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Biphasic anaphylactic reactions: occurrence and mortality

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Abstract

Background: Monitoring after complete resolution of anaphylactic reactions is recommended. The aim of this study was to define the occurrence of biphasic – and clinically important biphasic – anaphylactic reactions, the number of transfers to intensive care units (ICU) because of anaphylaxis, and the number of deaths within 10 days of presentation to the emergency department (ED).
Methods: Clinical records of patients visiting the ED of a tertiary care hospital were analysed retrospectively. Hospital databases, direct contact with patients and caregivers, and the Internet were used to obtain mortality rates.
Results: Of 259 557 ED presentations from February 2001 through to August 2013, 1334 (0.51%) episodes of allergic reactions were detected, and 532 (0.20%) episodes in 495 patients fulfilled the definition of anaphylaxis. In 227 (44.8%) episodes, the length of hospital stay was ≥8 h (median 22 h, IQR 16–24). There were 507 uniphasic and 25 (4.5%) biphasic anaphylactic reactions. Twelve (2.3%) were clinically important, including 2 (0.36%) that occurred during hospital stay, one of whom (0.19%) was transferred to ICU for shock. No risk factors for biphasic reactions could be found. Eight patients were lost to follow-up. There were no deaths during the 10-day follow-up.
Conclusion: Biphasic anaphylactic reactions, especially clinically important ones, occurred rarely, and no mortality was found, whether the monitoring was for ≥8 h or for <8 h. Our study could motivate physicians to consider discharging patients after complete resolution of an anaphylactic reaction and to dispense with prolonged monitoring.

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction with a sudden onset after contact with an anaphylaxis-causing agent. The most common triggers of anaphylaxis are foods, medications and insect stings (1). In a study comprising 940 000 inhabitants of the Swiss Canton of Bern, the incidence of anaphylaxis with circulatory symptoms was 8.9 per 100 000 per year, and death from anaphylaxis was reported only in three cases within 3 years (2). Promptly administered adrenaline, antihistamines and corticosteroids are recommended as treatments in anaphylaxis (1). To our knowledge, 14 prospective and retrospective studies were performed in different countries and settings between 1984 and 2013 to analyse biphasic anaphylactic reactions in adults and children, using different definitions of a biphasic anaphylactic reaction (see Table S1 in the Supplementary Appendix) (3–16). A biphasic anaphylactic reaction appears to occur in between less than 1% and up to 20% of patients. The reported time intervals between the primary reaction and the beginning of the secondary reaction range from 1 to 72 h, but most secondary events seem to occur within 8 h of the resolution of the primary event (17). Thus, current guidelines recommend the monitoring of patients for at least 4 h and, if indicated, for 8–10 h or longer (1). We performed a retrospective single-centre study to define the occurrence of biphasic anaphylactic reactions, to define risk factors for a biphasic anaphylactic reaction, to assess the number of patients admitted to intensive care units (ICU) and to assess mortality.

Methods

Study design and setting

This retrospective study was performed at the University Hospital, Basel, Switzerland, a tertiary care university hospital with a census of 46 000 ED presentations. The study

protocol and the waiver of the patients' informed consent were approved by the local ethics committee. Physicians are required to write a discharge letter for every patient seen in the ED, containing at least one diagnosis, a summary of all procedures, findings of physical examinations, vital parameters, medications administered, prescriptions and follow-up arrangements. Administrative staff check the completeness of discharge letters. In the case of missing letters, physicians are repeatedly reminded to complete and sign discharge letters. Additionally, since January 2007, an ICD-10 code has been required to discharge patients from the ED. Since December 2008, institutional guidelines, which can be rapidly and easily consulted online, recommend that patients with anaphylaxis should stay in hospital for 24 h (18).

Data collection

For this analysis, the electronic database of the hospital (IsMed, ProtecData, Boswil, Switzerland) was screened from February 2001 to August 2013 for ED patients with the discharge code or discharge diagnosis 'anaphylaxis', 'anaphylactic reaction', 'anaphylactic shock', 'allergy' or 'allergic reaction'. From 2001 to 2006, discharge diagnoses were screened, and from 2007 to 2013, discharge codes were screened. Analysis of data was performed by the first author. To define cases meeting the definition of anaphylaxis, the electronic discharge information of all patients was analysed. In the case of anaphylaxis, all components of clinical records were analysed – including physician's reports, physician's notes, physician's orders and nurse's notes, including clinical observations, documentation of vital parameters and application of drugs. Follow-up was assessed by the first and second authors. Patients were considered to have survived if (i) there was evidence of a visit in any department of the hospital in the electronic database after discharge; (ii) patients could be contacted by telephone; (iii) patient's proxies testified that the patient was alive; (iv) patient's family physician, healthcare insurance or nursing home approved the date of the patient's last visit, last bill paid or last stay; (v) survival of the patient – as defined by first name, family name, date of birth and one of the following: private address, private telephone number, address of employer, address of private business or business telephone number – was evident in the Internet; or (vi) government officials testified to survival.

Patients included

All adult patients presenting to the ED between February 2001 and August 2013 were screened and included if they met the following criteria for anaphylaxis:

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   and at least one of the following
   - **a** Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxaemia)
   - **b** Reduced blood pressure (BP) or associated symptoms of end organ dysfunction (e.g. hypotension, 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., generalized 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. hypotension, collapse, syncope, incontinence)
   - **d** Persistent gastrointestinal symptoms (e.g. abdominal cramps, or pain, vomiting)
3 Reduced BP after exposure to known allergen for the specific patient (minutes to several hours):
   - **a** Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline (19).

Outcome measures

Outcome measures were as follows:

1 The occurrence of a biphasic anaphylactic reaction (i.e. appearance of any symptom such as rash, pruritus, mucosal swelling, respiratory, gastrointestinal or circulatory compromise, after complete resolution of the primary reaction);
2 The occurrence of a clinically important biphasic anaphylactic reaction (i.e. worsening symptoms or new symptoms fulfilling the definition of anaphylaxis, after resolution of the primary reaction). If the primary reaction did not meet the criteria of anaphylaxis, but the secondary reaction did, the episode was considered to be a clinically important biphasic anaphylactic reaction;
3 Disposition to intensive care unit (ICU); and
4 Death within 10 days of admission to the ED.

Statistical analysis

All statistical analyses were performed by an independent biostatistician. To compare different groups (all uniphasic with biphasic, and uniphasic, length of hospital stay (LOS) $\geq$8 h, with biphasic that occurred during hospital stay), the t-test, the Kruskal–Wallis test, the chi-squared test or Fisher's exact test were used as appropriate. A P-value of <0.05 was considered to be statistically significant. All calculations were performed with the statistical package R (The R Foundation for Statistical Computing Version 3.0.1).

Results

From February 2001 through to August 2013, there were 259 557 presentations to the ED, and 1334 (0.51%) episodes were found to be allergic reactions. Of these, 532 (0.20%) episodes in 495 patients met the definition of anaphylaxis. Figure 1 gives an overview of results and follow-up. Complete data were available for all episodes included, except

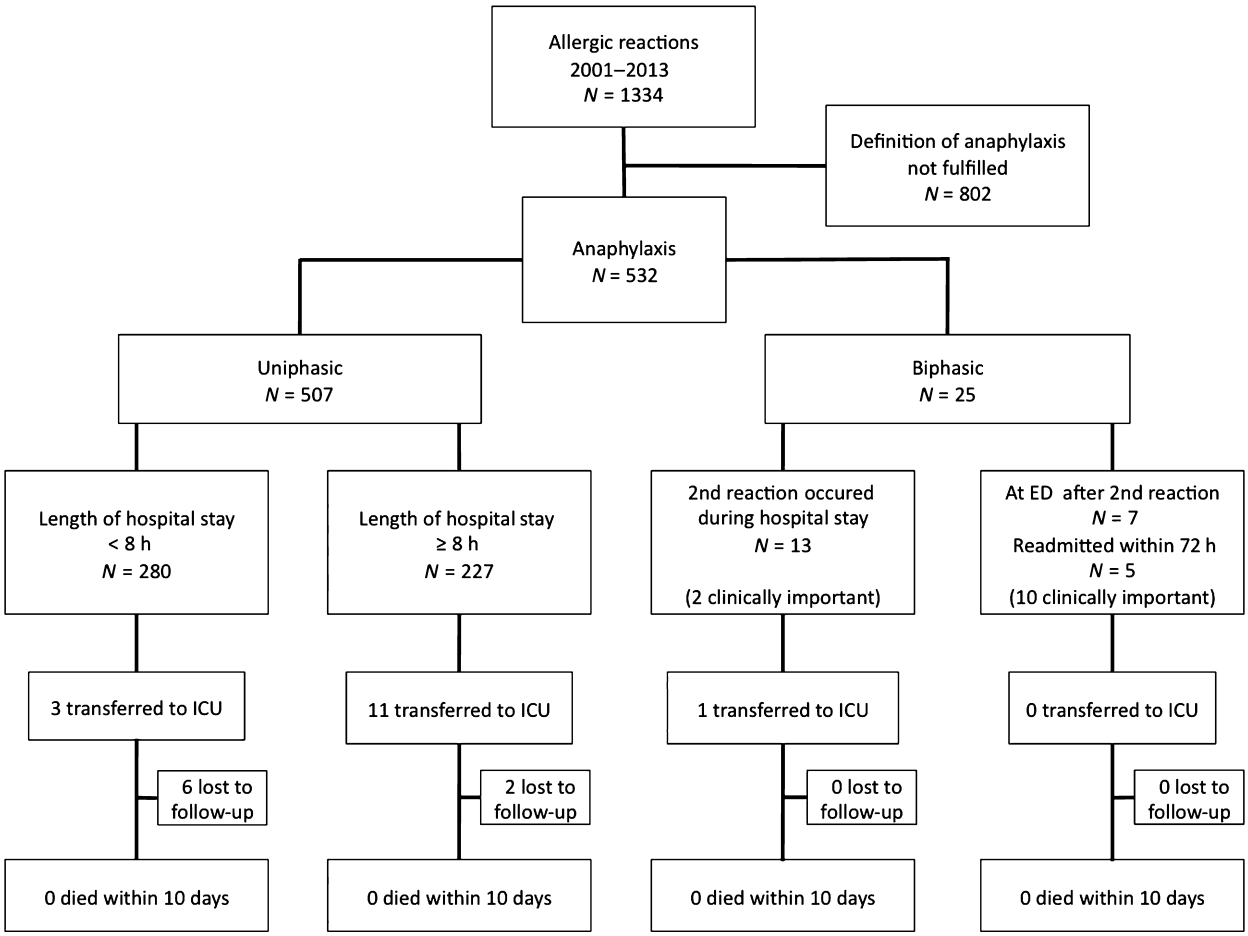

Figure 1 Overview of results and follow-up. Uniphasic denotes uniphasic anaphylactic reaction; biphasic denotes biphasic anaphylactic reaction (i.e. appearance of any symptom such as rash, pruritus, mucosal swelling, respiratory, gastrointestinal or circulatory compromise, after complete resolution of the primary reaction); clinically important denotes clinically important biphasic reaction (i.e. worsening symptoms or new symptoms fulfilling the definition of anaphylaxis, after resolution of the primary reaction); ED denotes emergency department; ICU denotes intensive care unit.

nurses' notes, which were missing in 43 cases because clinical records of outpatients were kept for 10 years only, and LOS, which was missing for 42 short-stay patients. We assumed that these patients had an LOS of less than 8 h.

A total of 507 (95.5%) uniphasic and 25 (4.5%) biphasic anaphylactic reactions were detected. In 227 (44.8%) uniphasic episodes, LOS was ≥8 h (median 22 h, IQR 16–24). The median LOS of uniphasic episodes with a LOS of <8 h was 2.5 h (range 0.5–7.5 h, information available in 239 of 280 episodes only). In 82 (15.4%) episodes, patients refused to stay in the hospital for 24 h and were discharged after signing a waiver. In patients not transferred to ICU, vital parameters (i.e. at least measurement of blood pressure and pulse) were measured 6 (median, IQR 3–8) times during hospital stay. Table 1 outlines the characteristics of all anaphylactic episodes, of uniphasic episodes and of the primary reaction of biphasic episodes. The characteristics of episodes with biphasic anaphylactic reactions compared with episodes with uniphasic anaphylactic reactions were similar, except that in episodes with biphasic anaphylactic reactions, there was less dyspnoea (48.0% *vs* 75.3%, OR 0.3, 95% CI 0.13–0.69 $P = 0.005$), less corticosteroid use (84.0% *vs* 97.6%, OR 0.13, 95% CI 0.04–0.5, $P = 0.005$) and less H_1-antihistamine drug use (84.0% *vs* 98%, OR 0.10, 95% CI 0.03–0.42, $P = 0.003$) to treat the initial reaction. If uniphasic episodes with LOS of ≥8 h were compared with biphasic episodes that occurred during the hospital stay, these differences disappeared (see Table S2 in the Supplementary Appendix). Table 2 outlines characteristics of the 25 secondary reactions of biphasic anaphylactic reactions. Twelve (2.3%) episodes met the definition of a clinically important biphasic reaction, of which 2 (0.36%) occurred during the hospital stay, including one (0.19%) who was transferred to the ICU because of shock. Survival during follow-up was demonstrated as follows: documented subsequent visits to any department of the hospital proved

Table 1 Characteristics of all episodes of anaphylactic reactions

	Overall $n = 532$	Uniphasic $n = 507$	Biphasic* $n = 25$	*P*-value
Age, years, mean (SD)	42.4 (17.3)	42.4 (17.4)	42.3 (15.2)	0.98
Female sex, *n* (%)	310 (58.3)	291 (57.4)	19 (76.0)	0.066
History of allergy, *n* (%)	218 (41.0)	209 (41.2)	9 (36.0)	0.62
History of anaphylaxis, *n* (%)	83 (15.6)	80 (15.8)	3 (12.0)	0.66
History of asthma, *n* (%)	50 (9.40)	48 (9.47)	2 (8.00)	0.87
ICU, *n* (%)	15 (2.82)	14 (2.76)	1 (4.00)	0.67
ICU because of shock, *n* (%)	11 (2.07)	10 (1.97)	1 (4.00)	0.5
Refusal to stay for 24 h, *n* (%)	82 (15.4)	78 (15.4)	4 (16.0)	0.89
LOS, hours, median (IQR)	7.75 (2.50–22.0)	6.38 (2.50–22.0)	15.0 (8.88–23.0)	0.96
Vital parameters†, *n* median (IQR)	6.00 (3.00–8.00)	6.00 (3.00–8.00)	6.00 (5.00–9.50)	0.036
Triggers				
Foods, *n* (%)	208 (39.1)	199 (39.3)	9 (36.0)	0.76
Drugs, *n* (%)	134 (25.2)	128 (25.2%)	6 (24.0)	0.92
Hymenoptera venoms, *n* (%)	75 (14.1)	72 (14.2%)	3 (12.0)	0.81
Other, *n* (%)	37 (6.95)	37 (7.30%)	0 (0.00)	–
Unknown, *n* (%)	78 (14.7)	71 (14.0%)	7 (28.0)	0.078
Symptoms				
Pruritus, *n* (%)	301 (56.7)	286 (56.5)	15 (60.0)	0.74
Rash, flush or urticaria *n* (%)	360 (67.7)	344 (67.9)	16 (64.0)	0.68
Mucosal swelling, *n* (%)	279 (52.4)	268 (52.9)	11 (44.0)	0.4
Dyspnoea, *n* (%)	394 (74.1)	382 (75.3)	12 (48.0)	0.005
Feeling of tightness, *n* (%)	126 (23.7)	118 (23.3)	8 (32.0)	0.33
Dizziness or collapse, *n* (%)	110 (20.7)	105 (20.7)	5 (20.0)	0.98
Tachypnoea‡, *n* (%)	43 (8.08)	41 (8.09)	2 (8.00)	0.95
Wheezing, *n* (%)	112 (21.1)	109 (21.5)	3 (12.0)	0.26
Stridor, *n* (%)	17 (3.20)	16 (3.16)	1 (4.00)	0.75
Arterial hypotension§, *n* (%)	65 (12.2)	60 (11.8)	5 (20.0)	0.25
Tachycardia¶, *n* (%)	116 (21.8)	110 (21.7)	6 (24.0)	0.76
Hypoxaemia**, *n* (%)	18 (3.38)	16 (3.16)	2 (8.00)	0.25
Hypotension and tachycardia, *n* (%)	25 (4.70)	23 (4.54)	2 (8.00)	0.44
Gastrointestinal symptoms, *n* (%)	140 (26.3)	135 (26.6)	5 (20.0)	0.49
Therapy				
H_1-antihistamines, *n* (%)	518 (97.4)	497 (98.0)	21 (84.0)	0.003
Corticosteroids, *n* (%)	516 (97.0)	495 (97.6)	21 (84.0)	0.005
Salbutamol/Ipratropium bromide, *n* (%)	146 (27.4)	140 (27.6)	6 (24.0)	0.72
Adrenaline, *n* (%)	59 (11.1)	56 (11.0)	3 (12.0)	0.836
Emergency kit††, *n* (%)	390 (73.3)	371 (73.2)	19 (76.0)	0.784
Steroid/antihistamines 1–3 days, *n* (%)	368 (69.2)	351 (69.2)	17 (68.0)	0.88

ICU, intensive care unit; LOS, length of hospital stay.

*Primary reaction of anaphylaxis.

†Number of measurements of at least blood pressure and pulse during hospital stay, if not admitted to ICU. Data not available in 43 episodes.

‡>25 breaths per minute.

§Systolic blood pressure <90 mmHg.

¶Heart beat >100 beats per minute.

**Oxygen saturation <90%.

††Contained an adrenaline autoinjector in 66 (12.4%) episodes additionally to an antihistamine drug and a steroid.

the survival of 350 patients; 51 patients were contacted by telephone; patient's proxies confirmed the survival of 24 patients; family physicians, healthcare insurances or nursing homes confirmed the survival of 29 patients; evidence of the survival of 27 patients was found in the Internet; and government officials confirmed the survival of six patients. Eight patients (1.5%) were lost to follow-up (seven were tourists and went back to their home countries, and one patient's identity could not be proven sufficiently by the Internet). The documented median survival was 760 days (range 11–4125) since the day of admission to the ED. No deaths occurred during follow-up.

Table 2 Characteristics of 25 subsequent reactions

Clinically important reaction*, *n* (%)	12 (48)
Occurred during hospital stay, *n* (%)	2 (7)
Transferred to ICU, *n* (%)	1 (4)
Primary reaction not anaphylactic†, *n* (%)	5 (20)
Hours to subsequent reaction, median (range)	12 (1–36)
Symptoms	
Prutitus, *n* (%)	7 (28)
Rash, flush or urticaria, *n* (%)	8 (32)
Mucosal swelling, *n* (%)	8 (32)
Dyspnoea, *n* (%)	11 (44)
Feeling of tightness, *n* (%)	5 (20)
Stridor, *n* (%)	1 (4)
Hypoxaemia‡, *n* (%)	1 (4)
Dizziness, *n* (%)	1 (4)
Arterial hypotension§, *n* (%)	2 (7)
Tachycardia¶, *n* (%)	4 (16)
Therapy	
H_1-antihistamines, *n* (%)	17 (68)
Corticosteroids, *n* (%)	16 (64)
Adrenaline, *n* (%)	5 (20)
Salbutamol/Ipratropium bromide, *n* (%)	3 (12)

ICU, intensive care unit.
*Worsening symptoms or new symptoms fulfilling the definition of anaphylaxis, after resolution of the primary reaction.
†Primary reaction did not fulfill the definition of anaphylaxis.
‡Oxygen saturation <90%.
§Systolic blood pressure <90 mmHg.
¶Heart beat >100 beats per minute.

Discussion

Of 532 anaphylactic reactions of patients presenting to our ED during the last 13 years, 25 (4.5%) were biphasic. Twelve (2.3%) secondary reactions were clinically important, one patient (0.19%) had to be transferred to the ICU because of a secondary reaction with shock, but no patient died within 10 days of follow-up. In order not to miss a biphasic episode because of the retrospective design of our study, a biphasic anaphylactic reaction was defined as the re-appearance of any symptom after resolution of the primary reaction, and episodes with a primary reaction not meeting the definition of anaphylaxis, but with a secondary reaction meeting it, were also included and classified as clinically important. These definitions allowed us to detect biphasic reactions more sensitively. During hospital stay, clinical evaluation and measurements of vital parameters by nursing staff were repetitively performed (median 6 times during hospital stay, IQR 3 – 8), and, if transferred to ICU, patients were monitored continuously. Thus, it is not likely that a biphasic reaction was missed during the hospital stay. Nevertheless, we have found only a small number of biphasic reactions, which is consistent with the majority of published data (see Table S1 in the Supplementary Appendix): the low frequency of clinically important biphasic reactions and the lack of deaths within 10 days of follow-up are in line with a recent retrospective study, in which a clinically important biphasic reaction occurred in 2 of 496 anaphylactic episodes in patients presenting to the ED, with no deaths within 7 days of follow-up (16). If three episodes of clinically important biphasic reactions are included in which the primary reaction did not meet the definition of anaphylaxis, 5 (1%) episodes met the definition of a clinically important biphasic reaction as defined in our study, which is comparable to our observation of 2.3%. Six more studies using a similar definition of anaphylaxis analysed adults and children presenting to the ED: two studies including adult patients defined a biphasic reaction as the re-appearance of any symptom after the resolution of the first reaction and found 3% (2 of 67) and 5% (15 of 282) biphasic reactions (5, 8). One study that did not define a biphasic reaction included adults and children and found 6% (13 of 208) biphasic reactions (11), and one study analysed 340 children and found 3 (0.9%) biphasic reactions (14). However, a biphasic course occurred in 19% of anaphylactic reactions in a study that analysed 134 ED and inpatients, including 10 children (9). But only 2 of 103 patients with available follow-up information presented with a more severe secondary reaction than the first reaction, which is comparable to the frequency of clinically important biphasic reactions in our study. Another small study found 18% (6 of 34) biphasic reactions (6). In that study, however, the occurrence of one symptom only was enough to fulfil the definition of an anaphylactic reaction, and a biphasic reaction was defined as the development of further symptoms requiring adrenaline. Given these different definitions, it may not be appropriate to compare these results with the result of our study. Of these studies, all but one (9) assessed mortality, and no deaths occurred during follow-up. However, follow-up time in these studies was less than 72 h. Seven more studies analysed biphasic anaphylactic reactions in adults and children (3, 4, 7, 10, 12, 13, 15). As these studies represent different patient populations, it may not be appropriate to compare their findings with those of our study.

In our study, we compared characteristics of uniphasic and biphasic reactions. The frequency of dyspnoea, use of corticosteroids and use of H_1-antihistamine drugs were significantly lower in the group of biphasic reactions. However, five episodes were biphasic reactions in which the primary reaction lacked respiratory compromise and therefore did not meet the definition of anaphylaxis, and seven episodes of biphasic reactions presented to the ED with a secondary reaction after complete resolution of the primary reaction outside the hospital. In three of these seven episodes, neither H_1-antihistamine drugs nor steroids were used after the primary reaction, as it was recorded that the patients had no medication, and one patient took a steroid only, without an antihistaminic drug. When episodes of uniphasic reactions with an LOS of ≥8 h were compared with episodes of biphasic reactions in which the secondary reaction occurred during the hospital stay, there was no significant difference between groups. Thus, the difference in dyspnoea, use of H_1-antihistaminic drugs and use of corticosteroids may reflect a selection bias more than a true risk factor for biphasic reactions. We could not identify predisposing factors for a biphasic reaction, although these were mentioned in previous reports and include older age, oral administra-

tion of antigen, presence of hypotension during the initial event, and initial reactions not treated by corticosteroids (17). This is in line with the results of three studies performed in EDs, which could not find predisposing factors, such as absence of corticosteroid or antihistaminic drug treatment, or initiators such as drugs or foods (8, 9, 11). We do not think that our study has the power to answer the question of the role of these factors in the risk of biphasic anaphylaxis. Of note, a Cochrane review failed to show the effectiveness of corticosteroids in the treatment for anaphylaxis (20).

Our study has several limitations. Firstly, it was a retrospective study. However, our retrospective case definitions were based on clinical signs and symptoms, which were well documented and which could be reliably retrieved from clinical records. Secondly, only in 227 (44.8%) uniphasic episodes, patients stayed at the hospital for 8 h or longer, and in 280 uniphasic episodes, LOS was <8 h. As the majority of secondary reactions seem to occur around 8 h after the resolution of the primary reaction and can occur up to 72 h later, it is possible that secondary reactions were missed. However, even if secondary reactions were missed, no patient died, even if discharged early. Finally, our study was a single-centre study. Thus, our findings might not be generalizable. However, our results are comparable to recently published data in similar settings and different countries, as described above. In conclusion, biphasic anaphylactic reactions, especially secondary clinically important reactions and secondary reactions occurring during hospital stay, were exceedingly rare. During 13 years, only one patient had to be transferred to ICU because of a secondary reaction, and there were no deaths due to anaphylaxis, irrespective of early discharge or refusal to be hospitalized for 24 h. We have not found any parameters that might reflect true risk factors for a biphasic reaction. Our study could motivate physicians to consider discharging patients after complete resolution of an anaphylactic reaction and to dispense with prolonged monitoring.

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Author Contributions

All authors contributed to the manuscript.

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Disclosures

None.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Overview of studies analysing biphasic anaphylactic reactions.

Table S2. Comparison of uniphasic episodes with length of hospital stay ≥8 h with biphasic reactions that occurred during hospital stay.

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