

Repeated adrenaline requirements for anaphylaxis

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Abstract

We examined the pattern of adrenaline administration in patients presenting with anaphylaxis. Forty-four percent required repeated adrenaline administration, among whom there had been greater cardiorespiratory compromise. Repeated administration was more frequent in males and older patients, and those triggered by insect sting or unknown cause; no other patient factors were identified. This study supports the provision of two adrenaline auto-injectors to all anaphylaxis patients.

Anaphylaxis requires early recognition and management, with a lifetime prevalence as high as 5.1%.¹ Furthermore, anaphylaxis presentations and hospitalisations in Australia continue to rise.²⁻⁴ The severity of a reaction has implications on morbidity, hospitalisation and mortality. Despite the availability of numerous tools,⁵⁻⁷ grading of severity remains challenging in the absence of objective markers of severity. Stratification by adrenaline requirements is a pragmatic surrogate for severity assessment, although this can be confounded by variations in clinical care.

There is a growing list of predictors of severity, including older age, male sex, history of anaphylaxis or asthma, psychological burden, medication triggers, delayed adrenaline administration and clinical signs of dyspnoea, wheeze, flushing and hypotension.^{8,9} The presence of cofactors, such as antihypertensive or non-steroidal anti-inflammatory use, alcohol ingestion, exercise and concurrent infection, can also potentiate more severe reactions.^{10,11} Understanding augmenting factors for anaphylaxis severity may inform the development of strategies to prevent severe anaphylaxis.

We analysed the pattern of anaphylaxis presentations at our health network, Alfred Health, a large metropolitan health service in Melbourne, Victoria. We aimed to: first, determine the proportion of patients requiring repeated doses of adrenaline; second, examine if management was commensurate to clinical severity; and third, identify those at highest risk for increased adrenaline requirements.

We conducted a retrospective electronic chart review of all patients presenting with anaphylaxis to Alfred Health, from 1 January 2016 to 31 December 2018, incorporating two emergency departments (ED): the Alfred Hospital, a tertiary metropolitan centre, and Sandringham Hospital, a community hospital. The study was approved by the Alfred Health Research and Ethics Committee (Project Number 427/19).

Using the International Classification of Diseases 10th Revision Australian Modification (ICD-10-AM), we included patients with either an initial triage or final diagnosis of anaphylaxis. A pre-specified analysis grouped patients with anaphylaxis into those requiring either no intramuscular adrenaline or a single dose only (0–1 dose), and those requiring repeated doses of intramuscular adrenaline (≥ 2 doses), including adrenaline administered both in the community by patients and/or ambulance services. Clinical features and suspected triggers were recorded. Cofactors were recorded if present within <6 h of the time of symptom onset.

Comparisons between the two groups for categorical variables were evaluated using Chi-squared test. Univariate logistic regression models were used to evaluate associations between predictor variables and number of required adrenaline doses. Correction for multiple statistical tests was not applied to the univariate analysis. A multivariate logistic regression model was developed using stepwise selection of clinical variables that were significant in univariate analysis. All statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA). Statistical significance was considered when $P < 0.05$.

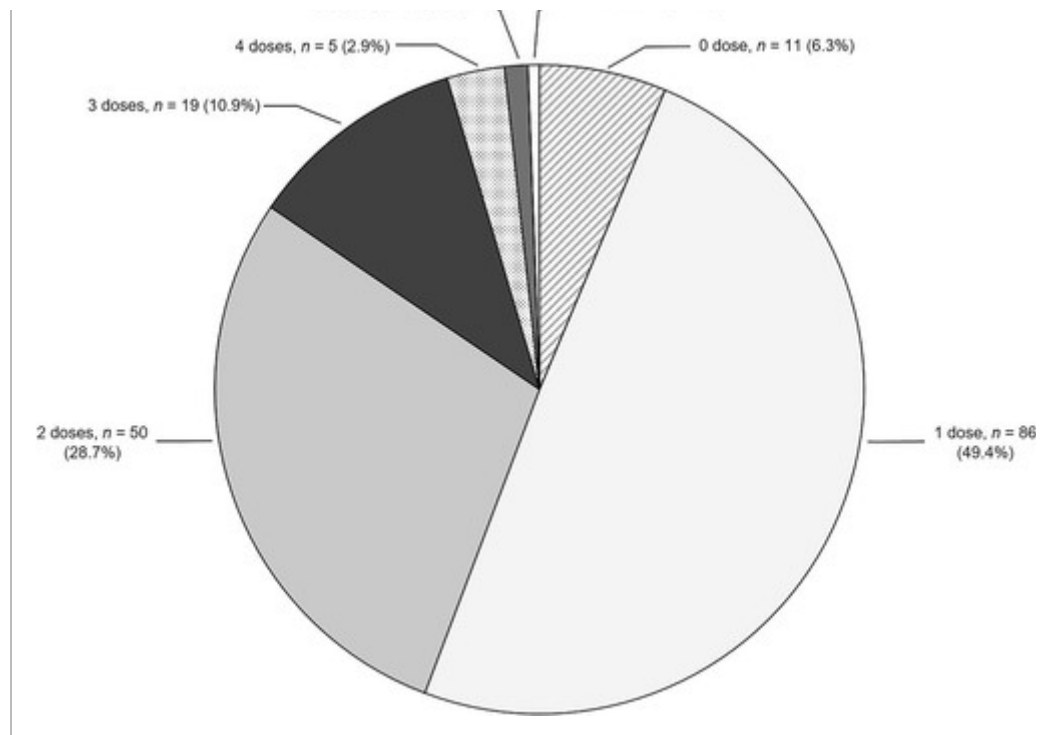
We identified 193 suspected anaphylaxis presentations, from which 174 had true anaphylaxis included for analysis based on clinical criteria,^{5, 7} as defined by any of the following three criteria being fulfilled:

1. The acute onset of an illness with the combination of cutaneous with respiratory or cardiovascular involvement.
2. Following the exposure of likely allergen with any two of cutaneous, respiratory, cardiovascular or gastrointestinal involvement.
3. Hypotension after exposure to a known allergen.

ED triage detected 115 (66%) presentations of true anaphylaxis. Food was the most common suspected trigger, accounting for 101 (58%) presentations. The frequency of adrenaline doses is shown in Figure 1.



5 doses, $n = 2$ (1.2%) 6 doses, $n = 1$ (0.6%)

**Figure 1**[Open in figure viewer](#) | [PowerPoint](#)

Total number of intramuscular adrenaline administrations. Values are given as *n* (frequency) with percentage of overall.

Of the 174 patients, 77 (44.3%) had repeated doses of adrenaline (Group 2). Demographics and triggers were compared between those requiring repeated adrenaline doses and those requiring no more than one dose (Table 1). Individuals requiring repeated doses of adrenaline were more likely to be older (37.3 vs 29.7 years, $P = 0.026$) and male (44% vs 29%, $P = 0.036$), and the episode was more likely to be triggered by insect sting ($P < 0.05$) or unknown/unidentified triggers ($P < 0.036$). Asthma was present in 30% of patients overall with no difference between groups (34% vs 27%; $P = 0.319$). Prior history of anaphylaxis was not associated with repeated adrenaline requirement (62% vs 61%; $P = 0.839$).

Table 1. Demographics and history of patients requiring repeated adrenaline doses compared with those receiving no more than one dose

Characteristics	All (<i>n</i> = 174)	≤1 doses adrenaline (<i>n</i> = 97)	≥2 doses adrenaline (<i>n</i> = 77)	<i>P</i> -value
Age, mean (SD) (years)	33.1 (16.3)	29.7 (14.0)	37.3 (18.1)	0.026*
Male sex, no. (%)	62 (36)	28 (29)	34 (44)	0.036*
Suspected trigger, no. (%)				
Food	101 (58)	61 (63)	40 (52)	0.146
Sting	6 (3)	1 (1)	5 (6)	0.05*

Characteristics	All (n = 174)	≤1 doses adrenaline (n = 97)	≥2 doses adrenaline (n = 77)	P-value
Drug	27 (16)	17 (18)	10 (13)	0.411
Exercise	12 (7)	9 (9)	3 (4)	0.164
Unknown	37 (21)	15 (15)	22 (29)	0.036 [*]
Past medical history, no. (%)				
Asthma	52 (30)	26 (27)	26 (34)	0.319
Anaphylaxis	107 (62)	59 (61)	48 (62)	0.839
Other atopy	46 (26)	25 (26)	21 (27)	0.824

* $P < 0.05$ was considered statistically significant. Data are represented as counts with %, unless otherwise specified.

NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

Clinical features are shown in Table [A1](#). Patients who received repeated doses of adrenaline had higher rates of dyspnoea (70% vs 50%; $P = 0.009$), tachypnoea (25% vs 10%; $P = 0.012$) and hypoxia (32% vs 2%; $P < 0.001$). Similarly, altered Glasgow Coma Scale (GCS, 18% vs 1%; $P < 0.001$) and cardiovascular features, such as hypotension (44% vs 15%; $P < 0.001$), were more common. Urticaria was more common in patients requiring repeated doses of adrenaline (79% vs 61%; $P = 0.009$), but pruritus (52% vs 65%; $P = 0.083$) and angioedema (64% vs 62%; $P = 0.809$) were not significant.

Clinical management is shown in Table [A2](#) (pre-hospital) and Table [A3](#) (hospital). Patients who received repeated doses of adrenaline had a higher rate of ambulance transfer to hospital (68% vs 44%; $P = 0.001$), greater pre-hospital use of intravenous (i.v.) fluids (21% vs 4%; $P = 0.001$), less pre-hospital use of antihistamines (14% vs 37%; $P = 0.001$) and no differences in pre-hospital corticosteroid or inhaled salbutamol use. Of the 77 patients who received repeated doses of adrenaline, 35 (60%) received adrenaline in the community, while 15 (19%) patients also received i.v. adrenaline infusion (7 for refractory hypotension, 4 for severe airway angioedema and 4 for peri-respiratory arrest). Patients requiring repeated doses of adrenaline were more likely to be admitted to hospital (48% vs 7%; $P < 0.001$). Only one patient required endotracheal intubation for airway angioedema and no patient died. The majority (96%) of patients were observed for the recommended time period of >4 h.

On multivariate logistic regression (Table [A4](#)), age and sex were no longer significantly different between groups, but features of cardiorespiratory compromise and urticaria

remained more frequent in those requiring repeated adrenaline doses. Patients who received pre-hospital antihistamines received fewer doses of adrenaline (37% vs 14%; $n = 47$; $P = 0.001$), with an odds ratio of 0.32 (95% CI 0.13–0.78; $P = 0.012$); however, this finding was not demonstrated in patients who received antihistamines in hospital (64% vs 74%; $n = 119$; $P = 0.154$). The impact of pre-hospital corticosteroid use on adrenaline requirement was not significant (10% vs 18%; $P = 0.135$).

Discussion

Our results show that 44% of patients presenting to the ED with anaphylaxis require repeated adrenaline doses. Increased doses of adrenaline reflected higher rates of cardiorespiratory compromise. Older age, male sex, insect sting trigger and an unknown trigger were all risk factors for repeated adrenaline requirements, although not significant on multivariate analysis. No other predisposing factors were identified in this analysis.

The requirement for more than one dose of adrenaline was higher in our cohort than in previous studies that have reported rates of 8–13% among patients presenting to the ED.^{8, 12} Australian guidelines currently advocate for two devices in adult patients with previous hypotensive or near-fatal anaphylaxis, previous adrenaline requirement >1 dose, limited access to medical care, systemic mastocytosis or elevated body mass index. The present study suggests all patients should be prescribed and carry two adrenaline auto-injectors. This is particularly important given the average ambulance response time in Victoria, Australia, of around 10 min¹³ and the reported negative outcomes with delayed adrenaline administration, including admission to ward and intensive care unit, and mortality.^{12, 14} Furthermore, our data suggest the need for ongoing patient-directed anaphylaxis education. Despite high rates (62%) of prior anaphylaxis, only 55% of patients requested ambulance assistance, and only 38% administered their adrenaline auto-injector prior to ambulance attendance. We did not specifically study barriers to adrenaline use or ambulance requests; some have previously been identified.¹⁵

Consistent with our findings, age has previously been identified as a risk factor for severe anaphylaxis,¹⁶ and male sex is a risk factor for severe anaphylaxis in patients allergic to venom,¹⁷ drugs or foods.¹⁶ Asthma is generally considered a risk factor for fatal events,¹⁸ but did not predict requirement for repeated adrenaline in our study.

Specific triggers, particularly medications and stings, have been associated with increased anaphylaxis severity.² The low number ($n = 6$) of sting reactions in our study likely reflects our metropolitan setting. We identified patients with an unknown trigger to be more likely to require repeated adrenaline. Larger registries have identified drug-elicited anaphylaxis to be higher risk of severe anaphylaxis compared with other triggers,¹⁶ but this was not reflected in our study. This study had few patients with documented use of antihypertensives and non-steroidal anti-inflammatory drugs, so we did not identify a trend in adrenaline usage.

Consistent with other data,¹² patients in the present study who received pre-hospital antihistamines received fewer doses of adrenaline. These observational data could be explained by patients and healthcare personnel moving directly to adrenaline for more severe reactions.

Our study is limited by its observational design and reliance on effective documentation of the encounter. Nationwide multicentre studies would more accurately represent the risk factors associated with severe anaphylaxis in Australia.

In conclusion, the present study identifies a high rate of repeated adrenaline requirements in patients presenting with anaphylaxis. Apart from older age, male sex, insect sting and unknown triggers, it was difficult to identify other predictors for such increased requirements. This supports current recommendations that patients diagnosed with anaphylaxis should carry two adrenaline auto-injectors. Self administration of adrenaline autoinjectors was low despite known prior history of anaphylaxis, suggesting a need for improved anaphylaxis education.

Appendix A.

Table A1. Clinical features of patients requiring repeated adrenaline doses compared with those receiving no more than one dose

Characteristics	All patients (<i>n</i> = 174)	≤1 doses adrenaline (<i>n</i> = 97)	≥2 doses adrenaline (<i>n</i> = 77)	<i>P</i> -value
Cutaneous, no. (%)				
Pruritus	103 (59)	63 (65)	40 (52)	0.083
Erythema	74 (43)	41 (42)	33 (43)	0.938
Urticaria	120 (69)	59 (61)	61 (79)	0.009*
Angioedema	109 (63)	60 (62)	49 (64)	0.809
No cutaneous	10 (6)	7 (7)	3 (4)	0.35
Upper airway oedema, no. (%)	25 (14)	13 (13)	12 (16)	0.684
Stridor	12 (7)	5 (5)	7 (9)	0.318
Hoarseness	25 (14)	14 (14)	11(14)	0.978
Respiratory features, no. (%)				
Dyspnoea	103 (59)	49 (50)	54 (70)	0.009*

Characteristics	All patients (<i>n</i> = 174)	≤1 doses adrenaline (<i>n</i> = 97)	≥2 doses adrenaline (<i>n</i> = 77)	<i>P</i> -value

* $P < 0.05$ was considered statistically significant. Data are represented as counts with %, unless otherwise specified.

GCS, Glasgow Coma Scale.

Table A2. Pre-hospital management

Characteristics	All patients (<i>n</i> = 174)	≤1 doses adrenaline (<i>n</i> = 97)	≥2 doses adrenaline (<i>n</i> = 77)	<i>P</i> -value
Antihistamines, no. (%)	47 (27)	36 (37)	11 (14)	0.001 [*]
Corticosteroids, no. (%)	24 (14)	10 (10)	14 (18)	0.135
Adrenaline, no. (%)				
i.m. – self	47 (27)	24 (25)	23 (30)	0.438
i.m. – bystander	15 (9)	5 (5)	10 (13)	0.067
i.m. – GP	3 (2)	1 (1)	2 (3)	0.43
i.m. – ambulance	62 (36)	14 (14)	48 (62)	<0.001 [*]
i.v. infusion	6 (3)	0 (0)	6 (8)	0.005 [*]
Inhaled salbutamol, no. (%)	19 (11)	9 (9)	10 (13)	0.436
i.v. fluids, no. (%)	20 (11)	4 (4)	16 (21)	0.001 [*]
Ambulance called, no. (%)	96 (55)	43 (44)	53 (68)	0.001 [*]

* $P < 0.05$ was considered statistically significant. Data are represented as counts with %, unless otherwise specified.

GP, general practitioner; i.m., intramuscular; i.v., intravenous.

Table A3. Hospital management

Characteristics	All patients (<i>n</i> = 174)	≤1 doses adrenaline (<i>n</i> = 97)	≥2 doses adrenaline (<i>n</i> = 77)	<i>P</i> -value
Antihistamines, no. (%)	119 (68)	62 (64)	57 (74)	0.154
Corticosteroids, no. (%)	135 (78)	70 (72)	65 (84)	0.054
Adrenaline, no. (%)				
i.m. adrenaline	76 (44)	37 (38)	39 (51)	<0.001 [*]
Nebulised	22 (13)	5 (6)	16 (21)	0.004 [*]
i.v. infusion	15 (9)	0 (0)	15 (19)	<0.001 [*]
i.v. fluids, no. (%)	65 (37)	22 (23)	43 (56)	<0.001 [*]
Inhaled salbutamol, no. (%)	29 (17)	14 (14)	15 (19)	0.375
Intubation, no. (%)	1 (1)	0 (0)	1 (1)	0.254
Supplemental oxygen, no. (%)	23 (13)	4 (4)	19 (25)	<0.001 [*]
Observation >4 h, no. (%)	167 (96)	93 (96)	74 (96)	0.94
Admission	44 (25)	7 (7)	37 (48)	<0.001

* *P* < 0.05 was considered statistically significant. Data are represented as counts with %, unless otherwise specified.

i.m., intramuscular; i.v., intravenous.

Table A4. Multivariate logistic regression for patients requiring repeated adrenaline doses

Characteristics	Odds ratio (95% CI)	<i>P</i> -value
Age	0.99 (0.96–1.02)	0.553
Female sex	0.75 (0.34–1.66)	0.476
Trigger		
Unknown	1.92 (0.77–4.80)	0.162
Sting	2.02 (0.13–32.77)	0.620
Clinical feature		

Characteristics	Odds ratio (95% CI)	P-value
Urticaria	3.05 (1.28–7.27)	0.012 [*]
Hypoxia	2.25 (1.42–12.71)	0.010 [*]
Hypotension	2.23 (0.95–5.28)	0.067
Altered GCS	4.38 (0.47–41.13)	0.196
Pre-hospital management		
Antihistamines	0.32 (0.13–0.78)	0.012 [*]
Tryptase collection	1.18 (0.54–2.61)	0.676

* $P < 0.05$ was considered statistically significant.

GCS, Glasgow Coma Scale.

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