

ORIGINAL ARTICLE

Inaccurate diagnosis of paediatric anaphylaxis in three Australian Emergency Departments

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Aim: To determine the accuracy of emergency department (ED) paediatric anaphylaxis diagnosis, and to identify factors associated with misdiagnosis.

Methods: Retrospective chart review of children aged 0–18 years with allergic presentations to three Victorian EDs in 2014. Cases were included if an ED diagnosis of anaphylaxis was recorded, or the presentation met international consensus criteria for anaphylaxis.

Results: Of the 60 143 paediatric ED presentations during the study period, 1551 allergy-related presentations were identified and reviewed. One hundred and eighty-seven met consensus criteria for anaphylaxis, and another 24 were diagnosed with anaphylaxis without meeting criteria. Of the 211 presentations, 105 cases were given an ED diagnosis of anaphylaxis and 106 cases were given an alternative diagnosis in ED. ED assessment had a sensitivity of 43.2% (95% confidence interval (CI) 36.1–50.7%) and specificity of 97.9% (95% CI 96.9–98.7%) for anaphylaxis. Multiple logistic regression demonstrated that an ED anaphylaxis diagnosis was associated with previous anaphylaxis (odds ratio (OR) 3.20; 95% CI 1.52–6.75), arrival by ambulance (OR 2.80; 95% CI 1.36–5.74), a high-acuity triage category (OR 4.51; 95% CI 2.20–9.25) and presentation to a tertiary hospital (OR 2.86; 95% CI 1.44–5.67). ED diagnosis of anaphylaxis was less likely in those with resolution of symptoms and signs in at least one organ system prior to arrival (OR 0.27; 95% CI 0.12–0.62).

Conclusion: In children with allergic presentations, ED assessment has a low sensitivity but high specificity for anaphylaxis. Attention to resolved pre-hospital symptoms and awareness of diagnostic criteria are important considerations for accurate ED diagnosis of anaphylaxis.

Key words: allergy; anaphylaxis; diagnosis; emergency department; paediatrics.

What is already known on this topic

- 1 Paediatric anaphylaxis is an increasingly common presentation that is often underdiagnosed.
- 2 Both the immediate and long-term management of paediatric anaphylaxis appears suboptimal.
- 3 Accurate diagnosis is key to the management of paediatric anaphylaxis.

What this paper adds

- 1 Emergency department assessment has a low sensitivity but high specificity for paediatric anaphylaxis.
- 2 Anaphylaxis is more likely to be diagnosed if a child has a past history of anaphylaxis, arrives by ambulance, is given a high acuity triage category or presents to a tertiary hospital.
- 3 Anaphylaxis is less likely to be diagnosed if symptoms resolve prior to arrival in emergency department.

Anaphylaxis is a life threatening allergic reaction that occurs unexpectedly, often in young and otherwise healthy people. The prevalence of allergic conditions is rising, with a corresponding increase in patients presenting to emergency departments (EDs) with anaphylaxis. Anaphylaxis admission rates in Australia increased by 1.5 fold between 2005–2006 and 2011–2012.¹

While internationally accepted clinical criteria for anaphylaxis were established in 2005,² these criteria appear to be underused.

International studies report that between 57 and 87% of patients meeting these criteria are given an alternative diagnosis.^{3–5}

Treatment guidelines all emphasise early use of intramuscular adrenaline, a period of observation due to the risk of biphasic reactions, prescription of an adrenaline autoinjector and follow-up with an allergist.^{6–11} Despite this previous Australian^{12–14} and international^{3,15,16} studies have demonstrated that both immediate and long-term management of paediatric anaphylaxis appears suboptimal.

Accuracy of diagnosis is essential to ensure appropriate management; patients who have unrecognised anaphylaxis are less likely to receive recommended management, including allergist follow-up. This study aimed to examine the accuracy of ED diagnosis of anaphylaxis, and to determine any factors associated with under-diagnosis.

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Conflict of interest: None declared.

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Table 1 Anaphylaxis criteria (Adapted from Sampson *et al.*,² with permission.)

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

- 1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus, or flushing, or swollen lips-tongue-uvula) and at least one of the following:
 - a Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
 - b Reduced BP or associated symptoms of end-organ dysfunction (hypotonia (collapse), syncope, incontinence)
- 2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)
 - a Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips-tongue-uvula)
 - b Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxaemia)
 - c Reduced BP or associated symptoms (e.g. hypotonia (collapse) syncope, incontinence)
 - d Persistent gastrointestinal symptoms (e.g. Crampy abdominal pain, vomiting)
- 3 Reduced BP after exposure to known allergen for that patient (minutes to several hours)
 - a <3 months = <60 mmHg
 - b 3–12 months = <65 mmHg
 - c 1–4 years = <70 mmHg
 - d 5–12 years = <80 mmHg
 - e Over 12 years = <95 mmHg

PEF, peak expiratory flow; BP, blood pressure.

Methods

A retrospective structured chart review was conducted of paediatric patients who presented to three hospitals in south east Melbourne, Australia with allergic symptoms in 2014. Our hospital network consists of a paediatric tertiary centre with a dedicated paediatric ED, and two secondary hospitals with mixed adult/paediatric EDs.

Ethics approval was obtained from the Monash Health and Monash University Human Research Ethics Committees.

Patient selection

An initial database was established from our institution's ED electronic medical record (Symphony, version 2.29.3. Ascribe Ltd. Bolton, UK). Patients were included if there were under the age of 18 and had a recorded presenting complaint or final ED diagnosis that was compatible with anaphylaxis or an allergic reaction. Screened presentations included those with a specific triage presenting complaints included 'allergic reaction' and 'anaphylaxis' or ED diagnostic codes including 'allergy', 'anaphylaxis', 'urticaria', 'angioedema', 'food allergy', 'rash due to food', 'drug reaction', 'hay fever' and 'rash due to drug'. If a child had repeated visits, each was included as a separate presentation.

Patients were excluded if they left ED before treatment was completed, if they were transferred for observation from another hospital or clinical notes were missing.

Classification of anaphylaxis

Anaphylaxis was defined using criteria from the 2005 Second Symposium on the definition and management of anaphylaxis (Table 1).² We defined hypoxaemia as an oxygen saturation of less than 90% regardless of age or oxygen therapy.

Severity of anaphylaxis was graded using a scale proposed by Brown (Table 2).¹⁷

Triage categories

Triage categories referred to are the Australasian Triage scale which divides patients into five categories based on clinical urgency. This ranges from category 1, life threatening cases to be seen immediately, to category 5, non-urgent cases to be seen within 2 h.¹⁸

Data extraction and processing

A standard data extraction form was developed in consultation with emergency physicians and allergists within our institution, and was tested and modified prior to implementation in the study. The primary investigator who conducted the screening and data collection was not blinded to the study objective.

Table 2 Anaphylaxis severity grading system (Adapted from Brown,¹⁷ with permission.)

Grade	Defined by
Mild (skin and subcutaneous tissue only)	Generalised erythema, urticaria, periorbital oedema or angioedema
Moderate (respiratory, cardiovascular or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain
Severe (hypoxia, hypotension or neurological compromise)	Cyanosis or SpO ₂ < 90%, hypotension (systolic blood pressure of <90 mmHg in adults), confusion, collapse, loss of consciousness or incontinence

Periodic meetings were held with the supervising emergency physician to discuss and gain consensus on any points of ambiguity.

The primary data sources were the ED medical and nursing notes. Additional information regarding pre-hospital care and clinical features was obtained from ambulance records. Medication and intravenous fluid charts were the main data source regarding ED medication administration. Nursing notes and observation charts were used to identify timing of change in clinical status or drug administration.

Variables assessed

Variables to be assessed were based on previous studies of anaphylaxis.^{3,12,13,16,19–24} These variables included age, sex, history of anaphylaxis and atopic diseases, details of anaphylactic events (allergen, exposure timing, location), vital signs and clinical manifestations (including involvement of cutaneous, respiratory, gastrointestinal or cardiovascular systems). If more than one possible food trigger could be identified from the history, the eliciting agent was recorded as 'mixed'. As 'persistent gastrointestinal symptoms' were not explicitly defined in the diagnostic criteria used, we applied a threshold of 30 min.

Data analysis

Data entry and analysis were performed using SPSS Statistics (SPSS Statistics for Macintosh, Version 22.0; IBM Corp. Armonk, NY, USA). Data queries were addressed by at least two investigators reviewing the original record. Descriptive statistics were reported as percentages for discrete variables. Continuous data was described as median with interquartile ranges (IQR). Differences between nonparametric continuous variables were determined using the Mann–Whitney U test. Differences between groups for categorical variables were determined using Fisher's exact test for two by two tables and χ^2 -test for larger contingency tables. Values of $P < 0.05$ were considered statistically significant.

Test characteristics of ED diagnosis were calculated by determining sensitivity, specificity and positive and negative likelihood ratios, with 95% confidence intervals (95% CI). These test characteristics were calculated using the complete Second Symposium diagnostic criteria (Table 1), as well as restricting the gold standard anaphylaxis diagnosis to those meeting only the first criteria.

To determine predictors for ED diagnosis of anaphylaxis, we determined the association between each variable and an ED diagnosis of anaphylaxis by calculating crude odds ratios (ORs) with a 95% CI in logistic regression models. Binary logistic regression using the backward stepwise method was then undertaken using all variables with $P < 0.10$ in univariate analysis which had data available for at least 50% of the study population.

Results

During the study period there were 60 143 paediatric ED presentations across the three hospitals. A total of 1551 clinical records were identified and manually reviewed (see Fig. 1). A total of 1335 children presented with possible allergic disease. Of these, 105 presentations received a diagnosis of anaphylaxis

on ED discharge (81 fulfilling anaphylaxis criteria and 24 not). A total of 106 presentations met criteria for anaphylaxis but received an alternative diagnosis on discharge from ED. The most common alternative diagnoses were food allergy and allergy.

The 211 presentations meeting clinical criteria or diagnosed with anaphylaxis occurred in 199 children. Anaphylaxis made up 0.35% of paediatric ED presentations, giving an annual incidence of 3.5:1000 paediatric ED presentations.

In those children presenting with a possible allergic reaction, the prevalence of anaphylaxis was approximately 14%. Using established clinical criteria for anaphylaxis as a gold standard reference, ED assessment had a low sensitivity, but very high specificity (see Table 3).

With the gold standard of anaphylaxis diagnosis restricted to those presentations meeting criterion 1 of the Second Symposium diagnostic criteria, we found a lower prevalence (12.3%, 95% CI 10.6–14.2%), and similar sensitivity and specificity of ED assessment (see Table S1, Supporting Information).

Univariate analysis: Demographics and comorbidities

There were no significant differences between those diagnosed with anaphylaxis and those with anaphylaxis but given an alternative diagnosis with respect to age or gender (see Table S2). Overall, there was a median age of 6 years, with a slight male predominance. A history of atopic disease was common in both groups. On univariate analysis, children were significantly more likely to receive a diagnosis of anaphylaxis if they had a previous history of anaphylaxis, with an OR of 3.35 (95% CI 1.80–6.24), $P < 0.001$.

Univariate analysis: Allergen

There was no difference between those diagnosed with anaphylaxis and those with anaphylaxis but given an alternative diagnosis in terms of the allergen class, specific trigger, or reaction setting (see Table S3 and Fig. S2). When an allergen was identified, food was the most common trigger causing more than 80% of all reactions. Drugs accounted for 3.8% of all anaphylactic reactions, and insect stings accounted for two reactions. Home was the most common setting in both groups, followed by school and childcare. (For further details see Tables S2, S3 and Fig. S1.)

Univariate analysis: Presentation

Patients were more likely to be diagnosed with anaphylaxis if they had severe anaphylaxis, if they presented to a tertiary ED compared to a non-tertiary ED, if they presented with a higher acuity triage scale, if they arrived by ambulance or if they presented sooner after their exposure. The majority of anaphylaxis cases were given a triage category of 2 or 3. Half of all anaphylaxis patients were brought to ED by ambulance. Overall only a small number of anaphylaxis cases arrived in ED within an hour of the exposure, with the majority arriving either between 1–3 or 4–6 h after. The seniority of the initial clinician did not impact on

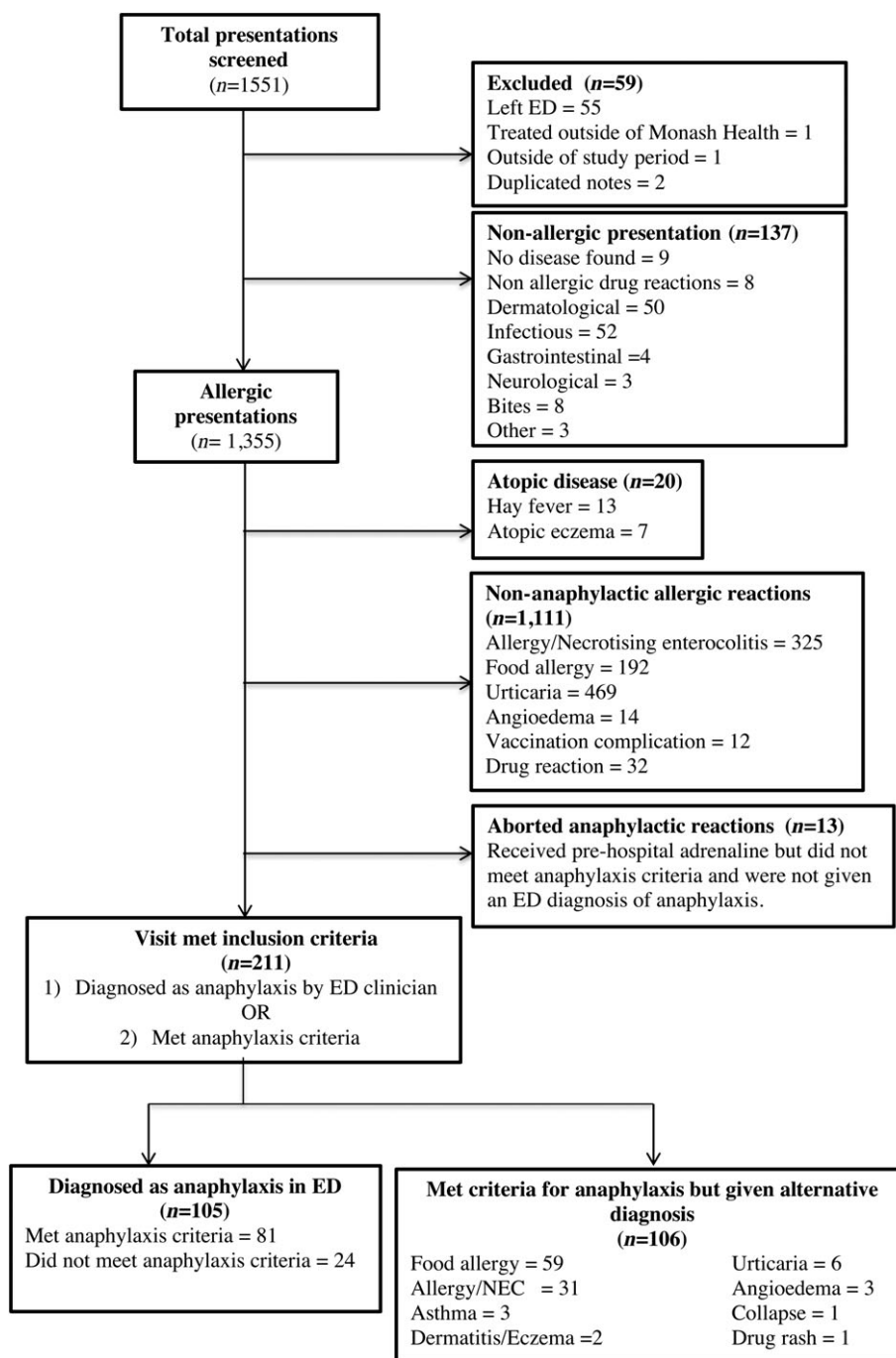


Fig. 1 Study flow.

the accuracy of anaphylaxis diagnosis. There were no fatal reactions.

Univariate analysis: Clinical symptoms

During the anaphylaxis episode, cutaneous and respiratory features dominated in both groups. Patients were more likely to be correctly diagnosed with anaphylaxis if they presented with neurological involvement. Respiratory features were more common in those not correctly diagnosed with anaphylaxis. Cutaneous,

cardiovascular and gastrointestinal involvement was similar between the two.

There was no significant difference between the two groups in terms of the specific signs and symptoms reported except that patients were more likely to be correctly diagnosed with anaphylaxis if they presented with nausea or abdominal pain (see Table S4).

Biphasic reactions

There were seven biphasic reactions identified. This represented a rate of 3.3%. The median time to biphasic reactions from

Table 3 Test characteristics of emergency department assessment of possible anaphylaxis (*n* = 1335)

Statistic	Value	95% confidence intervals
Sensitivity (%)	43.2	36.1–50.7
Specificity (%)	97.9	96.9–98.7
Positive likelihood ratio	20.7	13.5–31.8
Negative likelihood ratio	0.58	0.51–0.66
Prevalence (%)	14	12.2–16
Positive predictive value (%)	77.1	67.9–84.8
Negative predictive value (%)	91.4	89.7–92.9

resolution of initial symptoms was 115 min (IQR 68.5–144.5). Of those that experienced a biphasic reaction, three (42.9%) were given an ED diagnosis of anaphylaxis, three (42.9%) were diagnosed with food allergy and one (14.2%) was diagnosed with allergy. The second phase was anaphylactic in six of the reactions (85.7%), while one of the reactions involved only respiratory features. In the seven initial reactions, three patients required adrenaline and three patients received steroids. Five of the second phase reactions required adrenaline. Two of the patients with biphasic reactions were discharged from ED.

Multiple logistic regression analysis

After applying multiple logistic regression, the factors which predicted ED diagnosis of anaphylaxis were previous anaphylaxis, arrival by ambulance, high-acuity triage category and presentation to a tertiary hospital. Resolution of symptoms and signs of at least one organ system prior to arrival was associated with reduced odds of an ED diagnosis of anaphylaxis (Table 4).

Discussion

To our knowledge, this is the largest cohort of paediatric anaphylaxis patients identified in the Australian literature and one of the largest internationally within a 1-year study period. It is notable that ED staff did not record a diagnosis of anaphylaxis in many children who met clinical criteria for anaphylaxis.

Of the 211-anaphylaxis cases identified, only 105 (49.8%) were given an ED diagnosis of anaphylaxis. Similar international

studies have noted misdiagnosis rates from 57% to 87%.^{3–5} This is in contrast to Nogic *et al.* who found that anaphylaxis was accurately diagnosed in 55 cases presenting to a Victorian ED.²⁵ This difference in results is likely due to our inclusion of all children with the triage presenting complaint of 'allergic reaction' and the inclusion of additional diagnostic codes, such as allergy and angioedema.

How patients present to ED appears to influence how clinicians diagnose anaphylaxis. Multiple logistic regression identified four factors associated with ED diagnosis of anaphylaxis: previous anaphylaxis, arrival by ambulance, high-acuity triage category and attendance to a tertiary hospital. Resolution of signs and symptoms of at least one organ system prior to arrival was associated with reduced odds of an ED diagnosis of anaphylaxis.

Previous studies have reported that anaphylaxis is often missed in infants. Rudders *et al.* found that 94% of infants meeting anaphylaxis criteria were given a lesser diagnosis.²⁶ Similarly, we found that of the 22 infants who met anaphylaxis criteria, 14 were given an alternative diagnosis. In young children, many presentations of anaphylaxis are initial episodes,¹² therefore clinicians should not rely on past history of allergy to make the diagnosis of anaphylaxis in this age group.

Patients given a correct diagnosis were also more likely to have arrive by ambulance, be given a high triage category and attend a tertiary hospital. However, we did not identify any differences between the two groups in terms of the specific signs and symptoms reported. Previous research by Huang and colleagues found that anaphylactic reactions were less likely to be diagnosed correctly if they did not include rash, hives, shortness of breath, wheeze, vomiting and abdominal pain.³ While Sargant *et al.* proposed that anaphylaxis can masquerade as severe asthma,²⁷ in our cohort only three patients meeting anaphylaxis criteria were diagnosed with asthma. The higher likelihood of anaphylaxis diagnosis in patients presenting to the tertiary hospital may be due to preferential transport of more severely ill children by pre-hospital services, more experienced staff, or other factors.

It is notable that ED assessment of children with potential allergic disease yields a low sensitivity for diagnosis of anaphylaxis. Many children's symptoms had at least partially resolved prior to ED arrival; around 30% were symptom-free on arrival to the ED, and half of these had not been administered any adrenaline prior to arrival. This may explain the relatively low administration rates of adrenaline in other studies of paediatric anaphylaxis.^{28,29}

Our finding that resolved symptoms and signs of anaphylaxis reduce the likelihood that a child will leave the ED with a diagnosis of anaphylaxis highlights the need to take a careful history and to pay close attention to reports from caregivers and pre-hospital providers. The use of standardised event recording forms, such as those produced by the Australasian Society of Clinical Immunology and Allergy (ASCIA) may be helpful to accurately document the clinical manifestations of allergic reactions.³⁰

Although adrenaline administration may not necessarily be indicated if symptoms have completely resolved prior to arrival, it is still important to ensure appropriate ED observation and allergist follow-up. This not only allows accurate determination of the likely allergen, but provision of avoidance advice and education on the safe use of adrenaline autoinjectors when indicated.³¹

Table 4 Predictors of emergency department diagnosis of paediatric anaphylaxis (after multiple logistic regression)

Predictor	Odds ratio (95% CI)	P-Value
Previous anaphylaxis	3.20 (1.52–6.75)	0.002
Australasian Triage Scale category 1 or 2	4.51 (2.20–9.25)	<0.001
Arrival by ambulance	2.80 (1.36–5.74)	0.003
Attendance to a tertiary hospital	2.86 (1.44–5.67)	0.003
Resolution of signs/symptoms of involvement of at least one organ system	0.27 (0.12–0.62)	0.002

Limitations

The primary limitation of this study is the retrospective design and reliance on complete documentation in the clinical records. We were unable to determine whether the medical record accurately described all signs and symptoms present at the time of assessment in ED. Additionally, we do not have a paediatric allergy service in our hospital network, so we were unable to obtain the opinion of a specialist paediatric allergist on each medical record. However, in keeping with recommended practice for chart review studies,^{32,33} our data points were clearly defined, and a standardised data extraction form was used to improve accuracy and consistency of data collection. We applied diagnostic criteria from established guidelines on the diagnosis of anaphylaxis to each patient's data, ensuring uniform interpretation of recorded clinical features.

Conclusion

In children presenting with allergic disease, ED assessment has a low sensitivity but high specificity for anaphylaxis. Anaphylaxis is more likely to be diagnosed if a child has a past history of anaphylaxis, arrives by ambulance, is given a high-acuity triage category or presents to a tertiary hospital, while it is less likely to be diagnosed if at least one organ system's symptoms and signs are resolved prior to arrival. Attention to resolved pre-hospital symptoms and awareness of diagnostic criteria are important considerations for accurate ED diagnosis of anaphylaxis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Test characteristics of emergency department assessment of possible anaphylaxis, using only criterion 1 of the Sampson *et al.* criteria. (Adapted from Sampson *et al.*,² with permission.) ($n = 1355$).

Table S2. Demographic and historical features of ED presentations meeting criteria for anaphylaxis. P values calculated using Mann–Whitney test (age; gender), and Fisher's exact test (all others).

Table S3. Clinical features of ED presentations meeting criteria for anaphylaxis. P values calculated using χ^2 for groups with more than one option (e.g. causative agent/allergen and time from allergen exposure to ED arrival), and Mann–Whitney was used for organ systems involved. Fisher's exact test was used for all others.

Table S4. Specific physical signs and symptoms noted. P values were calculated using Fischer's exact test.

Fig. S1. Likely causative agents for all presentations either diagnosed as anaphylaxis, or meeting clinical criteria for anaphylaxis but receiving an alternative diagnosis. †Vaccination reaction occurred post 6-month vaccinations, which include vaccines for diphtheria, tetanus, pertussis, hepatitis b, polio, influenza, pneumococcal and rotavirus.

Fig. S2. Setting where onset of anaphylactic reaction took place. †Community space represents the combined data for public space, café, restaurant, shopping centre and church. ‡Transport includes both car and public transport. Outdoors includes sporting groups.



Rainbow zebra by Yuna Shin (age 5)

Supplementary data table E1. Test characteristics of emergency department assessment of possible anaphylaxis, using only criterion 1 of the Sampson et al criteria.

(Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006;47(4):373-80.) (n=1355)

Statistic	Value	95% confidence intervals
Sensitivity	43.7	36.1 – 51.6
Specificity	97.3	96.2 – 98.1
Positive likelihood ratio	16.2	11.1 – 23.8
Negative likelihood ratio	0.58	0.51 – 0.66
Prevalence	12.3	10.6 – 14.2
Positive predictive value	69.5	59.8 – 78.1
Negative predictive value	92.5	90.9 – 93.9

Supplementary data table E2. Demographic and historical features of ED presentations meeting criteria for anaphylaxis.

P values calculated using Mann-Whitney test (age; gender), and Fisher's exact test (all others).

		Overall (n= 211) n(%)	ED Diagnosis of anaphylaxis (n=105); n(%)	NO ED diagnosis of anaphylaxis (n=106); n(%)	Odds ratio (95% CI)	P value
Demographics	Age in years , median (IQR)	6 (2-11)	6 (3-11.5)	5 (2-10.3)	N/A	0.18
	Boys, n (%)	131 (62.1)	64 (60.9)	67 (62.2)	N/A	0.74
Allergic comorbidities	Any allergic comorbidity	104 (49.3)	54 (51.4)	50 (47.2)	1.19 (0.69– 2.04)	0.58
	Asthma	69 (32.7)	36 (34.3)	33 (31.1)	1.15 (0.65 – 2.05)	0.66
	Asthma medication	27 (12.8)	15 (14.3)	12 (11.3)	1.31 (0.58 – 2.94)	0.54
	Eczema	49 (23.2)	27 (25.7)	22 (20.8)	1.32 (0.70 – 2.51)	0.42
	Hay fever	8 (3.8)	4 (3.8)	4 (3.8)	1.01 (0.24 – 4.15)	1
	Urticaria	2 (0.9)	1 (1.0)	1 (0.9)	1.01 (0.06 – 16.37)	1
	Angioedema	6 (2.8)	3 (2.9)	3 (2.8)	1.01 (0.20 – 5.12)	1

	Family history of atopy	10 (4.7)	5 (4.8)	5 (4.7)	1.010 (0.28 – 3.60)	1
Anaphylaxis History	Previous anaphylaxis	66 (31.3)	46 (43.8)	20 (18.9)	3.35 (1.80 – 6.24)	<0.001
	Prior anaphylaxis to the same allergen	30 (14.2)	22 (20.9)	8 (7.5)	3.25 (1.37 – 7.68)	<0.01
	Previous ED visit with anaphylaxis	41 (19.4)	29 (27.6)	12 (11.3)	2.99 (1.43 – 6.25)	<0.01
	Previous autoinjector prescription	71 (33.6)	48 (45.7)	23 (21.7)	3.04 (1.67 – 5.54)	<0.001
	Known allergy to exposure	55 (26.1)	30 (28.6)	25 (23.6)	1.30 (0.70 – 2.40)	0.44
	Family Hx Anaphylaxis	5 (2.4)	2 (1.9)	3 (2.8)	0.67 (0.11 – 4.08)	1

Supplementary data table E3: Clinical features of ED presentations meeting criteria for anaphylaxis.

P values calculated using Chi-squared for groups with more than one option (e.g. causative agent / allergen and time from allergen exposure to ED arrival), and Mann-Whitney was used for organ systems involved. Fisher's exact test was used for all others.

<u>Clinical feature</u>	Overall (n= 211); n(%)	ED diagnosis of anaphylaxis (n=105); n(%)	No ED diagnosis of anaphylaxis (n=106); n(%)	Odds ratio (95% CI)	P value
Causative agent / allergen					
Food	173 (82.0)	91 (86.7)	82 (77.4)	N/A	0.35
Drugs	8 (3.8)	3 (2.9)	5 (4.7)		
Insect	2 (0.9)	1 (0.9)	1 (0.9)		
Other / unknown	28 (13.3)	10 (9.5)	18 (16.9)		
ATS category 1 or 2	71 (31.3)	52 (49.5)	19 (17.9)	4.41 (2.37 – 8.08)	<0.0001
Arrival by ambulance	106 (50.2)	66 (62.9)	40 (37.7)	2.79 (1.60 – 4.88)	<0.001
Tertiary ED	134 (63.5)	80 (76.2)	54 (50.9)	3.08 (1.68 – 5.44)	<0.001

Senior doctor as initial treating clinician	64 (30.3)	34 (32.4)	30 (28.3)	1.21 (0.67 – 2.18)	0.55
Time from allergen exposure to ED arrival [†]					
<1 hour	5 (2.4)	4 (3.8)	1 (0.9)	N/A	0.01
1-3 hours	66 (31.3)	48 (45.7)	18 (17.0)		
4-6 hours	112 (53.1)	45 (42.9)	67 (63.2)		
7-12 hours	26 (12.3)	8 (7.6)	18 (17.0)		
Organ system involved					
Cutaneous	203 (96.2)	97 (92.4)	105 (99.1)	0.12 (0.02 – 0.94)	0.02
Respiratory	159 (75.3)	70 (66.7)	89 (84.0)	0.38 (0.20 – 0.74)	<0.01
Gastrointestinal	53 (25.1)	32 (30.5)	21 (19.8)	1.77 (0.94 – 3.34)	0.08
Cardiovascular	23 (10.9)	14 (13.3)	9 (8.5)	1.66 (0.68 – 4.02)	0.28
Neurological	27 (12.8)	19 (18.1)	8 (7.5)	2.71 (1.13 – 6.50)	0.02

Median (IQR) number of organ systems involved during episode	2 (2-2)	2 (2-2)	2 (2-3)	N/A	0.62
Median (IQR) number of organ systems involved at time of ED arrival	1 (0-1)	1 (0-1)	1 (0-2)	N/A	0.29
At least one organ system resolved prior to ED	157 (74.4)	68 (64.7)	89 (83.4)	0.35 (0.18 – 0.68)	0.001
All symptoms resolved prior to ED arrival	60 (28.4)	28 (26.7)	32 (30.2)	0.84 (0.45 – 1.54)	0.65

Severe anaphylaxis (as per Brown et al)	28 (13.3)	20 (19.0)	8 (7.5)	2.88 (1.21-6.88)	0.02
Pre-hospital treatment					
Antihistamine	99 (46.9)	53 (50.5)	46 (43.4)	1.33 (0.78 – 2.28)	0.34
Steroid	22 (10.4)	13 (12.4)	9 (8.5)	1.52 (0.6 – 3.63)	0.38
Adrenaline Autoinjector	51 (24.2)	37 (35.2)	14 (13.2)	3.58 (1.8 – 7.21)	<0.001
Ambulance treatment (n=106)					
Adrenaline	22 (20.8)	21/66 (31.8)	1/40 (2.5)	19.05 (3.0 – 202.6)	0.0001
Nebulised adrenaline	2 (1.9)	1/66 (1.5)	1/40 (2.5)	0.6 (0.03 – 11.67)	1.000

Oxygen	12/106 (11.3)	12/66 (18.2)	0/40 (0)	∞ (2.6 – ∞)	0.003
Beta agonist	14/106 (13.2)	12/66 (18.2)	2/40 (5)	4.38 (0.97 – 20.4)	0.074
Steroids	8/106 (7.5)	6/66 (9.1)	2/40 (5)	1.9 (0.44 – 9.59)	0.71
Fluids	3/106 (2.8)	3/66 (4.5)	0/40 (0)	∞ (0.52 - ∞)	0.29

[†] Time not recorded for two patients.

Supplementary table E4: Specific physical signs and symptoms noted.

P values were calculated using Fischer's exact test.

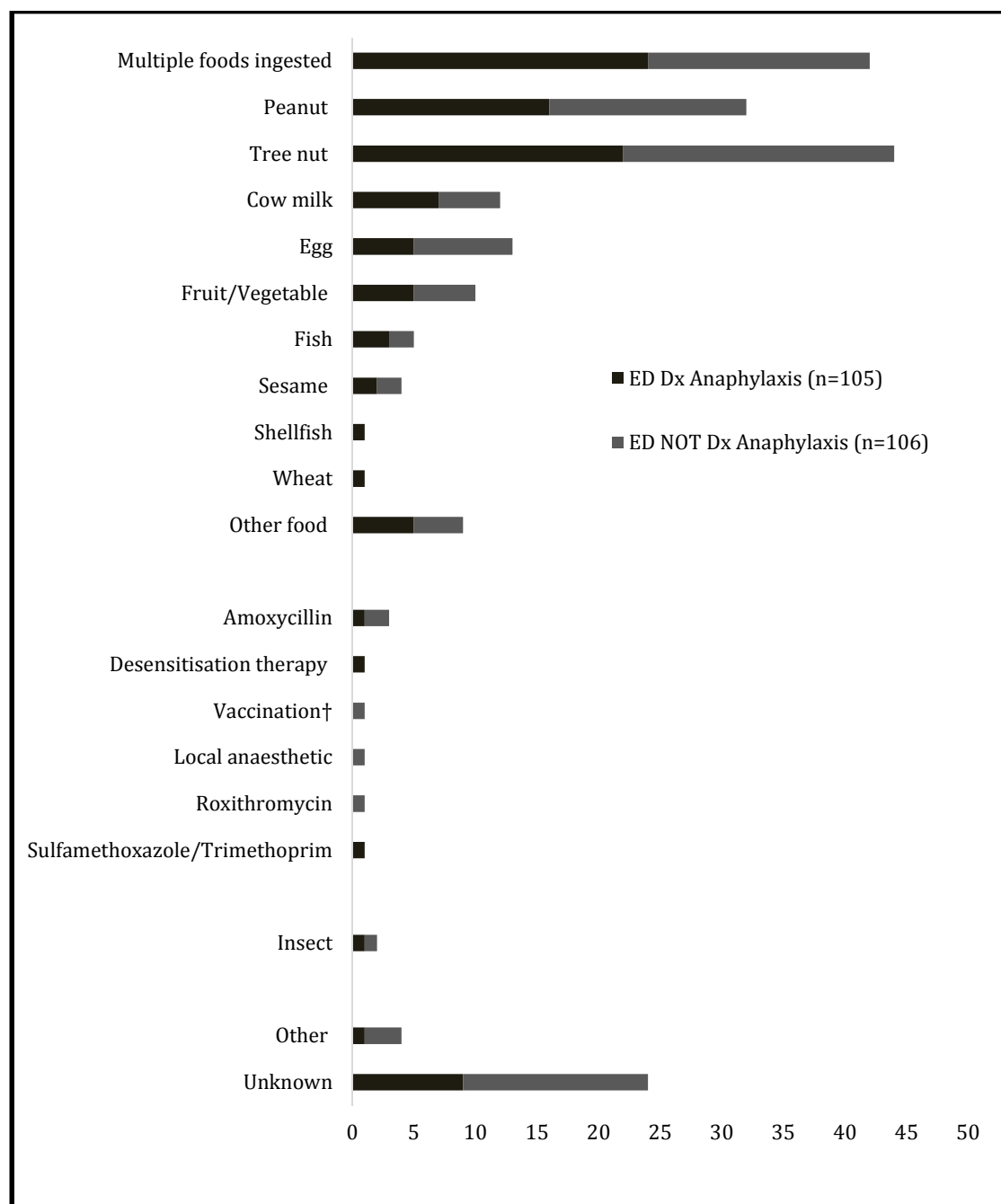
	Overall (n= 211); n(%)	ED diagnosis of anaphylaxis (n=105); n(%)	No ED diagnosis of anaphylaxis (n=106); n(%)	Odds ratio (95% CI)	P value
Cutaneous					
Urticaria	143 (67.8)	72 (68.6)	71 (67.0)	1.08 (0.60 – 1.92)	0.88
Pruritus	72 (34.1)	33 (31.4)	39 (36.8)	0.79 (0.45 – 1.39)	0.47
Flushed	15 (7.1)	8 (7.6)	7 (6.6)	1.17 (0.41 – 3.34)	0.80
Angioedema	127 (60.2)	67 (63.8)	60 (56.6)	1.35 (0.78 – 2.35)	0.33
Diaphoresis	0	0	0	N/A	N/A
Conjunctivitis	9 (4.3)	7 (6.7)	2 (1.9)	3.71 (0.75 – 18.32)	0.10
Local – erythema	11 (5.2)	4 (3.8)	7 (6.6)	0.56 (0.16 – 1.97)	0.54

Generalised – erythema	15 (7.1)	10 (9.5)	5 (4.7)	2.13 (0.70 – 6.45)	0.19
Periorbital oedema	29 (13.7)	16 (15.2)	13 (12.3)	1.29 (0.59– 2.83)	0.56
Respiratory					
Dyspnoea	98 (46.4)	43 (41.0)	55 (51.9)	0.64 (0.37 – 1.11)	0.13
Wheeze	100 (47.4)	49 (46.7)	51 (48.1)	0.94 (0.55 – 1.62)	0.89
Stridor	13 (6.2)	9 (8.6)	4 (3.8)	2.39 (0.71 – 8.02)	0.16
Reduced PEF	0	0	0	N/A	N/A
Hypoxia	17 (8.1)	12 (11.4)	5 (4.7)	2.61 (0.88– 7.68)	0.08
Chest tightness	11 (5.2)	7 (6.7)	4 (3.8)	1.82 (0.52 – 6.42)	0.37
Cough	31 (14.7)	19 (18.1)	12 (11.3)	1.73 (0.80 – 3.78)	0.18
Throat tightness	42 (19.9)	26 (24.8)	16 (15.1)	1.85 (0.93– 3.70)	0.09
Difficulty talking	21 (10.0)	12 (11.4)	9 (8.5)	1.39 (0.56 – 3.46)	0.50
Cardiovascular					
Hypotension	16 (7.6)	11 (10.5)	5 (4.7)	2.36 (0.79 – 7.05)	0.13

Hypotonia	5 (2.4)	2 (1.9)	3 (2.8)	0.67 (0.11– 4.08)	1
Incontinence	0	0	0	N/A	N/A
Syncope	6 (2.8)	4 (3.8)	2 (1.9)	2.06 (0.37 – 11.50)	0.44
Dizziness	7 (3.3)	7 (6.7)	0 (0)	16.22 (0.91 – 287.91)	0.02
Cyanosis	5 (2.4)	5 (4.8)	0 (0)	11.66 (0.64 – 213.68)	0.07
Pallor	6 (2.8)	4 (3.8)	2 (1.9)	2.06 (0.37 – 11.50)	0.44
Gastrointestinal					
Abdominal pain	28 (13.3)	19 (18.1)	9 (8.5)	2.38 (1.02 – 5.542)	0.04
Vomiting	33 (15.6)	18 (17.1)	15 (14.2)	1.26 (0.60 – 2.65)	0.58
Diarrhoea	10 (4.7)	4 (3.8)	6 (5.7)	0.66 (0.18 – 2.41)	0.75
Nausea	24 (11.4)	20 (19.0)	4 (3.8)	6 (1.97 – 18.24)	<0.001
Neurological					
Confusion	1 (0.5)	1 (1.0)	0 (0)	3.06 (0.12 – 75.97)	0.50
Irritable	17 (8.1)	12 (11.4)	5 (4.7)	2.61 (0.88 – 7.68)	0.08

Decreased consciousness	8 (3.8)	6 (5.7)	2 (1.9)	3.15 (0.62 – 15.99)	0.17
GCS < 13	5 (2.4)	4 (3.8)	1 (0.9)	4.16 (0.46 – 37.86)	0.21

Supplementary figure E1: Likely causative agents for all presentations either diagnosed as anaphylaxis, or meeting clinical criteria for anaphylaxis but receiving an alternative diagnosis. †Vaccination reaction occurred post 6-month vaccinations, which include vaccines for Diphtheria, Tetanus, Pertussis, Hepatitis B, Polio, Influenza, Pneumococcal and Rotavirus.



Supplementary figure E2: Setting where onset of anaphylactic reaction took place.

†Community space represents the combined data for public space, café, restaurant,

shopping centre and church. ‡Transport includes both car and public transport.

Outdoors includes sporting groups.

