respectively) in the case specifically mentioning anaphylaxis. The prescribing patterns of allergists and generalists showed no significant differences for 9 of 10 cases reports. For the remaining case, which described a child with oral allergy syndrome, all specialists reported that they would not prescribe an auto-injector 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. 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.

The evidence suggested a need for further training and support for healthcare professionals to ensure guideline implementation and appropriate use adrenaline auto-injectors. However, a key limitation was the study design and self-selection of respondents.

Another study[13] assessed the ability of physicians to use adrenaline auto-injectors in four tertiary hospitals in Turkey using a questionnaire and practical session. Correct use of the auto-injector improved significantly from 23.3% of participants at baseline to 74.2% at 6-month follow-up. The mean time taken for administration reduced significantly from 28.01±6.22 seconds to 19.62±5.01 seconds

Although conducted in a non-UK setting, it was considered that the study highlighted the importance of providing healthcare professionals with an educational programme to ensure the correct use of auto-injectors, and highlighted the importance of repeating training to reinforce learning.

A survey[9] of all the GPs in Scotland explored how patients with potentially life-threatening allergies were managed. The survey found that 90% of the 613 respondents had prescribed adrenaline auto-injectors. 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.

The evidence in the study highlighted 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. However, these findings may not have been generalisable to the whole of the UK.

Patient education on anaphylaxis and auto-injector use

A prospective questionnaire-based study[14] assessed patients' ability to use adrenaline auto-injectors during anaphylactic reactions and explored why auto-injectors were not used in situations in which they were clinically indicated. Of the 466 participants who experienced an allergic reaction during the previous year, 245 experienced anaphylaxis. Of the 245 patients that experienced anaphylaxis only 41 (16.7%) used their adrenaline auto-injector. Multivariate analysis showed that symptoms significantly associated with auto-injector use were loss of consciousness, difficulty swallowing, feeling of impending doom, difficulty breathing, and swelling. In the majority of cases, adrenaline was administered by parents (55%), followed by healthcare professionals (38%) then patients themselves (4%). Of the 41 patients with anaphylaxis in the previous year who had used their auto-injector, 13 (32%) received more than 1 dose. The 204 participants who experienced anaphylaxis in the previous year but did not use their auto-injector 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%).

Although the study revealed a low level of auto-injector use in children and young people experiencing anaphylaxis in the UK, when clinically indicated during an anaphylactic episode, it highlighted the importance of education on when and how to use these devices.

A qualitative study[15], conducted in Scotland, explored the attitudes of young people with a history of anaphylaxis towards adrenaline auto-injectors. In total, 26 patients with anaphylaxis and 2 parents participated in interviews. Of the 25 young people prescribed an auto-injector, 18 had anaphylaxis when auto-injectors were close to hand but 11 reported not using their auto-injector. Barriers were identified at all stages required for the appropriate use of an auto-injector including: 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 auto-injectors are carried at all times, while neglecting other barriers that precluded appropriate and effective use.

It was considered that the study enhanced understanding of the multiple and complex barriers to use of auto-injector devices appropriately and effectively in young people.

Three additional studies[16-18] were identified. They were mainly consistent with guideline recommendations; however, it was considered that study limitations precluded drawing conclusions from reported results. One study[16], performed in the USA, explored what proportion of children with food allergy had their adrenaline auto-injector readily available, and factors associated with carrying it at all times. Only 59% of children had their auto-injector with them at the clinic. This was significantly more likely among children of parents who reported being trained in adrenaline auto-injector use. A third of parents reported that children had their auto-injector 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 auto-injector at the clinic visit as an outcome measure, misclassification bias due to the definition of food allergy used, recall bias that may have affected questionnaire answers, lack of questionnaire validation and the small number of participants.

Another study performed in the USA[17] assessed the proportion of adults who regularly carried their auto-injector, and explored knowledge about its use. Most patients (88%) had never used their auto-injector, although 92% stated that they knew how to use it. 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 auto-injector (95% vs 59%, $p<0.05$). Limitations of the study included a possible overestimate of ability to use the auto-injector 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 auto-injector.

Another study[18] evaluated the benefit of an instruction session on the use of an adrenaline auto-injector, 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. 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 reported that the auto-injector was carried at all times. However, only 47% of participants had the auto-injector with them at the clinic visit and in 21% of these cases, the device had passed its expiry date. Thus, 37% of participants carried a valid auto-injector 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. Lack of detail about the selection of participants and potential confounders limit the strength of the evidence.

Overall conclusion

Taken together, the evidence from the identified studies highlighted 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 occurred, and the correct and appropriate use of adrenaline auto-injectors. This was considered to be consistent with the recommendations of NICE guideline CG134. The evidence also suggested that auto-injector training should be comprehensive, addressing psychological and emotional

barriers to the use of emergency medication as well as practical aspects.

4-year surveillance summary

One RCT[19] investigated the effects of a structured patient education intervention on knowledge, emergency management skills and psychological parameters in patients with previous episodes of anaphylaxis (n=98) and care givers of affected children (n=95). Participants were randomly allocated to receive 3 hour schooling modules of group education (intervention group) or standard auto-injector training (control group). Knowledge was significantly higher in the intervention group than the control group at 3-month follow-up. No detail was provided in the abstract about what knowledge was assessed. Compared to the control group, participants in the intervention group displayed significantly better competencies in emergency management of anaphylactic episodes. Authors reported that the intervention significantly reduced anxiety of caregivers. No significant changes in depression scores were observed in both groups.

One RCT[20] compared the usability of a new model of epinephrine auto-injector with that of an older version. Interns were given a three-step written and visual instruction sheet and were asked to demonstrate use with a new or old auto-injector trainer unit. The performance of each participant was measured using a standardised scoring system. The number of participants who correctly demonstrated auto-injector use was not significantly different between groups. The rates of unintentional injections and placing the wrong tip into the outer thigh were significantly lower in the new auto-injector group compared to the old auto-injector group.

Topic expert feedback

Topic experts suggested that there are uncertainties about whether people with nut allergies should be advised to avoid all nuts or ones that cause allergic reactions, until referral for an outpatient appointment.

Impact statement

Some studies identified in the evidence update highlighted the importance of training for healthcare professionals. Although relevant, healthcare professional competence is not directly relevant to what information should be given to people after an anaphylactic reaction, and before referral. Other studies identified in the evidence update highlighted the ongoing need that patients have for information about anaphylaxis. It was considered that they were consistent with guideline recommendations.

During this 4-year surveillance review, 2 studies were identified which highlighted the potential benefits of patient education interventions. These were in mainly line with guideline recommendations which state that clinicians should provide patients with appropriate information. One study highlighted potential benefits of structured patient education interventions. The other study highlighted that following written and visual instruction there was no difference in the proportions of patients who could correctly use new or old adrenaline injectors.

Topic experts suggested that there is an ongoing debate about what potential triggers should be avoided by patients with nut allergy. No additional evidence that meets the inclusion criteria for this 4-year surveillance review was identified to support this view.

New evidence is unlikely to change guideline recommendations.

134–07 What model or organisation of care should be adopted to improve the diagnosis of anaphylaxis post-reaction?

Recommendations derived from this question

1.1.12 Each hospital trust providing emergency treatment for suspected anaphylaxis should have separate referral pathways for suspected anaphylaxis in adults (and young people) and children.

Surveillance decision

No new information was identified at any surveillance review.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 01 Aside from mast cell tryptase, which other chemical inflammatory mediators offer potential as indicators of anaphylaxis?

No new information was identified at any surveillance review.

Surveillance decision
This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.

RR – 02 What are the frequency, timing, severity and predictors of biphasic reactions in people who have received emergency treatment for anaphylaxis?

2-year evidence update
No relevant evidence was identified.

4-year surveillance summary
One systematic review[21] of 27 observational studies, including 4,114 patients, evaluated the time of onset and predictors of biphasic reactions. The median time of onset was 11 hours (range 0.2 to 72.0). If food was the trigger of anaphylaxis, it was associated with a decreased risk of a biphasic reaction (pooled OR 0.62, 95% CI, 0.4 to 0.94). Unknown triggers were associated with an increased risk of a biphasic reaction (pooled OR 1.72, 95% CI, 1.0 to 2.95). Initial presentation with hypotension was also associated with the development of a biphasic reaction (pooled OR 2.18, 95% CI, 1.14 to 4.15).

Topic expert feedback
Topic experts suggested that observation times due to risk of biphasic reactions have changed. No further information was provided.

Impact
New evidence was found but an update is not planned because the new evidence is insufficient to trigger an update. The systematic review identified during the 4-year surveillance review indicated timings of biphasic reactions and outlined potential triggers. No evidence was identified in relating to frequency and severity of biphasic reactions. It was considered that additional evidence is needed to update this question. This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 03 For how long should a person who has received emergency treatment for anaphylaxis be observed?

2-year evidence update
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
Topic experts highlighted an ongoing national audit of perioperative anaphylaxis after administration of anaesthesia (the NAP6 study). “The project will collect comprehensive information concerning perioperative anaphylactic events, enabling the anaesthetic and allergy communities to collaborate in order to make recommendations for the improvement of the quality of patient care”. Experts felt that the scale and scope of the study is such that it is likely to produce data that is of direct relevance to this clinical question.

Impact
In light of the ongoing study, highlighted by topic experts, this research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 04 What is the annual incidence of anaphylaxis and its related outcomes within the UK?

2-year evidence update
An ecological study[22] analysed the frequency of admissions for anaphylaxis from critical care units in the UK over the period 2005–09. 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 and male children were admitted (rate ratio [RR]=0.88; 95% CI, 0.64 to 1.20) but there were significantly more adult female admissions than male (65% vs 35%, RR=1.83, 95% 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/ 81) for children and survival to hospital discharge was 92% (1166/1269) for adults.

The evidence update concluded that this study provided national data from comprehensive, robust and validated sources. Moreover, it was considered that the study may provide context for NICE guideline CG134. However, although the guidance does not exclude anaphylaxis originating in hospital, it mainly focuses on anaphylaxis originating in the community.

4-year surveillance summary

One systematic review[23] which assessed the epidemiology of anaphylaxis in Europe reported that the incidence of all-cause anaphylaxis ranged from 1.5 to 7.9 per 100,000 person-years. The data indicated that approximately 0.3% (95% CI, 0.1 to 0.5) of people experience anaphylaxis at some point in their lives.

Another systematic review[24] explored the incidence of anaphylaxis in people with food allergy: no particular country or region was specified. Authors reported that the incidence rate of food anaphylaxis was 0.14 per 100 person-years (95% CI, 0.05 to 0.35). In people below 19 years, the incidence rate of anaphylaxis in food allergic people was 0.20 per 100 person-years (95% CI, 0.09 to 0.43). In children below 4 years, studies reported incidence rates up to 7.0 per 100 person-years. The overall incidence rate of hospital admission due to food anaphylaxis was 0.09 per 1000 person-years (95% CI, 0.01 to 0.67). In people below 19 years, the incidence rate of hospital admission due to food anaphylaxis was 0.20 per 1000 person-years (95% CI, 0.10 to 0.43) whereas the incidence rate was 0.50 per 1000 person-years (95% CI, 0.26 to 0.93) in children below 4 years.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact

New evidence was found but an update is not planned because the study populations were not representative of the UK population. This meant that the findings were not generalisable to a UK setting which was a criterion of the research recommendation. As a result, there is insufficient evidence to trigger an update. This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

RR – 05 For people who have experienced suspected anaphylaxis, what is the effect on health-related quality of life of (a) referral to specialist allergy services and (b) provision of adrenaline injectors, when compared with emergency treatment alone?

2-year evidence update

No relevant evidence was identified.

4-year surveillance summary

In 1 RCT[25], 52 children with food allergy and/or their carers were randomised to receive 24-hour access to a telephone specialist support line (intervention group) or to receive usual care (control group). In the intervention group, food-allergy-related quality of life scores were significantly improved at 6-month follow-up. No significant improvements in food-allergy-related quality of life scores were observed in the control group at 6-month follow-up. As a result, improvements in quality of life were significantly better in the intervention group. Follow-up questionnaires, 6 months after withdrawal of access to the support line, revealed that the significant differences in quality of life between groups were sustained.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact

New evidence was found but an update is not planned because the new evidence is insufficient to trigger an update. The identified new study was had a small sample size and followed patients up for a short time period. This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

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