

A systematic review and cost-effectiveness analysis of specialist services and adrenaline auto-injectors in anaphylaxis

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Executive summary

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Executive summary

Background

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by 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).

There is considerable geographic variation in both practice and service provision for anaphylaxis, specifically in reviews after emergency treatment for anaphylaxis and decisions about when and whether or not to refer to a specialist allergy clinic [specialist service (SS)] {'... 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' [p. 9, National Institute for Health and Care Excellence (NICE) guideline CG134, www.nice.org.uk/nicemedia/live/13626/57474/57474.pdf]}. There are professional guidelines on the emergency treatment and management of anaphylaxis, but there is currently no relevant national guidance for England and Wales on assessment after the event to confirm an anaphylactic episode or on the decision to refer after emergency treatment.

There are approximately 20 anaphylaxis deaths reported each year in the UK, although this may be a substantial underestimate. There are observational data that the risk of death is increased by delayed use of adrenaline. In order to reduce the delay, adrenaline injectors (AIs) are often prescribed following anaphylaxis, but there is a perception that they are often not used in time or correctly.

Objectives

For the NICE clinical guideline CG134 'Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode', we, as the Technology Assessment Group, were asked to address six questions:

1. In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?
2. What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause?
3. What are the effects of providing adrenaline auto-injectors, including by whom?
4. After assessment, when should referral take place?
5. What is the cost-effectiveness of referral to specialist allergy clinics for the diagnosis of anaphylaxis and for the prevention of future episodes and the reduction in morbidity and mortality from future episodes?
6. What is the cost-effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis, including the cost implications of training in the use of the auto-injectors?

Questions 1–4 aimed to shed light on clinical aspects of anaphylactic episodes, whereas questions 5 and 6 addressed the cost-effectiveness of diagnosis, prevention and treatment of anaphylaxis.

Methods

Clinical aspects (questions 1–4)

The search strategies for the review questions were developed by the information specialist with advice from the systematic review team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free-text terms. The strategies were run across 10 databases [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), Science Citation Index (SCI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, from inception up to March 2011] with no date restrictions imposed on the searches.

Studies [randomised controlled trials (RCTs) or non-RCTs, observational studies, and prognostic studies that have included a multivariable analysis], published in English, which focused on patients who received emergency treatment for suspected anaphylaxis or severe allergic reactions, were eligible for inclusion if they reported history-taking, physical examination, provision of adrenaline auto-injectors or referral to specialist allergy clinics. Relevant clinical outcomes were subsequent episodes, morbidity and mortality, as well as the impact on the treatment plan and test failure rates. There was no limitation regarding age of patients and setting.

Economic aspects (questions 5 and 6)

In order to answer both questions 5 and 6, an objective of the study was constructed to assess the cost-effectiveness of referral to specialist allergy clinics (SSs) as opposed to standard care (SC), i.e. no referral after the acute event, with or without prescription of AIs for the treatment of anaphylaxis.

In order to achieve this objective, first a review of the extant cost-effectiveness analysis (CEA) literature was conducted, which revealed that the cost-effectiveness of SS had never been estimated before. One study had examined AI, but only in the general allergic population as opposed to those who have had anaphylaxis, and it had not estimated quality-adjusted life-years (QALYs).

Therefore, informed by expert opinion from the Guideline Development Group, a Markov model was constructed to model the possibility of recurrence over a lifetime in each of the subgroups by cause of anaphylaxis: insect, food, drug and idiopathic origin. It modelled the effect of SSs in terms of rate reduction via a mechanism that depended on the trigger, assuming that all patients had anaphylaxis and that trigger was identified with certainty. AI (prescription of two injectors) effect was modelled as having an effect only on mortality due to recurrence. Of the five studies retrieved to answer questions 1–4, only one, an Australian observational study on risk of recurrence, was used to inform the model. All other parameter estimates were informed by a review of evidence based on clinical guidelines and expert opinion.

Results

Clinical aspects (questions 1–4)

The searches of electronic searches yielded in 11,058 references. After screening of titles and abstracts, 10,951 references were excluded. The remaining 107 references were obtained and the full texts screened. Five studies were included, none of which was a RCT. Another 60 studies were highlighted as possibly relevant for the background and/or the CEA. All five included studies were prospective observational studies reporting on risk of recurrence. The studies, conducted in five countries (Australia, Germany, Italy, Spain and the USA), included 1725 patients overall.

Risk of recurrence was estimated to be between 30% and 42.8%. One study suggested the rate of a third event to be 5.2% with a higher risk of recurrence for women [relative risk (RR) 2.14, 95% confidence interval (CI) 1.17 to 3.9]. In children of <12 years, an overall recurrence of 27% was reported, with food being the most frequent allergen (71%). One larger study (432 patients) reported serious recurrences in 45 patients (10.4%), of whom 18 (40%) received adrenaline.

Economic aspects (questions 5 and 6)

The results showed that, in the base case of a lifetime horizon, discount rate of 3.5%, SS with AI had an incremental cost-effectiveness ratio (ICER) of about £1800 (model run probabilistically or deterministically, i.e. all parameters set at expected value) and, therefore, would be cost-effective according to a threshold of no less than this figure. Any SC strategy (with or without AI) was dominated, i.e. found to be less effective and more costly than another strategy. SS with no AI would be cost-effective only below a threshold of about £740. The cost-effectiveness acceptability curve also revealed that above a willingness to pay of about £2000, SS plus AI was also the most likely (highest probability) to be cost-effective.

Given the complexity of the model and much uncertainty there was in many parameters, extensive sensitivity analysis in the form of threshold analyses was performed. This revealed that variation in most parameters would not change the strategy that would be cost-effective. Indeed, only relatively extreme values for rate of food caused anaphylaxis following SS could cause a change to SC. Similarly, only relatively extreme values for the cost of injector, probability of dying with the injector or utility improvement factor (essentially the proportion of the utility decrement due to living with the risk of anaphylaxis that would be restored as a result of prescription of an injector) could cause a change to SS with no injector. One possible exception was that SS no AI might be cost-effective below a probability of correct use of AIs of 0.77, assuming no utility increment with AIs (e.g. due to reassurance).

Conclusions

The results of the systematic review revealed only five studies that directly addressed any of the research questions in terms of history-taking, physical examination, provision of adrenaline auto-injectors or referral to specialist allergy clinics for those with anaphylaxis. None of these studies was a RCT.

The results of the CEA showed that SS with AI was cost-effective at a threshold of £20,000 per QALY. However, given the lack of RCTs, the model had to be informed by observational studies and expert opinion.

Given that the results that both referral to a SS and prescription of AIs are likely to be cost-effective and that this study has been used to inform a NICE guideline, it does potentially have important implications for policy. The guideline was published in December 2011.

Research recommendations

The lack of good data to inform the effectiveness of anaphylaxis intervention means that we recommend consideration of RCTs or at least well-designed observational studies of the components of care in SSs. These components include all of those that formed the CEA model, including AIs, trigger avoidance measures, venom immunotherapy and idiopathic anaphylaxis treatment.

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