Appendix E Evidence tables

Review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?

Table 1

Evidence table 1 for review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?											
Bibliographic reference	Study type and objective	No of pts	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
Brown et al (2004)	Cross-sectional (prospective) Diagnostic test accuracy study as part of a RCT to evaluate the effect of venom immunotherapy (using a sting challenge)	64	17% (11/64) had severe systemic allergic reactions to sting challenge	Participants with a history of anaphylactic reactions to the jack jumper ant (*Myrmecia pilosula*) who had an anaphylactic reaction to a sting challenge (see 'definition of anaphylaxis in 'reference standard' column). Age and gender not reported.	Serum mast tryptase (UniCAP Tryptase) measured at baseline (prior to the sting challenge) then 15 min and 60 min after the challenge. Manufacturer's normal range<12µg/l; detection limit 1.0µg/l	Clinical diagnosis of anaphylaxis (severe systemic reaction involving respiratory or CV compromise [dyspnoea, wheeze, stridor, O_2 saturations<92%, or SPB<90mmHg])	Cut-off: peak tryptase 12.0µg/l (manufacturer's level) sens: 36% (11% to 69%) spec: 89% (77% to 96%) Cut-off: peak tryptase 9.0µg/l (derived from the ROC curve) sens: 55% (23% to 83%) spec: 87% (75% to 95%) Cut-off: delta	(calculated by analyst) Cut-off: peak tryptase 12.0µg/l (manufacturer's level) PPV 40% (12% to 74%) NPV 87% (75% to 95%) Cut-off: peak tryptase 9.0µg/l (derived from the ROC curve) PPV 46% (19% to 75%) NPV 90% (79% to 97%) Cut-off: delta	Information on timing was only reported in chart form and it was difficult to extract data from this chart.	Royal Hobart Research Foundation Dick Buttfield Memorial Scholarship NSL Health Ltd Cosy Cabins Tasmania	Patients in this study present with anaphylaxis after a sting challenge; it is possible that patients presenting with experimentally induced anaphylactic reactions are different from those presenting with anaphylaxis naturally. It is not clear if this difference is likely to affect the measurement of MCT. Patients with mild reactions were excluded.

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							tryptase 2.0µg/l (change from baseline) sens: 73% (35% to 93%) spec: 91% (79% to 97%)	tryptase 2.0µg/l (change from baseline) PPV 62% (32% to 86%) NPV 94% (84% to 99%)			Histamine levels were not reported in this study.
Enrique et al (1999)	Cross-sectional (probably prospective) Aim to asses usefulness of UniCAP Tryptase to identify episodes of anaphylaxis	30	57%	Patients presenting at emergency room within clinical symptoms of allergic reaction of less than 6 h duration. Of 17 with anaphylaxis: mean age 41 y (range: 18 to 79), 53% female. Causes were idiopathic (4), walnut (2), dipirone (2), immunothera	UniCAP Tryptase which permits measurement of active and inactive forms of both α and β tryptase (serum samples taken and stored at -20°C) Serum levels ≥ 13.50 ng/ml were considered positive	Clinical data taken within 2 weeks (including detailed clinical history, measurement of complement proteins and activity antinuclear antibodies, skin tests to aeroallergen foods and drugs) 'Anaphylaxis' if sudden onset of symptoms AND 2 or more of areas involved:	With 13.50 ng/ml threshold: sens: 35.29% (CI 15.73 – 59.51%) spec: 92.31% (CI 67.52 – 99.62%) With 8.23 ng/ml threshold (ROC cut-off level): sens: 94.12% (CI 74.25 – 99.71%) spec: 92.31%	(calculated by analyst) With 13.50 ng/ml threshold: PPV: 86% (95% CI 42 – 100%) NPV: 52% (95% CI 31 – 73%) With 8.23 ng/ml threshold (ROC cut-off level): PPV: 93% (95% CI 66 – 100%) NPV: 75% (95% CI 48 –	Study reported that there was no relationship between the time elapsed from the beginning of the reaction to the time of sampling and serum tryptase levels (but exact timing of sampling after reaction	Not reported	Serum samples taken when patients arrived at hospital but exact timing after onset of symptoms not clear. If it was taken at an inappropriate time, this could explain the low sensitivity of the test. Serum samples stored at -20°C before the index test was performed. Timing between index test and reference standard was not clear and results

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				py (2), and snail, atriacurium, tomato, honey, fish, amoxicillin, cefuroxime (1 each). Of the 13 with no anaphylaxis: mean age 34 y (range: 7 to 85), 46% female. Causes were idiopathic (6), scombroidosis (2), dipirone (1), chronic urticaria (1), sulphites (1), anxiety (1), and unknown (1)		- bronchial tree - oropharynx - subcutaneous tissue/skin - GI tract - CV system	(CI 67.52 – 99.62%)	93%)	was not reported so it was not clear how the authors came to this conclusion).		from one may have had an effect on the interpretation of the other giving an overestimation of the accuracy of the test (incorporation or review bias). Only 21 had second blood test 1-2 months later to determine baseline tryptase level. Ratio of reaction to baseline serum tryptase was 2.85 in the 17 with anaphylaxis and 1.29 in those without anaphylaxis. This study only includes one paediatric patient (aged 7) who was one of the 13 patients without anaphylaxis.

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Malinovsky et al (2008)	Cross-sectional (prospective) Aim to evaluate incidence of hypersensitivity reactions during anaesthesia by using histamine and tryptase measurements and allergological investigations to investigate suspected or unexplained reactions	31	71%	Patients with suspected hypersensitivity reaction to anaesthetics (29 general, 2 regional) at University Hospital Nantes from May 2001 to April 2003 (hypersensitivity reaction determined if presented with cutaneous symptoms *i.e. urticaria and//or angioedema) isolated or in association with other clinical symptoms like bronchospasm, hypotension, or cardiovascul	Tryptase measurements from radioimmunoassays (RIA, Immunotech, Beckman-Coulter, Marseille) 30 min when not life threatening and between 30 and 60 min when life threatening Serum levels > 11 nmol/l were considered positive; thresholds of both 12 and 25 µg/l were tested	Hypersensitivity reaction diagnosed based on clinical history, mediator concentration in blood and skin tests (both prick and intradermal tests performed 4 weeks later)	(confidence intervals calculated by analyst) With 12 µg/l threshold: sens: 63.6% (95% CI 40.7 – 82.8%) spec: 100% (when calculated by analyst specificity was 88.9% with 95% CI 51.8 – 99.7%) With 25 µg/l threshold: sens: 40.9% (95% CI 20.7 – 63.6%) spec: 100% (95% CI 66.4 – 100%)	(confidence intervals calculated by analyst) With 12 µg/l threshold: PPV: 100% NPV: 53% (when calculated by analyst these values were PPV: 93.3% [95% CI 68.1 – 99.8%] NPV: 50% [95% CI 24.7 – 75.3%] With 25 µg/l threshold: PPV: 100% (95% CI 66.4 – 100%) NPV: 41% (95% CI 20.7 – 63.6%)	Of the ratio between T_0 to T_{24h}: sensitivity: 63% specificity: 83% PPV: 92% NPV: 42%	Not reported	Unclear if the definition of hypersensitivity reaction in the study was anaphylaxis. Patients with just urticaria and/or angioedema alone were included and these patients are not likely to be considered to have anaphylaxis. 8 patients excluded from analysis because they did not undergo skin prick tests. Tryptase (and histamine) tests formed part of the reference standard leading to possible incorporation bias (which could lead to inflated agreement between index and reference

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				ar collapse or if circulatory inefficacy in close relation with anaesthetic drug injection in absence of other explanation Patients with IgE-mediated hypersensitivity reactions: Median age: 43 y (range: 8-80) 45% (10/22) male, 55% (12/22) female Patients without IgE-mediated hypersensitivity reactions: Median age: 45 y (range: 19-78)							tests and an inflated measure of diagnostic accuracy).

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				56% (5/9) male, 44% (4/9) female							
Mertes et al (2003)	Cross-sectional (retrospective) Aim to survey of allergic and non immunity-mediated reaction during anaesthesia, description of clinical characteristics, and identification of possible factors and responsible drugs	789 with adverse reaction during anaesthesia in France between Jan 1999 and December 2000	68% (of the 259 tested for tryptase)	Of the 518 diagnosed with anaphylaxis, 70% were female and in those 15.5% had atopy, 10.7% asthma, 18.1% drug intolerance. Of the 271 with anaphylactoid reaction, 66% were female, 12.7% had atopy, 9.8% had asthma and 19.8% drug intolerance. There was no difference in atopy, asthma and drug intolerance	UniCAP Tryptase (serum samples taken and test performed 'during adverse reaction' in 259 patients only) Serum levels ≥ 25 µg/l were considered positive	Anaphylaxis (immune-mediated reaction) diagnosed with clinical history, skin tests (prick and intradermal), and / or IgE assay results	(confidence intervals calculated by analyst) With 25 µg/l threshold: sens: 64% (95% CI 56.4 – 71.1%) spec: 89.3% (95% CI 80.6 – 95.0%)	(confidence intervals calculated by analyst) With 25 µg/l threshold: PPV: 92.6% (95% CI 86.3 – 96.5%) NPV: 54.3% (95% CI 45.7 – 62.8%)	Not reported	From institutional and/or departmental sources (not specified)	Retrospective nature of study may preclude ability to blind assessors to results of index test when performing reference standard. Also, timing of reference standard was not clear. Serum samples taken 'during reaction' but exact timing after onset of symptoms not clear. The timing of the test could have an impact on its sensitivity. Authors include only 32.8% (259/789) of patients in whom tryptase concentrations

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				except in anaphylaxis group Age not reported.							were determined at the time of the reaction. Details of other patients and reasons why tryptase tests were not performed at the time of reaction not reported; this may lead to selection bias. The accuracy of histamine was also reported.
Abbreviations: CI, confidence interval; h, hour; IgE, immunoglobulin E; MCT, mast cell tryptase; min, minutes; NPV, negative predictive value; PPV, positive predictive value; RIA, radioimmunoassay; sens, sensitivity; spec, specificity; SD, standard deviation; t1/2, half-life; y, years											

Table 2

Studies included for information on timing only:

Evidence table 2 for review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?							
Bibliographic reference	Study type and objective	No of patients	Patient characteristics	Type of test	Timing	Source of funding	Additional comments
Kanthawatana et al (1999)	Case series Aim to retrospectively analyse the clinical value of an elevated level of α-protryptase (≥20 ng/mL) with normal or slightly elevated (≤5 ng/mL) level of β-tryptase	19	Samples received in a diagnostic immunology laboratory over a 3.5-y period from patients with suspected anaphylaxis that had elevated total tryptase levels (≥20 ng/mL) and normal β-tryptase levels (< 1 ng/mL) or modestly elevated (≤ 5 ng/mL) Mean age 39 y (range: 19 to 55), 52.6% (10/19) male.	B12 mAb used to measure total tryptase and biotinylated G4 and G3 mAbs used,; β-tryptase also measured to calculate a ratio of total to β-tryptase (ELISA)	Timing of sample collection after onset of signs and symptoms was from 20 min to 12 h. The study reported that there is not apparent correlation between timing of blood collection and either total tryptase values, β-tryptase values or total tryptase/β-tryptase ratios.	Partly supported by National Institutes for Health grant	There were 30 cases of suspected anaphylaxis but 11 of these had died (and specimens were post-mortem). The results from these deceased patients have not been reported here. The study also analysed 22 patients with suspected mastocytosis to look at tryptase values to help diagnose mastocytosis.
Laroche et al (1991)	Case control Aim to determine if tryptase is a consistent and reliable marker for anaphylaxis	19 cases, 19 controls	Patients with adverse reaction to drugs compared with 35 anaesthetised patients. Of those with the drug reactions, - 12 occurred immediately after induction with	MCT measured by plasma or serum by immunoradiometric assay (Tryptase RIACT kit, Pharmacia, Uppsala, Sweden; lower limit of detection	In 3 cases, the half life was 90 min and in one it was 5 h. In one patient with a reaction to injection of tetanus vaccine, tryptase levels were higher 2 h after the reaction than 1 h before.	Tryptase kits were supplied by the manufacturer	There was also a comparator group of non-anaesthetised controls but they have not been included here because they did not have exposure to anaesthetics.

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Bibliographic reference	Study type and objective	No of patients	Patient characteristics	Type of test	Timing	Source of funding	Additional comments
			anaesthesia [all but one with muscle relaxant] - 4 appeared unrelated to the anaesthetic drug injection [2 after gelatine infusion, 1 after Peruvian balsam, 1 after 1 h], - 3 were not related to anaesthetics but occurred immediately after a single drug injection (penicillin, tetanus vaccine and contrast medium) Cases: mean 55.1 y (range: 24 to 81; SD 14.6) Controls: mean 51 y (range: 18 to 79; SD 17) Gender not reported.	is 0.5 U/l).			Not clear if patients had anaphylaxis.
Laroche et al (1992b)	Case series Aim to compare the diagnostic value of plasma histamine and mast	33	Patients referred following adverse reactions to drugs, mostly general anaesthesia with cutaneous, cardiovascular or bronchopulmonary clinical signs	MCT measured with immunoradiometric assay (tryptase RIACT kit, Pharmacia, Uppsala, Sweden) Values > 2 µg/l	Tryptase was high in 15 and normal in 18. In all subjects with elevated levels of tryptase, this persisted 2 h after reaction but usually disappeared by 24 h except in one patient who deceased after being in a prolonged coma. Tryptase half-life, measured in 3 patients,	Pharmacia France supplied tryptase kits	Not clear if patients had anaphylaxis.

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	cell tryptase *in vivo* histamine-release during anaphylactoid reactions.		(associated or not) Age and gender not reported.	appears to have been considered elevated	was 90 min.		
Laroche (1998)	Case-control Aim to investigate mechanisms of immediate reactions	20 (and 20 controls)	Participants if experienced allergic-type reactions (immediate anaphylactoid reactions) after the administration of contract media 20 (15 male; 5 female) Mean age 51 yrs (range: 17 to 79; SD 17)	Serum mast tryptase (Tryptase RIACT) Levels considered elevated if ≥3 µg/l Samples taken as soon as possible after the reaction or when resuscitation had been started; then at 30 min, 2 and 24 h.	Values of tryptase remained at pathologic levels (not defined) for 2, 3, or 4 h depending on severity grade of the reaction (no details). All patients had normal concentrations the day after the reaction.	None acknowledged	The definition of anaphylactoid reactions was not clear. Since the patients in this study had reactions after the injection of contrast media, it is not clear how applicable these test results of MCT timing are to an unselected population presenting with suspected anaphylaxis
Ordoqui et al (1997)	Case series Aim to find a tool for the diagnosis of drug allergy	64 to clinic of which 27 were confirmed to have drug allergy: - 7 with	Patients with adverse drug reactions (including cutaneous or systemic symptoms) presenting at the allergology section	Tryptase levels measured with radioimmunoassay (Tryptase RIACT™ Pharmacia, Uppsala, Sweden) taken	Peak value of serum tryptase was in the first 30 min in 2 cases of anaphylactic shock from oral erythromycin and oral cotrimoxazole (post-reaction maximum level 53 U/l and 4.09 U/l) and in 2 cases of anaphylaxis caused by intravenous fluorescein and oral dipirone (post-reaction maximum 66.2 U/l and 9.05 U/l).	Not reported	Study reports that blood was taken 2 h after onset of symptoms but then the peak value of serum tryptase was reported to have been in the first 30

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		anaphylactic shock (cutaneous, digestive and/or respiratory symptoms with hypotension with or without consciousness) - 13 anaphylactic reactions (similar as above but normal arterial pressure) - 17 with urticaria-angioedema	and from the emergency unit at one hospital. Age and gender not reported.	from blood obtained 2 h after onset of symptoms and 7 days later (in the 7 with anaphylactic shock or anaphylaxis, sera was separated and stored at -20°C for later use) Not clear what level was considered elevated.	The highest level was detected after 2 h in a patient who developed anaphylactic shock with oral amoxicillin (5.87 U/l). Tryptase peaked 3-4 h after onset of symptoms in anaphylactic shock induced by oral amoxicillin (27.54-27.38 U/l) and at 6 h in another anaphylactic shock caused from oral amoxicillin (20.7 U/l). Serum tryptase decreased to baseline by 24 h in all patients. Timing of occurrence of serum tryptase was said not to be related to the severity of symptoms or the amount of protease released.		min. It is not clear how this is possible. Includes patients who have symptoms that do not appear to be anaphylaxis.
Schwartz et al (1987)	Case series Aim to describe use of particular assay to detect mast-cell involvement (both active and inactive	6	Patients with presenting with clinical evidence of anaphylaxis from penicillin, aspirin, melon ingestion, wasp sting, exercise (later found to be allergic to mountain cedar pollen or	Tryptase measured with sandwich ELISA from serum samples taken retrospectively from serum samples collected at the time of	In four patients in who follow-up was obtained, the time course of the disappearance of tryptase was analysed. In 3 patients with reactions from penicillin, wasp venom and exercise, tryptase levels had decreased to under 5 ng/ml in samples obtained after 24 h. In one patient with acute systemic anaphylaxis after eating honeydew melon,	Supported by grant from National Institutes of Health	Study included measurements of tryptase in patients with myocardial disease (n = 9), sepsis (n = 6, 3 with shock), systemic mastocytosis (n = 17) and 16 hospital controls.

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	tryptase) in patients with anaphylactic events or systemic mastocytosis		horse antilymphocyte globulin (to suppress rejection of kidney transplant). Age and gender not reported.	admission (and stored at stored at -20°C) or at the time of admission Levels from 9 to 75 ng/ml were considered elevated	tryptase had decreased from 39 to 18 ng/ml after 6 h (exact timing of initial test not reported).		
Schwartz et al (1989)	Case series (laboratory examination of stability of tests) Aim to analyse the levels of tryptase in circulation over time and to investigate the stability of serum samples	5	A: After bee sting challenge: 2 presenting with 'profound hypotension associated with pruritis' and 1 with 'pruritis and moderate inspiration and wheezing without a change in BP' All treated with injectable epinephrine with good response. B: 2 more presented with 'systematic anaphylaxis' (one 60-90 min after bee sting another rafter indomethacin ingestion)	Serum mast tryptase (sandwich ELISA) Levels considered elevated if ≥10 ng/l, and marginally elevated if 5-10 Samples taken as soon as possible after the reaction and up to 19 h post reaction	A: Histamine levels increased over baseline, reached a peak by 5-10 min after challenge, and declined to approx baseline by 30-40 min. Respective levels in two of these patients were not detectably elevated until 15 and 30 min after the challenge, reached a maximum at 1 and 2 h, and then declined with a $t_{1/2}$ of 1.5 and 2 h. In each case the clinical condition returned to normal at the time of the peak level of tryptase. The third patient had a biphasic pattern with an initial peak at 15 min and a second peak at 2 h; tryptase levels then declined with a $t_{1/2}$ of 1.5 h. B: One patient (with bee sting) had an initial tryptase level that was markedly elevated upon admission (60-90 min after bee sting) and declined with a $t_{1/2}$ of 2 h. The other showed initial tryptase levels that were clearly elevated and declined with at $t_{1/2}$ of 1.5 h.	National Institutes of Health grant Virginia Center for Innovative Technology Pharmacia	Not clear if all cases were true anaphylaxis. It is possible that the three patients presenting with experimentally induced anaphylactic reactions (from bee sting challenge) are different from those presenting with anaphylaxis naturally. It is not clear if this difference is likely to affect the measurement of MCT or the timing of its presence.

<table>
<tr><th colspan="8">Evidence table 2 for review question 1: Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?</th></tr>
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<tr><td>Schwartz et al (1994)</td><td>Case control

Aim to describe the production of a new monoclonal antitryptase antibody and its use as a capture antibody in an immunoassay capable of detecting tryptase in normal serum and plasma</td><td>9 with history of severe reaction, 20 with history of mild reaction</td><td>Patients given a sting challenge divided into 4 groups:
1) normal controls with no history of anaphylactic reaction;
and patients with a history of venom hypersensitivity
2) with no reaction
3) mild to moderate reactions (skin, gastrointestinal or airway)
4) severe reactions (at least 15 mmHg fall in arterial pressure)
(only those in the later two groups are included in this table)
Age and gender not reported.</td><td>Samples from a previously reported study which conducted insect sting-induced anaphylaxis were re-assayed with the new tryptase immunoassay (ELISA) up to 75 min after the sting challenge in the first 2 groups with no history of a reaction to venom and up to 60 min after the onset of symptoms in those in the two groups with a history of a reaction to venom (1 to 40 min after sting).</td><td>Samples taken at different time periods to give the time course for tryptase release was only available in a 9 of the 17 patients with a history of severe reactions to venom (reported as ‘hypotensive’) and 20 of the 22 patients with a history of mild reactions to tryptase. These samples were collected at baseline and 1, 5, 15 and 60 min after onset of symptoms.
Peak tryptase levels after onset of symptoms after venom challenge:
<table><tr><th>Time period</th><th>Patients with severe reaction</th><th>Patients with mild reaction</th></tr><tr><td>1 min</td><td>1</td><td>2</td></tr><tr><td>5 min</td><td>1</td><td>5</td></tr><tr><td>15 min</td><td>4</td><td>4</td></tr><tr><td>60 min</td><td>3</td><td>5</td></tr><tr><td>Total</td><td>9</td><td>20</td></tr></table>
In both groups, elevations above baseline levels were usually detected 1 to 5 min after onset of symptoms (despite the peak usually appearing later). The authors concluded that the maximal level of tryptase occurs from 15 to 60 min after the onset of symptoms.
Tryptase levels increased at least two-fold from baseline to the 60-min time point after the challenge in 10/22 patients with a mild reaction and 16/17patients with severe reactions (referred to as ‘hypotensive</td><td>Supported by grant from National Institutes of Health</td><td>The study also reported that baseline tryptase levels were higher in those with a more severe reaction.

Patients in this study present with anaphylaxis after a sting challenge; it is possible that patients presenting with experimentally induced anaphylactic reactions are different from those presenting with anaphylaxis naturally. It is not clear if this difference is likely to affect the measurement of MCT or the timing of its presence.</td></tr>
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					subjects') with levels from baseline to 60 min significantly higher in both groups (p = 0.005 and p = 0.0003). No patients in the first two groups had a twofold increase and the tryptase levels from baseline to 60 min were not significant.		
Stone et al (2009)	Case series Aim to identify cytokines and chemokines whose concentrations increase during anaphylaxis and see how they correlate with severity	36 (severe), 40 (moderate)	Patients presenting to emergency departments with acute-onset illness with typical skin features (hives, pruritus or flushing, swollen lips and/or tongue), with or without involvement or other organ systems or any acute onset of hypotension or bronchospasm where anaphylaxis was possible even if no skin features OR reactions occurring in response to treatment in the emergency department for other conditions. Median age 36 y (range 9 to 99)	MCT concentrations analysed with Phadia ImmunoCAP system Median time from enrolment to first sample was 60 min and to last sample was 288 min A deviation from 2.0 µg/L (ng/mL) between high and low values for each case was considered 'positive' (so that those with baseline MCT levels above normal and that do not change during event are considered negative)	Peak levels appeared both at time of enrolment (T_0), or approximately 1 h after enrolment (T_1, target time, or from 40 to 80 min), and occasionally before discharge from the emergency department (T_2). [see Lowess best fit curve after table to show relationship between interval from reaction onset and tryptase concentration]	Supported by grants from Food Allergy and Anaphylaxis network and 2 hospital research foundations.	Reactions were considered 'moderate' if they had features suggesting respiratory, cardiovascular or gastrointestinal involvement. They were considered 'severe' if hypoxemia, hypotension or neurologic compromise was present.
Abbreviations: ELISA, enzyme-linked immunosorbent assay; h, hour; MCT, mast cell tryptase; min, minutes; SD, standard deviation; $t_{1/2}$, half-life; y, years							

Review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Table 3

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?

Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
Brady (1996) USA	Retrospective case series Purpose to determine the rate of clinical significant recurrence of symptoms in patients treated for anaphylaxis in the emergency department (ED)	67 cases of anaphylaxis (5.3% of 1261 allergic reactions and 0.5% of total ED census)	Patients with anaphylaxis out-of-hospital, ED, hospital records over a 4.5 year period (1991–5). Identified from ICD-9 codes for allergic reaction, anaphylaxis and related phenomena. Mean age: 30.2 years Gender: 51% (34) male 49% (33) female	Anaphylaxis – an immediate, life-threatening, multi-system allergic reaction, representing a true medical emergency. Those with allergic reactions were considered to have anaphylaxis if they experienced a multi-system reaction involving ≥ 2 of the following organ systems: skin (urticaria and angioedema), cardiovascular	Causes (of the 70% with identified causes): | | % of patients | | Food | 40 % | | Animal or insect venom* | 35 % | | Medication | 18 % | | Other | 7% | *both with biphasic reactions had anaphylaxis from Hymenoptera envenomation Treatments received: | Antihist | 79% |	Treatment protocol and observation period not described. However, the 14 patients with uniphasic reactions who were admitted were observed for mean 63 hours. Both patients with biphasic reactions were observed for 4-7 hours.	3% (2/67) presented with urticaria and were subsequently seen again at the ED	26 hours (22-year old female) and 40 hours (19-year old male) after initial ED visit. Both were treated with subcutaneous epinephrine, IV steroid and IV antihistamine. Both were observed for 4-7 hours after symptom resolution of the index reaction. Ongoing antihistamine and steroids was given to the	No comparison made.	Not reported	Not clear how long all patients who were not admitted and did not have biphasic reactions were followed up. Records were taken from surrounding institutions within 75-mile radius but it is possible that some could have developed a biphasic reaction and presented elsewhere, beyond the 75-mile radius.

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
				system (distributive shock), and respiratory system (bronchospasm and airway angioedema). (GI symptoms noted but not used to define anaphylaxis) Complete response – if reaction resolved within 30 minutes of treatment Biphasic anaphylaxis – not defined	amine (H-1, IV) | Antihistamine (H-2, IV) | 57% Steroid (IV) | 69% Steroid (PO) | 16% Epinephrine (SQ | 63% β-agonist (nebulized) | 25% IV fluid (bolus) | 63% Vasopr or | 20% Intubation | 1%			male and antihistamine to the female. The first reaction was more serious (hypotension and upper airway angioedema) than the biphasic reaction (urticaria).			The authors state that those with biphasic reactions had an earlier onset of the initial reaction after antigen exposure than those reported in other studies and that the 'recurrence' was relatively minor. Serum markers not obtained in patients to distinguish between IgE and non-IgE reactions.
Brazil (1998) UK	Retrospective case series Objective: assess	34	Patients admitted to short-stay ward of medium sized accident and	Anaphylaxis: occurrence of one or more of generalised urticaria, upper or lower airway	Causes: Biphasic | Uniphasic Inse | 3 | 9	Adrenaline (intramuscular or subcutaneous) at conventional	18% (6/34)	Interval until development of the biphasic reaction: 4.5 to 29.5 hours	Patients with biphasic reactions required significantly more adrenaline	Not reported	Anaphylaxis definition only required one system to be affected; biphasic

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	how common clinically significant biphasic anaphylaxis occurs after apparently successful treatment after an anaphylactic reaction		emergency (A&E) department over 8 months with diagnosis of anaphylaxis requiring adrenaline. Gender: 56% (19) male 44% (15) female Age: 16 to 81 years	respiratory symptoms, gastrointestinal, central nervous system, or cardiovascular symptoms that occurred after antigen exposure. Biphasic reaction –when patient had completely improved after initial treatment only to develop further symptoms requiring adrenaline (without repeated exposure to causal agent).	ct bite/ sting Nuts 1 5 Penicillin 1 2 Cephalosporin - 1 Non-steroidal anti-inflammatory drugs (NSAIDs) 1 1 Shellfish - 1 Unknown - 9	doses until symptom resolution. Observation period not described.		(all but one occurred within 24 hours). Symptoms were similar to initial presentation.	than those with uniphasic reactions (mean 1.2 mg [0.5 to 2 mg] compared with 0.6 mg [0.3 to 1 mg]; p = 0.03). No other comparisons made (though authors stated that no other presenting clinical features predicted a biphasic response).		reaction needed to require adrenaline (biphasic was only rash + dyspnoea in one and rash + dysphagia in another). Clinical features of anaphylaxis of individual patients reported in study but not here because of space (and definitions of what was considered anaphylaxis were felt sufficient; this applies to other studies in this table). Not clear how long patients were followed up and if some could have

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					There were no deaths.						developed a biphasic reaction and presented at another A&E department or elsewhere.
De Swert (2008) Belgium	Prospective cohort Purpose to investigate frequency of anaphylaxis in paediatric population at tertiary or secondary referral level, demographic characteristics of these patients, clinical course and triggers, its	64 cases in 48 children	Consecutive paediatric patients seen for investigation of anaphylaxis at a paediatric department's outpatient allergy clinic, in a private practice for paediatric allergy, or in a private paediatric practice. Gender: 65% (31/48) male 35% (17/48) female Age: 6 months to 14.8 years	Anaphylaxis–a serious allergic reaction with rapid onset of symptoms occurring on a site that is remote from the contact site of the trigger and/or in at least two organ systems. Biphasic anaphylaxis – not defined	Causes: Food*,** 75 % (48) Medication 9% (5) Insect sting 7% (4) Latex 6% (3) Birch pollen 2% (1) Unidentified causes** 86 % (55/64) *12 peanut, 7 egg, 7 nut, 4 cow's milk, 3 kiwi, 2 apple, 1 in each of wheat,	Treatment protocol and observation period not described.	3% (2/64) of cases	After a 30-minute and 4-hour asymptomatic period	No comparison made.	Funded with grant from UCB, Belgium (global biopharma company)	Purpose was to look at frequency of anaphylaxis and rate of biphasic reactions was also reported but there was no comparison with uniphasic reactions. Not clear how long patients were followed up and if some could have developed a biphasic reaction and presented elsewhere. Authors

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	therapeutic approach and the coexistence of allergic symptoms and asthma. (not explicitly about biphasic anaphylaxis)		(mean and median: 6.9 years) 66.7% (32/48) with history of atopic disease 45.8% (22/48) were known to have asthma		lupine, fish, shellfish, 3 food additives **of those with no identified trigger, 6 had onset within minutes after ingestion of food but ingredients could not be fully identified (these have been included in 'food' category) All causes had been confirmed with skin prick test, CAP-system test or provocation test. Total duration of symptoms until complete recovery from 20 minutes to 120 hours Treatments received: Antihistamine 72 % (41) Corticosteroids 46 % (26)						suggested low rate of biphasic reactions compared with other studies could be because it may be lower in children or because of the use of corticosteroids in these patients but were unable to make conclusions.

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					Beta-2 mimetics: 25% (14) Adrenaline: 19% (11) Paracetamol: 1 None: 3						
Douglas (1994) USA	Retrospective case series Purpose to determine incidence of systemic biphasic anaphylactic reactions in both out and inpatients	94 Outpatient: 35 (44 reactions) (of 800 treated with 81,000 allergy injections over 3 years) Inpatients: 59 inpatient	Outpatient: patients who, during the 30-minute waiting period in the clinic, had experienced symptoms and signs consistent with anaphylaxis (between 1988 and 1991) Gender: 34% (12/35) male, 66% (23/35) female Mean age: 36 y (7 to 69) Inpatient:	Anaphylaxis – occurrence of one or more of the following: generalised urticaria or rash, laryngeal oedema with symptoms referable to this area such as throat tightness, hoarseness, dysphagia, dysarthria, wheezing, tightness, shortness of breath, sensation of impending doom, hypotension or	Outpatient causes: Pollen/dust/mould/mites: Biphasic 2, Uniphasic 28 Cat: - , 2 Venom*: - , 3 *1 yellow jacket, 1 white face hornet, 1 wasp or mixed vespid Inpatient causes:	Outpatient treatment – either adrenergic receptor agonist (subcutaneous epinephrine or inhaled Alupent or Proventil via nebulizer), H_1 receptor antagonist (oral diphenhydramine, terfenadine or hydroxyzine) or both as indicated	Outpatient: 5% (2/44) of reactions Inpatient: 7% (4/59) of patients	Outpatient: 22-24 hours and 6-8 hours Inpatient: 1, 24, 24 and 72 hours Of the 4 in the inpatient study group, 2 had biphasic reactions of greater severity than in the initial phase (the other 2 were of similar or less severity – only urticaria). Of the 2 in the outpatient group, the biphasic	Authors state that there were no distinguishing features between those with or without biphasic reactions. This includes the presence of hypotension or any other single sign of symptoms in the initial phase, such as urticaria. In the inpatient study, the absence of hypotension or severe upper or	Not reported	Anaphylaxis definition only required one system to be affected. Authors noted that reported rate of biphasic reactions is lower than in other publications. They could not determine why but suggested that, in the inpatient group, early intervention with glucocorticoste

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			patients admitted to medical ward or intensive care unit (Madigan Army Medical Centre) with diagnosis of systematic anaphylaxis (1986 to 1992) Gender: 71% (42/59) male 29% (17/59) female Mean age:35 y (6 months to 81 y)	cardiac or respiratory arrest after antigen exposure of any type (except in cases that were determined to be idiopathic). Biphasic reactions – occurred without repeat exposure to inciting antigen (not otherwise defined).	<table><tr><th></th><th>Biphasic</th><th>Uniphasic</th></tr><tr><td>Amoxicillin</td><td>2</td><td>1</td></tr><tr><td>Penicillin</td><td>-</td><td>2</td></tr><tr><td>Ampicillin</td><td>-</td><td>1</td></tr><tr><td>Other drugs[1]</td><td>-</td><td>14</td></tr><tr><td>Vaccine</td><td>-</td><td>2</td></tr><tr><td>Peanuts/peanut butter</td><td>-</td><td>3</td></tr><tr><td>Shrimp/crab</td><td>2</td><td>4[2]</td></tr><tr><td>Fish</td><td>-</td><td>2</td></tr><tr><td>Chicken</td><td>-</td><td>2[2]</td></tr><tr><td>Egg</td><td>-</td><td>1</td></tr><tr><td>Radiocontrast media</td><td>-</td><td>1</td></tr><tr><td>Skin</td><td>-</td><td>1</td></tr></table>	(none had glucocorticoteroids either during or after the initial episode). Outpatient observation – all were discharged after resolution of signs and symptoms but were instructed to return to either the clinic or hospital emergency room if symptoms recurred. Repeat history and physical examination by an allergist or telephone		symptoms were similar to the index reaction (urticaria for both in one patient and urticaria/angioedema followed by angioedema and rhinitis in the other)	lower respiratory tract obstruction did seem to distinguish those who did not have a late-phase reaction or biphasic pattern. See also 'characteristics of reaction'. Age: <table><tr><th>Setting</th><th>Biphasic</th><th>Uniphasic</th></tr><tr><td>Outpatient</td><td>39 and 7 years</td><td>7 1 69 ye</td></tr><tr><td>Inpatient</td><td>20, 52, 64, 77 years</td><td>6 m hs 81 ye</td></tr></table>		roids may have played a role (but noted the opposing findings by Stark et al [1986]). Outpatient observation period (12 or 24 hours) may not be long enough to detect biphasic reactions (in patient observation period not described).

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					test Hymenoptera sting - 3 Exercise - 5 Idiopathic - 12 [1]Codeine, aspirin, ibuprofen, tolmetin, captopril, lisinopril, or septra [2]in one patient, the agent was either shrimp or chicken There were no deaths.	contact by the clinic registered nurse occurred within 12 to 24 hours and detailed status was taken for the period 12 to 24 hours after initial episode. Inpatient treatment – adrenergic receptor agonist (subcutaneous epinephrine or inhaled β-receptor agent), H_1 and/or H_2 receptor antagonist, intravenous fluids, or glucocorticosteroids at the					

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						discretion of the patient. (observation period for inpatient group not described)					
Ellis (2007) Canada	Prospective cohort The objective was to determine the incidence, predictors and characteristics of biphasic anaphylactic reactions.	134 (FU only obtained for 103)	All patients with emergency department visits and all inpatients with a diagnosis of 'allergic reaction' or 'anaphylaxis' during 3-year period at a tertiary centre (1999–2001). Patients were contacted within 72 hours to establish symptoms and determine if they had biphasic activity.	Anaphylaxis (as per Canadian Pediatric Surveillance Program) – 'severe allergic reaction to any stimulus, having sudden onset and generally lasting less than 24 hours; a disorder involving at least two body systems, with multiple symptoms such as hives, flushing, angioedema, stridor, wheezing, shortness of breath, vomiting, diarrhoea or	Causes: % Number / Biphasic (n = 20) / Uniphasic (n = 83) Hymenoptera: 22% (18) / 22% (30) Food: Peanut: 11% (9) / 8% (11) Other nuts: 8% (7) / 8% (11) Seafood: 7% (6) / 9% (12) Milk: 2% (2) / 2% (3) Oth: 4% / 6%	Patients were contacted after 72 hours after the ED visit to see if biphasic reaction occurred. Average duration of ED observation time was 3.8 hours. (Treatment protocol not reported)	19.4% (20/103) of those available for follow-up (FU) had biphasic activity. 55% were clinically similar to the initial reaction, 35% were milder, 40% involved life-threatening manifestations (i.e. hypotension, throat or	Average 10 hours after initial reaction, range: 2 to 38 hours, but 40% (8) occurred more than 10 hours later. 20% (4) occurred after 20 h (most within 22 h, but one at 38h) All cases were carefully checked to ensure no further antigen exposure caused 2nd reaction (ex. food cases with 2nd reaction occurring > 20	Comparisons: (for difference in causes see 'characteristics of reaction') Biphasic (n = 20) / Uniphasic (n = 83) Median age: 25 / 33 Paediatric (< 13 years): 15% (3) / 8% (7) Females: 45% (9) / 47% (3) Prio: 35 / 47	Not reported	In those with late biphasic reactions (after 9 hours), a longer time to resolution of initial symptoms was the only predictor of a late reaction (193 minutes compared with 112 minutes for uniphasic reactions, p = 0.006). No biphasic reactions occurred in patients who responded completely to treatment in less than half

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			Median age: 33 y (11 months to 79 years) Gender: 54% (56/103) male 47% (48/103) female	shock.' Biphasic reaction –the reaction had to meet the same definition as above without further antigen exposure (recurrence of urticaria or another rash alone were excluded)	er (3) (8) Total 35% (29) 38% (51) Medication: Penicillin derivatives 1% (1) 2% (3) Other antibiotics 5% (4) 3% (4) NSAIDs 5% (4) 4% (5) Immunotherapy 1% (1) 3% (4) Other 6% (5) 5% (6) Total 18% (15) 16% (22) Unknown/idiopathic: Unknow 15% 14%		tongue swelling; usually these were also present in the initial reaction), 20% required more aggressive therapy to resolve symptoms. Urticaria occurred in all biphasic reactions but was not always present in the initial reaction.	hours later to exclude secondary antigen absorption). However, for the reaction that occurred at 38 h, it was not possible to determine cause and rule out repeated exposure.	r anaphylaxis % (7) % (39) Prior asthma 40% (8) 36% (30) 0.90 Median time to symptom onset 15 15 0.90 B-agonist use 10% (2) 28% (23) 0.15 Epi eph in e use 55% (11) 82% (68) 0.13 Total/median epin ephr 0.30 mg/0.21 mg 0.39 mg / 0.32 mg 0.048		hour. All 14 patients with symptom resolution within 30 minutes were treated with epinephrine (100% vs 73%, p = 0.03). They were also more likely to have had a history of anaphylaxis than biphasic reactors (57% vs 26%), and were slightly younger (median 22 vs 25 years) but these were not statistically significantly different. They were significantly younger than the others with uniphasic

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					n (12) (19) Idiopathic 7% (6) 5% (7) Total 21% (18) 19% (26) (occurrence rates between different antigens not significantly different between uniphasic and biphasic reactions, p > 0.25)				ine Corticosteroid use 35% (7) 55% (46) 0.07 Mean prednisone dose 31mg 63mg 0.06 H_1-antagonist use 95% (19) 95% (7) > 0.99 H_2 antagonist use 20% (4) 30% (25) 0.42 Time to resolution of initial sympto 133 min 112 min 0.03		reactions (median 22 vs 35 years, p = 0.03). Higher rate of biphasic reactions could be due to prospective nature (with retrospective designs not capturing all reactions); timing suggests previously recommender 1-8 hours is not sufficient.

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<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>ms
(medical records of those lost to FU did not reveal any ostensible differences in age).</td><td></td><td></td></tr>
<tr><td>Järvinen (2009)

USA</td><td>Retrospective case series

Objective: to determine the prevalence and risk factors of reactions requiring epinephrine and the rate of biphasic reactions during oral food challenges in children</td><td>50</td><td>Children with positive oral food challenges to diagnose allergy who had reactions requiring epinephrine.

34% (436/1273) of oral food challenges resulted in a reaction with 11% (50/436) requiring epinephrine

Reactions requiring epinephrine occurred in older children</td><td>Anaphylaxis – serious allergic reaction that is rapid in onset (within minutes to several hours after food ingestion) and affecting at least 2 major organ systems; all required epinephrine

Biphasic – recurrence of symptoms after resolution of the initial event in 1 to 78 hours</td><td>Causes:<table><tr><th></th><th>No. of patients</th></tr><tr><td>Egg</td><td>15</td></tr><tr><td>Milk</td><td>14</td></tr><tr><td>Peanut</td><td>10</td></tr><tr><td>Tree nuts</td><td>4</td></tr><tr><td>Soy</td><td>3</td></tr><tr><td>Wheat</td><td>3</td></tr><tr><td>Fish</td><td>1</td></tr></table>Median time of onset of reaction from last dose of food challenge: 5 minutes (range 1-60)

None were life-threatening</td><td>Patients observed for 4 hours after reaction.

Patients were treated with epinephrine if signs of a reaction.</td><td>2% (1/50)</td><td>1 hour</td><td>No comparison made.</td><td>One author is a consultant and shareholder for Allertein Pharmaceuticals and is 45% owner of Herbal Springs, LLC.</td><td>Patients only followed up for 4 hours and they could have developed a biphasic reaction beyond this period (so the rate may be an underestimate).</td></tr>
</table>

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<tr><th colspan="11">Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</th></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>(median 7.9 vs 5.8 years, p < 0.001) and were most often caused by peanuts (p = 0.006)

Children with positive challenges ranged from 1.25 to 18 years (median 6 years)

Gender: 60% (30) male, 40% (20) female</td><td></td><td>respiratory or cardiovascular compromise.

Treatment:
2 doses of epinephrine were required in 3 patients reacting to wheat, cow’s milk, and pistachio.
<table>
<tr><th></th><th>Epinephrine (n = 50)</th><th>No epinephrine (n= 386)</th></tr>
<tr><td>Antihistamine</td><td>98 % (49)</td><td>80 % (309)</td></tr>
<tr><td>Steroids</td><td>58 % (29)</td><td>5% (21)</td></tr>
<tr><td>Albuterol nebulization</td><td>14 % (7)</td><td><1 % (3)</td></tr>
<tr><td>IV fluid</td><td>8%</td><td><3 %</td></tr>
</table></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

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					s (4) (10) Oxygen 4% (2) 0%						
Jirapongsananuruk (2007) Thailand	Retrospective case series Objective: to describe the clinical characteristics of patients with anaphylaxis admitted to Siriraj Hospital	101	All inpatient department admissions for 5 years (1999–2004). ICD-10 codes: T78.0 (anaphylactic shock due to adverse food reaction), T78.2 (anaphylactic shock, unspecified), T78.3 (angioneurotic oedema, laryngeal oedema, Quincke oedema, urticaria-larynx), T80.5 (anaphylactic shock due to serum), T88.6 (anaphylactic shock due to adverse effect	Anaphylaxis – severe, life-threatening generalised or systemic hypersensitivity reaction as suggested by the World Allergy Organisation. In order to be considered anaphylaxis, one of the symptoms of generalised mediator release such as flushing, pruritis or paraesthesia of the lips, axilla, hands, or feet; general pruritis, urticaria or angioedema, lip tingling or paraesthesia, and conjunctivitis or	Causes: Unidentified causes: 15 Drugs Antibiotics: 21 Radiocontrast media: 7 Allergen immunotherapy: 7 Chemotherapy: 5 NSAIDs: 4 IV immunoglobulin/hydrochlorothiazide/10% Cocaine/I: 1 each (No. of patients)	Treatment protocol and observation period not described.	7% (4) of children and 2% (1) of adults	No more details provided	No comparison made.	Not reported	Not clear how long patients were followed up and if some could have developed a biphasic reaction and presented elsewhere. ICD codes identified 228 records; 2 authors selected 101 that met definition of anaphylaxis. Significantly more male paediatric patients experienced anaphylaxis than female paediatric patients; while

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			of correct drug of medicament properly administered), T63.2 (venom of scorpion), T63.4 (venom of other arthropods, insect bit or sting, venomous), T38.3 (angioedema), L50.0 (allergic urticaria), L50.9 (urticaria unspecified), J38.4 (oedema of larynx exclude laryngitis, croup), J46 and R11 (asthma and vomiting), J46 and R55 (asthma and syncope), R06.2 and R11 (wheezing and vomiting), R06.2 and	chemosis AND at least one of: 1) oral and gastrointestinal system (oral mucosal pruritus; intraoral angioedema or buccal mucosa, tongue, palate, or oropharynx; nausea, emesis, dysphagia, abdominal cramps, or diarrhoea, 2) respiratory system: rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnoea, wheezing, hypopharyngeal or pharyngeal oedema, or cyanosis or 3) cardiovascular system: chest	ron-sucrose/amifostine, unidentified drugs Total: 51 Food Seafood 11 Wheat 2 Wheat-dependent exercise 1 Milk 1 Fried insects/freshwater prawn/freshwater fished bread/freshwater fish maw 1 each Unidentified food 5 Total: 24 Insect sting/bite Fire ant 6 Wasp 3 Centiped 1						significantly more female adults experienced anaphylaxis than male adult patients.

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			T38.3 (wheezing and angioedema), J46 and T38.3 (asthma and angioedema) Mean age: 23.7 years (SD 21.8, range:2.8 months to 81.3 years) 54 were paediatric (≤ 16 years), 47 were adult Gender: 5% (53) male, 48% (48) female Gender of paediatric patients: 37 male, 17 female Gender of adults: 16 male, 31 female	pain, arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures or shock Biphasic anaphylaxis – not defined	e/rasp: each Treatments received: Antihistamine: 93 Corticosteroids: 83 IV fluid: 81 Epinephrine: 78 Inhaled β_2-agonist: 39 Dopamine: 9 O_2 therapy: 5 Sodium bicarbonate: 1						

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<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr>
<td>Lee (2000)

USA</td>
<td>Retrospective case series

Objective: 1 – determine incidence of biphasic reaction in children with anaphylaxis, 2 – establish risk factors, 3 – assess utility of inpatients observation for patients who appear to have resolved anaphylaxis</td>
<td>108 episodes in 106 patients

but only 77% (83) considered serious (see definitions column)</td>
<td>All children admitted to children's hospital inpatient service between 1985 and 1999 with acute anaphylaxis.

Medical records searched by ICD-9 classifications: 1) 995.0-995.3 (anaphylactic shock, angioneurotic oedema, unspecified adverse effect of drug, medicinal, biological substance, or allergy unspecified) 2) 995.6-995.69 (due to adverse food reaction)</td>
<td>Anaphylaxis – acute allergic reaction with involvement of at least 2 body systems: dermatologic, neurologic, gastrointestinal, respiratory, cardiovascular (chronic idiopathic cases and anaphylaxis that developed during hospitalisation for another condition excluded).

Biphasic reactions – worsening of symptoms requiring new therapy after resolution of anaphylaxis (defined as cessation of all symptoms requiring no</td>
<td>Causes:
<table>
<tr><th></th><th>Biphasic</th><th>Uniphasic</th></tr>
<tr><td>Food</td><td>2[1]</td><td>49[1]</td></tr>
<tr><td>Medications</td><td>2[2]</td><td>22</td></tr>
<tr><td>Insect bite</td><td>2</td><td>10</td></tr>
<tr><td>Immunotherapy</td><td>-</td><td>3</td></tr>
<tr><td>Immunization</td><td>-</td><td>1</td></tr>
<tr><td>Contrast dye</td><td>-</td><td>1</td></tr>
<tr><td>Unknown</td><td>-</td><td>16</td></tr>
</table>
[1] 14 tree nut, 12 peanuts, 8 seafood, 3 fruit, 2 eggs, 2 seeds, (biphasic:</td>
<td>Patients were observed if they had significant biphasic reaction within 24 hours of admission.

Of all patients, mean length of hospitalisation was 24 hours (median 19).</td>
<td>6% (6/105) (95% confidence interval [CI]: 2, 12)

3% (3/105) were considered significant (95% CI 0.6, 8).</td>
<td>Resolution of symptoms to onset of biphasic reaction: from 1.3 hours to 28.4 hours (all but one had occurred within 12 hours).

The same organ systems were involved. One patient experienced more serious respiratory symptoms in the second reaction and also experienced new onset stridor.</td>
<td>Comparison:
<table>
<tr><th></th><th>Biphasic (n = 6)</th></tr>
<tr><td>Male gender</td><td>50% (3)</td></tr>
<tr><td>Mean age (y)</td><td>8.0</td></tr>
<tr><td>Oral ingestion of trigger</td><td>67% (4)</td></tr>
<tr><td>Epinephrine given initially</td><td>100 %</td></tr>
<tr><td>Median time to initial dose of epinephrine (min)*</td><td>190</td></tr>
<tr><td>Steroids given initially</td><td>84% (5)</td></tr>
</table>
*p = 0.03 (Mann-Whitney U test)</td>
<td>Not reported</td>
<td>Only patients hospitalised for anaphylaxis so may not be representative of all those with anaphylaxis or biphasic reactions compared with those presenting to an ED.

24 hours may not be sufficient period to detect a biphasic reaction. One patient had a reaction beyond the 24 hours they were observed.

Unclear how long patients without a</td>
</tr>
</table>

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			3) 999.4 (due to serum) 62% (66) male 40% (42) female Median age: 8 years (range 6 months to 21 years) 64% (69) had positive atopic history for asthma, eczema, or allergic rhinitis	therapy for at least 1 hour). Significant biphasic reactions – requiring oxygen, vasopressors, intubation, subcutaneous epinephrine, unscheduled bronchodilator treatments	nut and fish), [3] dicloxacillin, trimethoprim-sulfamethoxazole (of those with identified trigger, 33% [30/92] with prior history of allergy to the same trigger). Route: Oral: 65 Subcutaneous: 18 Intravenous: 8 Inhaled: 2 Unknown: 15 2% (2/108) were fatal Time from exposure to allergen to onset of symptoms (available in 76 patients): mean 31 ± 71 minutes (from				No difference in serious respiratory or cardiovascular symptoms in initial reaction and no significant differences in the type of allergenic trigger.		significant reaction were observed so unable to tell if observed sufficiently to detect a biphasic reaction.

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
					< 1 minute to 9.7 hours), median 10 minutes. Time from onset of symptoms to first administration of subcutaneous epinephrine: mean 113 ± 176 minutes (from < 1 minute to 17.4 hours), median 50 minutes.						
Mehr (2009) Australia	Retrospective case series Objective was to determine predictive factors for biphasic reactions in children presenting with anaphylaxis	145 episodes in 138 children but 104 after exclusion criteria applied (see 'additional comments' column)	Children presenting with anaphylaxis to a major paediatric emergency department and admitted for more than 6 hours over 5 years (1998–2003). Medical records searched using International Classification	Anaphylaxis – multi-system allergic reaction characterised by one or more clinical features involving the respiratory and/or cardiovascular system (CVS) associated with one or more clinical features involving the skin and/or gastrointestinal tract (GIT) as described by the National Institute	Causes: Biphasic (n = 12) / Uniphasic (n = 95) Food: 75% (9) / 83% (79) Drug: 8% (1) / 7% (7) Insect bite: 0% (0) / 4% (4) Unknown: 17% (2) / 5% (5) (none of these	Treatment protocol not described. Patients included if they were admitted for at least 6 hours but time period they were observed after this was not described.	11% (12/109) Of these only 5 (4.6% of all) were 'anaphylactic' and 7 (6.4% of all) they were 'non-anaphylactic'. The biphasic reaction was milder in 58% (7/12), of	Median time from onset of original reaction to onset of biphasic reaction: 8.8 hours (range: 1.3 to 20.5)	*Comparison of patient characteristics:* Biphasic n=12 / Uniphasic n=95 Male gender: 67% (8) / 58% (55) Median age at presentation (y): 9.6 (0.2-16.7) / 5.3 (0.2-17.8) Presence of atopic disease: 58% (7) / 39% (37)	None declared	Not clear how long patients were followed up and if some could have developed a biphasic reaction and presented elsewhere. Exclusions: 23 episodes of patients observed for < 6 hours (0.9 to 4.4 hours) and discharged directly from

<table>
<tr><th colspan="11">Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?</th></tr>
<tr><th>Bibliographic reference</th><th>Study type and objective</th><th>n</th><th>Patient characteristics</th><th>Definitions</th><th>Characteristics of initial reaction</th><th>Anaphylaxis treatment protocol and observation</th><th>Rate of biphasic reactions</th><th>Timing of biphasic reaction and characteristics</th><th>Comparison of patients with biphasic to those with uniphasic reactions</th><th>Funding source</th><th>Additional comments</th></tr>
<tr>
<td></td><td></td><td></td>
<td>of Disease (ICD) version 10 with Australian Modification codes: anaphylactic shock due to adverse food reaction (T78.0), unspecified (T78.2), serum (T80.5), properly administered drugs (T88.6), allergy unspecified (T78.4) and other adverse food reactions not elsewhere classified (T78.1).

Median age: 2.5 years (range 0.2 to 18.8)
Gender: 60% (62) male, 40% (42)</td>
<td>of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network consensus definitions.

Biphasic – second reaction after initial recovery for at least 1 hour during which there were no new treatments or symptoms or re-exposure.

Protracted – no initial recovery period

Non-anaphylactic allergic reaction –characterised by one or more symptoms or signs involving the skin and/or</td>
<td>differences were statistically significant)

Route:
<table>
<tr><th></th><th>Biphasic (n = 12)</th><th>Uniphasic (n = 95)</th></tr>
<tr><td>Oral</td><td>75% (9)</td><td>86% (82)</td></tr>
<tr><td>Subcutaneous</td><td>0% (0)</td><td>4% (4)</td></tr>
<tr><td>Intravenous/ intramuscular</td><td>8% (1)</td><td>4% (4)</td></tr>
<tr><td>Topical</td><td>0% (0)</td><td>1% (1)</td></tr>
<tr><td>Unknown</td><td>17% (2)</td><td>4% (4)</td></tr>
</table>
(none of these</td>
<td></td>
<td>similar severity in 33% (4/12) and more severe in one case (9%).
One had hypotension requiring adrenaline infusion.</td>
<td></td>
<td>
<table>
<tr><td>Asthma</td><td>25% (3)</td><td>31% (28)</td></tr>
<tr><td>Prior anaphylaxis</td><td>17% (2)</td><td>11% (10)</td></tr>
<tr><td>Median time from exposure to anaphylaxis (min)</td><td>10 (2-210)</td><td>10 (1-450)</td></tr>
</table>
(none of these differences were statistically significant)

Comparison of adrenaline use at initial reaction:
<table>
<tr><th></th><th>Biphasic n=12</th></tr>
<tr><td>% administered</td><td>75% (9)</td></tr>
<tr><td>Median time to</td><td>28 (3-</td></tr>
</table>
</td>
<td></td>
<td>the emergency department, 13 episodes because of daily use of chemotherapeutic or biological agents (n = 10), corticosteroids (n = 2), or antihistamines (n = 1)

Need for > 1 adrenaline dose and / or fluid bolus during the initial reaction were calculated to be sensitive and moderately specific predictors of a biphasic reaction (sensitivity 92%, 95% CI 62-100%,</td>
</tr>
</table>

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions		Funding source	Additional comments
			female	GIT without involvement of either the CVS or respiratory systems (CVS-hypotension, loss of impairment of conscious state, pale and floppy presentation in an infant; respiratory-difficulty or noisy breathing, swelling of the tongue, swelling or tightness of the throat, difficulty talking, hoarse voice, stridor, wheeze, persistent cough, tachypnoea; GIT-abdominal pain, vomiting, diarrhoea; skin-angioedema, hives, urticaria, generalised pruritis, erythema).	differences were statistically significant) There was one death in a patient with a protracted reaction.				first dose (min)	130)		specificity 76%, 95% CI 66-84%). Absence of either risk factor was strongly predictive of the absence of a biphasic reaction (negative predictive value: 99%, 95% CI 93-100%) while presence of either factor was poorly predictive of a biphasic reaction (positive predictive value: 32%, 95% CI 17-51%).
									>1 dose[1]	58% (7)	22% (21)	
									Route of administration:			
									Parenteral	44% (4	75% (60)	
									Nebulized	11% (1)	6% (5)	
									Parenteral and nebulized[2]	44% (4)	15% (12)	
									Unknown	0% (0)	4% (3)	
									Administration site:			
									Royal Children's Hospital Emergency Department	56% (5)	48% (38)	
									Local emergency	33% (3)	16% (13)	

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									<table><tr><td>department</td><td></td><td></td></tr><tr><td>General practitioners</td><td>11% (1)</td><td>20% (16)</td></tr><tr><td>Parents</td><td>0% (0)</td><td>8% (6)</td></tr><tr><td>Ambulance</td><td>0% (0)</td><td>9% (7)</td></tr></table> [1] p=0.01, [2] p = 0.05 (all others not significantly different) *Comparison of other therapies at initial reaction:* <table><tr><td></td><td>Biphasic n=12</td></tr><tr><td>IV fluid bolus*</td><td>83% (10)</td></tr><tr><td>Median volume of fluid bolus (ml/kg)</td><td>20 (8-56)</td></tr><tr><td>Oxygen require</td><td>50%</td></tr></table>		

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									d (6) (29) Intubated 8% (1) 79% (75) *p = 0.01 (others not significant) There were also no significant differences in corticosteroid or antihistamine use or in the time to use of these drugs between groups.		
Poachanukoon (2006) Thailand	Retrospective case series Objective: estimate incidence of anaphylaxis in an emergency department	64 patients with 65 anaphylactic episodes (223/100 000 anaphylaxis occurrence rate)	Patients who attended emergency department at one hospital in Thailand during a one year period (2003–4) (based on ICD-9 and ICD-10 terms). 53% (34) male 47% (30) female	Anaphylaxis: presence of one symptom of generalised mediator release such as flushing; pruritis or paraesthesia of lips, axilla, hands, or feet; general pruritis; urticaria or angioedema; lip tingling; and conjunctivitis or chemosis INCLUDING at	Causes: Food[1] 40% (26) Drugs 36% (23) *Hymenoptera* 5% (3) Radiocontrast agent 2% (1)	Treatment protocol and observation period not described.	15% (8/52) of those with resolved initial anaphylactic symptoms	Timing not reported.	*Comparison:* Biphasic n=8 Age 22,6 y Male sex 50% (4) Atopy 50% (4) Shock in initial phase 38% (3) Mean time 48 min	Thammasat University research fund.	Not clear how long patients were followed up and if some could have developed a biphasic reaction and presented elsewhere. Rate of those with biphasic reactions is in patients with resolved symptoms

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Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			Median 26 years old (range: 1 month to 65 years) 55% (35) had atopy of allergic rhinitis, atopic dermatitis, asthma, urticaria or drug/food allergy.	least one symptom involving the oral and gastrointestinal, respiratory, or cardiovascular systems. Biphasic anaphylaxis–not defined	Unknown 17 % (11) [1] 22 seafood, 3 cow milk, 1 wheat [2] 8 NSAID, 9 penicillin and others like anti-tuberculosis drugs and muscle relaxants 1 patient with history of cardiovascular disease died (1.6% death rate) 89% (57) received epinephrine (40 intramuscular, 16 subcutaneous, 1 IV), 100% H_1-antagonists, 61% (39) H_2-antagonists, 77% (49) corticosteroids, 23% (15) beta-agonists.				after allergen exposure Epinephrine use 100 % (8) 91% (40) Steroid use 88% (7) 80% (35) Mean time to initial dose of epinephrine 263 min 82 min All p > 0.05.		from the initial episode. The reason why these patients' symptoms were unresolved was not stated (i.e. if protracted symptoms).
Sampson (1992)	Cross-sectional study	13	Children or adolescents with fatal or near-fatal	Near-fatal reaction–episode of anaphylaxis	Causes:	Treatment protocol and observation period not	3 patients included had biphasic	1 to 2 hours symptom-free period	No comparison made.	Not reported	Since the design of this study is cross-sectional, it

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USA	To identify reports of fatal or near-fatal anaphylactic reactions to food by children		anaphylactic reactions to foods identified from a review of emergency medical case reports, medical records, depositions by witnesses to the events, interviews with parents (and some patients). (in 3 metropolitan areas over a period of 14 months) Gender: 76% (10/13) female; 23% (3/13) male Mean age: 12y (2 to 17)	requiring admission to an intensive care unit for intubation, mechanical ventilation, and vasopressor support. Severe symptoms–obvious respiratory distress, retractions, wheezing, and in some cases, cyanosis or loss of consciousness Biphasic reaction–not defined	<table><tr><th></th><th>Number</th></tr><tr><td>Peanuts</td><td>4</td></tr><tr><td>Nuts</td><td>6</td></tr><tr><td>Eggs</td><td>1</td></tr><tr><td>Milk</td><td>2</td></tr></table>(all had known allergies) 6 had symptoms within 3 to 30 minutes but only two received epinephrine in the first hour. 6 died Of those that survived, all had symptoms within 5 minutes of allergen ingestion and all but one received epinephrine within 30 minutes.	described.	reactions (because of cross-sectional design, this study does not give information about the frequency)				does not give information on the frequency of biphasic reactions (the authors acknowledge this). Patients included have had very severe reactions (near-fatal or fatal) so are a very specific subgroup of patients and do not represent all patients presenting with anaphylaxis.
Scranton	Prospective cohort	60 (55 patients)	Patients treated with	Anaphylaxis–life-threatening	25% (15) occurred in children less than	Observation for 1 to 2	23% (14/60) of	Median time 5.5 hours (range 2	*Comparison of patient and*	Not reported	Precise definition of

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(2009) USA	Objective: to determine the incidence, clinical characteristics, and risk factors for biphasic reactions after allergen-specific immunotherapy	(of 10,932 immunotherapy injections in 330 patients at one site and 12.796 in 366 patients at the other site)	epinephrine for systemic reactions after allergen immunotherapy (with aqueous extracts; either Hymenoptera or aeroallergens) at 2 hospitals in 14 month period (2006–07). Mean age: 33 years (range: 6 to 76) Gender: 35% (19) male, 65% (36) female *Immunotherapy characteristics:* 62% were receiving 1:1 vol/vol vial and 13% 1:10	allergic reaction (symptoms assessed with a 31-symptom scoring system with 5 main categories: general, skin, gastrointestinal, respiratory, cardiovascular/neurologic). Biphasic reaction–any reaction occurring after discharge from the clinic up to 24 hours after their initial symptoms	18 years old. 63% (38) occurred during the build-up phase of immunotherapy. Time from allergen immunotherapy to initial systemic reaction was 25 minutes (range: 1-180)	hours after last dose of epinephrine. Subjects then instructed to observe and record any clinical symptoms during the next 24 hours when they were telephoned and results on the 31-symptom scoring system were recorded. Treatment protocol not reported.	reactions (none occurred in children)	to 24) Subjective severity of biphasic reaction was 10% or less in 64% (9) patients. 93% (13/14) considered the severity to be 25% or less of their initial reaction. Total symptom score was significantly less during the biphasic reaction compared with initial symptom scores (1.3 ± 0.5 and 4.1 ± 1.8, p < 0.001). Median duration of biphasic symptoms: 53 minute (from 1-480) and 57% lasted ≤1 hour.	*immunotherapy characteristics:* Biphasic n=14 Age[1] 41 y ±13 Male sex[2] 1 Build-up phase 9 Immunotherapy duration 2.3 y ±6.0 Aeroallergen immunotherapy Current asthma Daily antihistamine 11 Prior system 4		anaphylaxis not reported (though all required epinephrine). 24 hours may not be long enough to detect biphasic reactions. At site 1, 5 were excluded because they did not require epinephrine and 10 because the site investigator was not present when they were being treated. Site 2 excluded 4 patients who did not require epinephrine. Symptoms in the biphasic

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			vol/vol vial (average duration of immunotherapy was 1.2 ± 3.2 years) 70% aeroallergen vs 30% venom Of all that received immunotherapy at both sites, the rate of patients requiring epinephrine: Site 1 – 0.78% Hymenoptera, 0.38% aeroallergens (p = 0.32) Site 2 – 0.91% Hymenoptera, 0.23% aeroallergen (p < 0.0001).					None of the biphasic reactions required epinephrine or required a trip to the emergency department. 21% (3/14) took an additional oral antihistamine at the onset of biphasic symptoms, 21% (3/14) used their β_2-agonist rescue inhaler.	atic reaction to immunotherapy Less than 18 years old[3] 0 [1] p = 0.01, [2]p = 0.03, [3]p = 0.01 *Comparison of reaction and therapy:* Biphasic n=14 Symptom onset (min) 17 ±14 Time to epinephrine (min) 8.2 ± 12.8 > 1 dose epinephrine* 9	15	reaction were not as severe and none required epinephrine.

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									Oral antihistamine: 11 / 37 Oral corticosteroid: 1 / 6 Albuterol nebulization: 2 / 10 Time to >90% improvement (min): 20 ± 10 / 33 ± 37 *p = 0.001		
Smit (2005) Hong Kong	Retrospective case series Objective to describe the epidemiology, clinical characteristics, and management of acute	282 (9 were excluded – see 'additional comments')	Patients presenting consecutively to the resuscitation room of a large Hong Kong emergency department with a diagnosis of anaphylaxis	Anaphylaxis–included both anaphylactic (IgE-mediated systematic immune response) and anaphylactoid reaction (non-IgE-mediated systemic immune response).	Causes: Seafood: Biphasic (n=15) 33% (5); Uniphasic (n=267) 31% (84) Other: 0% (0); 13%	Median time spent in the observation ward was 10.6 hours (observation protocol: patients were admitted into the ED observation ward if the	5.3% (15/282)	Mean time from treatment to onset of biphasic reaction: 8 hours (range 1 to 23) (9 occurred more than 8h after initial presentation and 6 of these 8h after initial treatment).	*Comparison of patient characteristics & of first reaction:* Biphasic (n=15) Age: 33y (IQR 19-41.3	Not reported	Authors confirmed (with Hong Kong ID #) that no patients presented to other hospitals with a biphasic reaction within 5 days.

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	anaphylaxis in a population in Hong Kong to determine the incidence and nature of biphasic reactions and possibly predict progression to a biphasic reaction		from 1999 to 2003. Only those with hypotension, severe cutaneous manifestation, respiratory or airway compromise, cardiovascular compromise, cardiovascular compromise (such as hypotension or dysrhythmias, syncope or loss of consciousness), or any suspicious by the triage nurse of likely respiratory or circulatory compromise were triaged to resuscitation room.	Biphasic reaction-any reaction occurring after initial treatment and complete resolution of symptoms.	food 26 % (36) Drugs* 26 % (4) 37 % (98) Insect bite/ sting 7% (1) 6% (17) Plants and hair dye 0% (0) 1% (4) Gas inhalation 0% (0) 0.4 % (1) Unknown 13 % (2) 0% (0) Not documented 20 % (3) 0% (0) *including analgesia in 26 cases, antibiotics in 24 and 52 of other drugs (including 22 from Chinese medicine);	specialist emergency physician believed the patient was likely to be discharged within 12 and 24 hours but follow-up protocol length not described). Treatment protocol not described.		3 were paediatric patients (< 15 years) Most reactions were mild with the same clinical features as the same reaction. Mean time to presentation at the ED onset of biphasic reaction was 8.22 hours (SD 5.46, range 1.4-23); time from receiving treatment from onset of biphasic reaction: 7.57 hours (SD 5.46, range: 1.22-22.5)	) Male sex 67% (10) 59% (157) Time from onset to presentation* 3 h (IQR 2.0-6.3) 1.0 h (IQR 0.7-3.0) Time in ED* 1.42 (IQR 0.74-2.2) 0.72 (IQR 0.5-1.0) Time in hospital (observation and general ward)* 1.33 d (IQR 0.67-2.58) 0.53 (IQR 0.34-1.09) Asthmatic history 33% (1) 67% (53) Allergy history 39% (5) 47% (111) *p < 0.01 (all others not significant) *Comparison of therapy:*		Definition of anaphylaxis includes non-IgE-mediated reactions. 9 patients excluded (5 charts were unavailable and 4 had a final diagnosis that was not anaphylaxis – 3 asthma and 1 Steven Johnson's syndrome). 10.6 hours not likely to be long enough to detect biphasic reactions. Causes of anaphylaxis were as reported by patient (i.e. which food eaten) and not based on

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			All those logged as 'allergy, allergic reaction, anaphylactic reaction or shock, anaphylaxis, anaphylactoid reaction, bee stings or other insect bits, drug reactions, angioedema/angioneurotic oedema, or urticaria' were included but those without final diagnosis of anaphylaxis were excluded. Median age: 28 years (range: 1-91, interquartile range [IQR] 19-43) Gender: 59% (167) male,		this was the only comparison that was significantly different (p = 0.032) Median time from onset of symptoms to presentation at the department was: 1.3 hours (IQR 0.79-3.0). 6% (17) had antihistamines before arrival but only 6 received steroids and 2 epinephrine before arrival. None died. 1.4% (4) were discharged from ED, 3.2% (9) discharged themselves against medical advice, 40.8% (115) were admitted to hospital, 82% (93/115) to general ward, 19% 22/115) to ICU.						allergy testing.

	Biphasic (n= 15)	Uniphasic (n= 267)
IV fluids	20% (3)	32% (85)
Epinephrine	73% (11)	66% (177)
H1 antagonist	100 % (15)	95% (254)
H2 antagonist	0% (0)	1.5% (4)
Steroids	87% (13)	92% (245
Salbutamol*	7% (1)	35% (94)

*p = 0.023 (only significant difference)
There was also no significant difference in ipratroprium bromide use or intubation.

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Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			41% (115) female Previous history of asthma: 19% (54)		Median time spent as an inpatient was 1.45 days (range: 0.33-21.57).						
Stark (1986) USA	Prospective cohort Objective to analyse causes, presenting characteristics, and subsequent courses of patients with anaphylaxis to determine the incidence of recurrent or prolonged anaphylaxis and identify factors that	25	Consecutive patients presenting in a 2-year period (1982–84) with anaphylaxis (IgE and non-IgE-mediated) to one hospital. Adults: mean 41.8 years (range 17 to 71) Gender: 28% (7/25) males, 72% (18/25) female	Anaphylaxis–based on 2 criteria: 1) presence of acute, otherwise unexplained syndrome that included hypotension, laryngeal oedema, or lower respiratory obstruction and 2) clinical or immunologic phenomena supporting the diagnosis (concurrent presence of other symptoms or signs of mast cell-mediator release such as flushing, urticaria,	Causes: Biphasic (n=5); Uniphasic (n=20) Drugs: 5* ; 7** Antivenom: 0 ; 1 Insulin: 0 ; 1 Food: 0 ; 3 Unknown: 0 ; 1 * these included penicillin (2), cephalexin (2) and radiocontrast media (1); ** these included these	Cardiac monitoring, airway management, oxygen, epinephrine, diphenhydramine, cimetidine, theophylline, infused sympathatomimetrics and normal saline were administered in most instances according to published guidelines. Patients were observed for 12 hours,	20% (5/25)	Asymptomatic intervals between 1 and 8 hours. 3 of the 5 had initial treatment with glucocorticoids	*Comparison of patient characteristics and treatments:* Biphasic (n=5) Age: 35y (21–67) Male sex: 40% (2) Epinephrine: 80% (4) H1 antagonist: 100% (5) H2 antagonist: 60% (3) Steroids: 80% (4)	Not reporter	'Anaphylaxis' included non-IgE-mediated reactions (13 had evidence IgE mechanism). 12 hours may not be long enough to observe patients to detect biphasic reaction (and those with prolonged symptoms were not observed beyond resolution of symptoms which may also be inadequate to

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
	might predict or diminish their occurrence.			angioedema, or intense pruritis or evidence of the presence of IgE to the substance considered likely to have caused the reaction. Biphasic anaphylaxis–not defined	included penicillin (4), cephazolin (1) and radiocontrast media (2) 13 were shown to have had IgE mechanism involved Skin tests positive in 10 of 11 with penicillin and cephalosporin causes (1 had persistent antihistamine and α-adrenergic agonist therapy), both with insulin and antivenom, and one food-allergic patient (soy bean extract). The other 2 food-allergic patients did not have IgE-mediated reactions.	until the reaction ceased, if symptoms persisted longer than 12 hours, or until death. When probably IgE-mediated, specific IgE by immediate wheal-and-flare skin testing was used and patients were tested for sensitivity to penicillin, cephalosporin, insulin, equine antiserum and selected foods.			(percentages calculated by analyst from raw data)		detect biphasic reaction). 10 patients excluded from analysis because: course and treatment could not be verified (6), recurrent idiopathic anaphylaxis and self-treated at home (2), and believed not to have been anaphylaxis (2: one with hypotension and the other with bronchospasm and urticaria and chronic asthma).
Yang (2008)	Retrospective case series	138	Inpatients and outpatients (visiting the	Anaphylaxis–any 1 of the following 3	Causes:	Treatment protocol and observation	1.6% (3/138)	Not reported.	It was reported that no apparent sign or symptom	Not reported	Definition of anaphylaxis included

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
Korea	Objective was to study the incidence and mortality rate of anaphylaxis at a Korean hospital		allergy clinic or emergency department) with anaphylaxis over a 6-year and 7-month period (2000–6). ICD-10 codes: T78.0 (anaphylactic shock due to adverse food reaction), T78.2 (anaphylactic shock, unspecified), T80.5 (anaphylactic shock due to serum), T88.6 (anaphylactic shock due to adverse effect of correct drug of medicament properly administered). Food dependent	criteria: 1) abrupt skin reaction plus either cardiovascular or respiratory system involvement, 2) at least 2 cutaneous, respiratory, gastrointestinal, or cardiovascular symptoms shortly after exposure to a likely allergen for that patient, 3) reduced blood pressure after exposure to known allergen for that patient. Biphasic anaphylaxis–not defined	<table><tr><td></td><td>Number</td></tr><tr><td>Drugs</td><td></td></tr><tr><td>Radiocontrast media</td><td>20</td></tr><tr><td>NSAIDs</td><td>11</td></tr><tr><td>Antibiotics</td><td>8</td></tr><tr><td>Other</td><td>9</td></tr><tr><td>Total:</td><td>34 % (48)</td></tr><tr><td>Foods</td><td></td></tr><tr><td>Wheat flour</td><td>6</td></tr><tr><td>Buckwheat</td><td>4</td></tr><tr><td>Seafood</td><td>4</td></tr><tr><td>Other</td><td>9</td></tr><tr><td>Total:</td><td>21 % (29)</td></tr><tr><td>Idiopathic</td><td>13 % (18)</td></tr><tr><td>Food-dependent exercise-induced</td><td></td></tr><tr><td>Wheat</td><td>14</td></tr><tr><td>Apple</td><td>1</td></tr></table>	period not reported.	Causes: food (wild grape), NSAID, and exercise.		could help predict a biphasic reaction but no explicit comparisons were made.		patients with reduced blood pressure after exposure to known allergen. Not clear how long patients were followed up and if some could have developed a biphasic reaction and presented elsewhere. Authors state that low rate of biphasic reactions may be due to lack of prolonged observation of the patient after recovery. Patients with other forms of anaphylaxis not associated with clinical feature of

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			exercise-induced anaphylaxis and anaphylactic transfusion records were mapped to these 4 codes in the hospitals electronic Order Communication System and other forms of anaphylaxis not associated with clinical feature of shock are included in the study. Gender: 54% (74/138) male, 46% (64/138) female Mean age: 40y (5 to 76) 0-9y: 0.7% (1) 10-: 9%		Shrimp: 1 Unknown: 2 Total: 13 % (18) Insect stings Bee: 13 Ant: 1 Mosquito: 1 Unknown: 1 Total: 12 % (16) Exercise-induced: 2.9 % (4) Transfusion-related (platelet concentrates): 3% (4) Latex: 0.7 % (1) Causes were determined from clinical history of exposure to possible causative agents within 8 hours of reaction onset (used					shock are included.

Evidence table 3 for review question 2: Should people be observed after an anaphylactic reaction? And if so, for how long?											
Bibliographic reference	Study type and objective	n	Patient characteristics	Definitions	Characteristics of initial reaction	Anaphylaxis treatment protocol and observation	Rate of biphasic reactions	Timing of biphasic reaction and characteristics	Comparison of patients with biphasic to those with uniphasic reactions	Funding source	Additional comments
			19y (12) 20-29y 28% (38) 30-39y 17% (23) 40-49y 10% (14) 50-59y 19% (26) ≥ 60 y 16% (22) Atopy: 70% (52) History of: food allergy (15), asthma (11), allergic rhinitis (9), skin allergy (7), drug allergy (5)		provocation and skin tests).						

Review question 3: What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

No evidence

Review question 4: What information do people need after an anaphylactic reaction, and before referral?

Table 4

Evidence table 4 for review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Comments	Author's conclusions
Kastner, M. et al l(2010)	Systematic Review to investigate the gaps in anaphylaxis management at the level of physicians, patients and the community	Physicians, patients and community settings	[Studies assessing the gaps in knowledge of anaphylaxis management]	<u>Gaps at Physician Level</u> *Theme 1 – Lack of Knowledge* Signs and symptoms to correctly diagnose anaphylaxis Auto – injector provision, use and dose *Theme 2 – Anaphylaxis Management* Treatment with adrenaline and timing of administration *Theme 3 – Follow-up Care* Referral of patients to allergy service Prescribing auto injectors <u>Gaps at Patient & Community Level</u> *Theme 1 – Lack of Knowledge* Trigger avoidance, Availability of educational tools		Identified a total of 200 gaps in anaphylaxis management. Key themes that were common to all groups are insufficient knowledge of anaphylaxis and its management and how to use adrenaline injectors.

Evidence table 4 for review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Comments	Author's conclusions
				Instructions for use of auto injectors *Theme 2 – Anaphylaxis Management* Use of auto injectors Following anaphylaxis management plans *Theme 3 – Follow-up Care* Fear for restrictions of social activities and anxiety of subsequent reactions		

Evidence table 4 for review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Comments	Author's conclusions
Estelle, F. et al (2011)	World allergy organisation guideline summary – organised into 3 main sections: Assessment of patients with anaphylaxis Management of anaphylaxis in a health care setting Management of anaphylaxis at the time of discharge from a health care setting	Patients with anaphylaxis	n/a	Management of anaphylaxis at time of discharge from a health care setting Preparation of self treatment for anaphylaxis recurrence in the community Patients should be discharged with epinephrine or a prescription for epinephrine Patients should be taught why, when and how to inject epinephrine Equip patients with a personalised written anaphylaxis emergency action plan that helps them to recognise anaphylaxis symptoms and instructs them to inject epinephrine promptly and seek emergency assistance Anaphylaxis education before discharge Advise that patients have experienced a potentially life-threatening medical emergency Advise on biphasic reactions within 72 hours and use of the Epipen and call emergency services Advise that they are at increased risk of future episodes of anaphylaxis Advise patients they require a follow up by an allergy/immunology specialist Medical identification should be given e.g. bracelet or wallet card stating their diagnosis of anaphylaxis and any concomitant diseases and concurrent medications Prevention of anaphylaxis recurrence Personalised written instructions for avoidance of the confirmed specific trigger including various alternate names e.g. casein for milk.		At the time of their discharge from the healthcare setting equip patients with epinephrine for self-administration, an anaphylaxis emergency plan and medical identification to facilitate prompt recognition and treatment of anaphylaxis recurrence.

Evidence table 4 for review question 4: What information do people need after an anaphylactic reaction, and before referral?						
Bibliography (Ref ID)	Research question/ study design	Population	Intervention	Outcomes	Comments	Author's conclusions
Danica, B (2008)	Opinion Piece	n/a	n/a	Hospital discharge and follow-up after anaphylaxis Before discharge every patient successfully treated for an anaphylactic reaction should be given specific instructions on: prevention strategies identification of symptoms of anaphylaxis adrenaline administration	Continuing medical education activity	Before discharge all patients should receive patient education about anaphylaxis, a prescription for self-injectable adrenaline.
Lieberman, P. (2007)	Opinion Piece to provide an overview of the scientific literature documenting the inconsistencies and limitations in the management of anaphylaxis	n/a	n/a	Use of SAFE system in treating and managing anaphylaxis **S**eek support Advise patients there is a risk of recurrence **A**llergen identification and avoidance Advise on avoiding trigger **F**ollow-up for speciality care Advise the patient they require a follow-up with an allergy specialist **E**pinephrine for emergencies Instructions on use of adrenaline injectors and when to use them	Designed by expert panel of allergy specialists	It was noted that emergency department physicians who interact with patients in the immediate aftermath of an anaphylactic event are in a unique position to facilitate patient education about the importance of follow-up and ongoing disease management to prevent future allergic emergencies.

Review question 5: Who should be referred, when, and to where or whom?

Table 5

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
Cianferoni A, Novembre E, Pucci N, et al. 2004 Anaphylaxis: a 7 year follow-up survey of 46 children. Ann Allergy Asthma Immunol; 92:464-468 Italy	Observational retrospective	Low risk of bias but unclear how patients were selected	46 (of 76 from a previous cohort study, re-evaluated after a mean of 7 years) Inclusion for previous study: Patients with anaphylaxis referred to an allergy unit (Florence, Italy) who had at least 2 of the main indicators of anaphylactic reaction (hypotensi	Diagnosed anaphylaxis. Mean age 14 yrs (SD 4.92 yrs, range 7-26 yrs). Age at first episode: 5.8 yrs (SD 4.9, 1-18 yrs). 61% male. No details on weight and ethnicity. Aetiology, food 19.5% (9/46), exercise 4.4% (2/46), drug 2.2% (1/46), idiopathic 4.4% (2/46).	Age, gender, age at first episode, allergen, other medical conditions.	7 yrs (SD 1 yr, range 5-8.6 yrs)	Recurrence defined as the presence of another anaphylaxis episode: at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents. Defined risk factors for recurrence: history of atopic dermatitis, current urticaria/ angioedema, history to	Risk of recurrence: 30 % (14/46)	N/R	

[1] For those studies which were retrospective follow-up is defined as the length of time that was retrospectively considered.

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
			on, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents.				sensitivity to 1 food allergen.			
Decker WW, Bellolio MF, Campbell RE, et al 2008 Recurrent Anaphylaxis in patients presenting to the Emergency Department over a 10 year period. Annals of Emergency Medicine; 51 (4): 536 Abstract only USA	Observational prospective	Low risk of bias but no definition of recurrence given.	211 (visiting an ED). Diagnosed anaphylaxis criteria from the National Institutes of Health/Food and Allergy and Anaphylaxis network.	Mean age: 29.3 years (SD 18.2). 44.1 % male. No further details.	Gender, age, race, allergens (no details provided on how these were ascertained)	Mean 1.1 yrs (range 7 days to 13 yrs)	No details provided	2nd event in 45/211 (21.3 %). Median time of presentation: 395 days (range 7d-13yrs). 3rd event in 11/211 (5.2 %). Risk of recurrence for women higher (RR 2.14, 95 %-CI 1.17 to 3.9). No difference in age (p = 0.535)	N/R	

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
								or race (p= 0.743) for a subsequent event.		
Mehl A, Wahn U, Niggemann 2005 Anaphylactic reactions in children - a questionnaire based survey in Germany Allergy 2005: 60: 1445 Germany	Observational retrospective	Medium risk of bias as no definition of recurrence was given. Role of funding source unclear.	103 children (<12 yrs) Inclusion: reported accidental anaphylactic reactions occurring during 12 months in infants and children below 12 years of age. Reports reviewed individually by two paediatric allergologists. Exclusion: reported cases excluded if the reported episode	Median age 5 yrs (range 3 mths-12 yrs). 58% male. No details on weight and ethnicity. Causative allergen was known or strongly suspected in 95/103 (92%) of all patients. Overall: Food 57% (59/103), Insect sting 13% (13/103), SIT 12% (12/103), Medication 6% (6/103), Other* 4% (4/103), Unknown 8% (9/103). Foods only: 57% (59/103): Peanut 20% (12/59), Tree nut 20% (12/59), Cow's milk 14% (8/59), Fish 14%	Allergens investigated: Food (peanut, tree nut, cow's milk, fish, hen's egg, other); Insect sting; SIT; Medication; Other; Unknown. Allergy testing performed in 70 (68%) cases, not performed in 26 (25%) of cases, no information provided for 7 (7%) cases. Specific IgE serum concentrations determined in 63 children and/or skin prick tests	1 yr (patients identified over a period of 12 mths retrospectively)	Questionnaire covering demographic data, symptoms and physical findings of the episode, place of occurrence, suspected allergen, diagnostic tests, treatment modalities such as use of drugs, route of application, and drug administering person, hospitalisation and prescribed emergency set after the episode	'No significant difference was found for allergens looking only at severe reactions (grades III and IV)' (no data reported). Age differences: Food, 'patients significantly younger than the overall group' (mean 3.9 yrs, SD 3). SIT, 'significantly older' (mean 9.8 yrs, SD 1.9) Venom, 'patients significantly	Industry: InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany ('financial support')	

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
			was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not under the age of 12.	(8/59), Hen's egg 7% (4/59), Other* 25% (15/59)	performed in 28 cases. 10 children went through an allergen provocation and 4 underwent atopy patch testing.			older' (mean 7.6 yrs, SD 3.2) Recurrence: Overall 27 % (28/103). Food-related 71 % (20/28). Insect sting 7% (2/28). SIT 7% (2/28). Unknown 14.3 % (4/28). Same allergen as episode(s) in medical history 50% (14/28)		
Mugica Garcia M, Tejedor Alonso M, RojasPerez Ezquerra P, et al 2010 A study of the recurrence of anaphylaxis Allergy 65 (Suppl 92): 587 Abstract only	Observational retrospective	Medium risk of bias as only 58.7% of previous cohort were included and no details on age, gender, weight and ethnicity were reported.	933 (original cohort of 1590). Presented anaphylaxis and were followed in allergy unit (no further details).	Diagnosed anaphylaxis. Mainly urban community. No details on age, gender, weight and ethnicity.	Various allergens investigated: Latex, food, drug, anisakis, exercise, idiopathic, hymenoptera venom	N/R	Recurrence defined as any new episode of anaphylaxis irrespective of the cause of the first episode and whether the recurrence was the same or different. The recurrence of the same subtype of	Overall risk 325/933 (34.8%). Same type as first episode. Latex: 72.7% Food: 38.8% Unknown 32.9% Hymenoptera venom 33.3%	N/R	

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
Spain							anaphylaxis was considered when the same subtype of anaphylaxis (e.g. food, drugs, exercise) was responsible for both the first episode and for the recurrence.			
Mullins RJ 2003 Anaphylaxis; risk factors for recurrence Australia	Observational prospective	Low risk of bias but no definition of recurrence given.	432 patients referred for evaluation of possible anaphylaxis to community-based specialist medical practice between Feb 1995 and July 2000.	Mean age 27.4 yrs (SD 19.5, range: 1-82). 48% male. No details on weight and ethnicity. 1st episode during study course/before study: 71%/ 29%	Gender, allergen, co-morbidity.	2.2 yrs	Recurrence presented as proportion of patients relapsing. Rate of recurrence/ 100 patient-years of observation: calculated by dividing the cumulative length of observation by the number of recurrences involving that trigger.	130/304 (42.8 %) have experienced 386 episodes of recurrent symptoms (median 2, range 0-18). Risk of overall recurrence: 57/100 pat-years; Risk of severe recurrence: 10/100 pat-years. Risk factors for recurrence: exercise and idiopathic cause, female	N/R	

Evidence table for review question 5: Who should be referred, when, and to where or whom?										
Bibliographic reference	Study type	Study quality	Number of patients	Patient Characteristics	Prognostic factor(s)	Length of follow-up[1]	Outcome measures	Results	Source of funding	Additional comments
								gender. Risk of overall recurrence: 57/patient-years Risk of severe recurrence: 10/patient-years No deaths Serious recurrences: 10.4% (45/432); had adrenaline: 40% (18/45) No serious recurrences: 19.7 (85/432); had adrenaline: 1.2% (1/85)		

Review question 6: Who should be given an emergency treatment plan and when should that include an adrenaline injector?

No evidence

Review question 7: What model or organisation of care should be adopted to improve the diagnosis of anaphylaxis post reaction?

Bibliographic reference	Review type and objective	Study inc/exc criteria	Databases searched	Study quality assessment	Results	Author conclusions or recommendations	Source of funding	Additional comments
Kastner et al. (2010)	Systematic review To summarise studies that examined gaps in anaphylaxis management	Included if quantitative or qualitative studies that investigated gaps in management and could be addressed in the context of quality of life of patients at risk or their carers Excluded if basic science, animal studies, case reports, or narrative reviews.	Medline (1966 to 2008) Embase (1980 to 2008) Cinahl (1982 to 2008) Cochrane Database of Systematic Reviews, ACP Journal Club, Dare (no dates) Grey literature (websites and digital dissertations) Handsearching of named journals Reference lists Contacted	Assessed using various methods by study type Not clear how this was used in the results	59 studies included [Results on organisation of care only presented here] Referral to an allergy specialist was infrequently or not done after an acute reaction was identified as a gap (6 references). One study found that allergy testing and follow-up were more frequent in children attending hospital clinics. Settings included emergency departments (2), schools (1), community	No specific recommendations on referral, but general call for the development of interventional strategies and practice tools to address the knowledge and practice gaps in order to improve care.	King Pharmaceuticals Canada	Limited detail on methods Quality of studies not accounted for

Bibliographic reference	Review type and objective	Study inc/exc criteria	Databases searched	Study quality assessment	Results	Author conclusions or recommendations	Source of funding	Additional comments
			experts		paediatric services (1), army hospital (1), and a local authority (1). Countries included France (1), UK (3), and the US (2).			

Table 1 Evidence tables for primary studies on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Study type and objective	Number of participants	Description of study	Patient characteristics	Follow-up	Results	Source of funding	Additional comments
Krøigaard et al. (2005)	Retrospective record review To investigate whether the cause of reaction as identified by the anaesthetist was the same as that confirmed on subsequent investigation	107 patients (assumed adults) with 111 allergic reactions 1999 to 2003	Case notes of all patients with completed investigations at a single specialist allergy centre (Denmark; anaesthesia) Allergen confirmed with specific IgE analysis (Pharmacia UniCAP for latex [all patients], and succinylcholine, thiopental, fentanyl, morphine, and various antibiotics [if exposed before reaction]) and skin testing (prick testing and if negative, intradermal [except latex]) for all substances exposed to	Not reported	Not relevant	36/48 (75%) grade III and III+ reactions had a 'suggested' potential allergen; 25% had no suggested allergen. Overall, for all grades of reaction, 49/67 (73%) where a suggestion was made had no allergy confirmed (31/67; 46%) or had other allergens found	None reported	Single allergen Retrospective Single centre Investigated results may be susceptible to false positives/negatives.

Bibliographic reference	Study type and objective	Number of participants	Description of study	Patient characteristics	Follow-up	Results	Source of funding	Additional comments
			before reaction.			(18/67; 27%). 5/67 (7%) had a complete match between the suggested allergen and the investigation result. 13/67 (19%) had a partial match (because of additional allergens either suggested and not confirmed or confirmed but not suggested).		
Abbreviations: IgE, immunoglobulin E								

Table 2 Evidence tables for referral guidelines on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
Sweetman et al. (2006)	American Academy of Allergy Asthma and Immunology (AAAAI) Aims to assist patients and HCPs in determining when referral to an allergist-immunologist could	AAAAI	Limited detail provided on evidence base or consensus process	Clear recommendations with cited references Recommendations graded	Adults and children with suspected anaphylaxis	None reported Declarations of interest reported	The following patients should be referred to a allergist-immunologist: - Individuals with a severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger (After a severe allergic reaction without a known	None

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
	be helpful						cause, a trigger should be identified if at all possible. An allergist-immunologist is the most appropriate medical professional to perform this evaluation, which might include skin testing, in vitro tests, and challenges when indicated (including with exercise, see below). Major triggers for anaphylaxis are foods and food constituents, medications and biologic agents, latex, and insect stings. Future avoidance of the identified triggers should prevent subsequent anaphylactic episodes. Management of idiopathic anaphylaxis by an allergist-immunologist is associated with a reduction in hospitalisations and emergency department visits.) - Persons with anaphylaxis attributed to food (Food allergy is the most common cause of anaphylaxis outside of the hospital setting. Allergist-immunologists use diagnostic modalities to confirm the trigger and use their specific training and clinical experience to educate patients regarding avoidance	

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
							and immediate management to prevent potentially deadly outcomes.) - Exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis (After an anaphylactic reaction that appears to have a significant relationship to exercise, it is crucial to be certain whether exercise is the cause and to determine whether a food might be involved.) - Drug-induced anaphylaxis (Allergist-immunologists use diagnostic agents to confirm the drug responsible for the reaction, if these agents are available.) Based on non-randomised controlled intervention studies, observational, cohort or case controlled studies, and review articles or expert opinion.	
Waserman et al. (2010)	Various groups represented (Canada) To develop evidence-based recommendations for gaps in anaphylaxis management in	8 clinical experts in anaphylaxis (recruitment not described; not clear if patient/lay members or	Based on systematic review (see Kastner 2010 above) and NGT consensus process	Clear recommendations Recommendations graded	Adults and children with suspected anaphylaxis	Funded by King Pharmaceuticals Canada Declarations of interest not reported.	Referral to an allergist - After acute anaphylaxis patients should be assessed for future risk of anaphylaxis + Anybody who has any rapid onset systemic allergic reaction (GI, respiratory cardiac) or diffuse hives to	None

Bibliographic reference	Scope and purpose	Stakeholder involvement	Development process	Presentation	Applicability	Source of funding	Recommendations	Additional comments
	primary care	other relevant HCPs)					any food or stings + Anybody who has any rapid onset (i.e. minutes to hours) reaction of any severity to higher risk food such as peanuts, tree nuts, shellfish sesame - If uncertain, refer patient to allergist for evaluation Based on expert committee reports or opinions or clinical experience of respected authorities or both; or extrapolated from higher categories of evidence.	
Abbreviations: HCP, healthcare professional; NGT, nominal group technique.								

Question 7 Evidence tables for narrative reviews on the model or organisation of care for the diagnosis of anaphylaxis

Bibliographic reference	Conclusions or recommendations	Source of funding	Additional comments
Zeiger and Schatz (2000)	Defined the allergist as 'the specialist called on to identify the cause of an episode of anaphylaxis, to determine potential preventive measures, and to evaluate the patient who may need to receive a substance to which he or she has reacted previously.'	Novartis Pharmaceutical Corp	None