ANESTHESIOLOGY

Low Incidence of Biphasic Allergic Reactions in Patients Admitted to Intensive Care after Anaphylaxis

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ABSTRACT

Background: Biphasic allergic reactions—recurrence of allergy symptoms after a symptom-free period—are reported to occur in 1 to 23% of allergic reactions. Patients admitted to an intensive care unit after anaphylaxis potentially have more severe reactions and a higher risk of biphasic allergic reactions. The purpose of this study was to examine incidence, triggers, symptoms, and treatment of biphasic allergic reactions, in patients admitted to an intensive care unit.

Methods: Records of patients admitted to intensive care units with anaphylaxis from 2011 to 2014 were reviewed. Only patients with a reaction fulfilling internationally accepted criteria for anaphylaxis were included. Potential biphasic allergic reactions, defined as renewed allergy symptoms 1 to 72 h after initial symptoms had resolved, without further exposure to the trigger, were identified.

Results: A total of 83 cases of anaphylaxis were identified, and the most frequent triggers were medications (58 of 83 [70%]). Skin symptoms occurred in 69 (83%) cases, and circulatory and respiratory symptoms in 48 (58%) and 45 (54%) cases, respectively. In total, 82 (99%), 80 (96%), and 66 (80%) were treated with antihistamines, corticosteroids, and epinephrine, respectively. Only 10 patients presented with one or more relevant symptoms after the initial allergic reaction. Of these, three were possible, and one was a probable biphasic allergic reaction, giving a total incidence of 4 of 83 (4.8% [95% CI, 1.6 to 12.5]) or 1 of 83 (1.2% [95% CI, 0.1 to 7.46]), respectively. All cases were mild, presenting with skin symptoms only, occurring on average 14 h after initial reactions.

Conclusions: The authors observed a low incidence of biphasic reactions in patients admitted to an intensive care unit after anaphylaxis, at a rate equivalent to that reported in other patient groups.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Recurrent manifestations of anaphylaxis after treatment, termed biphasic reactions, are estimated to occur in 1 to 23% of reactions
- However, little is known about the incidence, triggers, symptoms, and management of biphasic reactions

What This Article Tells Us That Is New

- In 83 cases of patients admitted to intensive care units in Denmark after anaphylaxis, suspected biphasic reactions occurred in 4 (4.8%) of patients
- The incidence of biphasic reactions was low, 3 out of 4 were considered possible, and only 1 considered a probable biphasic allergic reaction

Anaphylaxis is defined as a serious, life-threatening, generalized hypersensitivity reaction, and it requires prompt diagnosis and treatment. Usually it involves either the cardiovascular or respiratory system with or without skin symptoms.[1] Common triggers of anaphylaxis include medications, foods, and insect venom.[2]

The incidence of anaphylaxis in Denmark was recently reported in a registry study to be 64.6 (95% CI, 63.1 to 66.2) per 1,000,000 person-years and has increased more than twofold in adults and tenfold for children since 1995.[3]

The time course of anaphylaxis can be classified into three groups: *uniphasic*, where the patient has a single episode of symptoms; *protracted*, where the symptoms take a long time to resolve despite relevant treatment; and *biphasic*, where the patient has a recurrence of symptoms after a symptom-free period.[4]

The term *biphasic allergic reaction* was first described in 1984 by Popa and Lerner.[5] Since then, the incidence of biphasic allergic reaction has been reported to be in the range of 1 to 23%.[6] There is no consensus on the definition of a biphasic allergic reaction, but mostly it is defined as a new reaction occurring within 1 to 72 h after the initial symptoms have resolved, without further exposure to the trigger.[7] Biphasic allergic reaction varies in severity from

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relatively mild skin symptoms to systemic anaphylaxis with circulatory collapse and respiratory insufficiency.

The underlying mechanism behind biphasic allergic reaction is unknown, but it is suggested to include various types of immune responses, large doses of antigen (*e.g.*, IV antibiotics), continuous exposure to the allergen (*e.g.*, food in stomach), inadequate treatment of the initial reaction, lack of postreaction treatment, or simply just a recurrence of a temporarily interrupted protracted initial reaction.[8,9]

At present, there is no consensus in international guidelines on how long a patient should be observed after anaphylaxis, and the recommended observation period varies in the range of 4 to 24 h, based on the perceived risk of biphasic reactions.[2,10] Working on the assumption that patients with the most severe symptoms may be at highest risk of protracted or biphasic reactions, this study investigated patients admitted to intensive care units for observation after anaphylaxis.

This study aimed to determine the incidence, triggers, symptoms, and treatment of biphasic reactions after anaphylaxis in patients admitted to five intensive care units in the Capital Region of Denmark.

Materials and Methods

Study Design

The study was conducted in 2015 as a retrospective analysis of medical records of adults and children admitted to five general intensive care units in the Capital Region of Denmark in the period January 1, 2011, to December 31, 2014. In Denmark, this type of retrospective study does not require ethical approval, but the required approval was obtained from the Danish Board of Health to access medical notes without informed consent from patients with j.nr. 3-3013-1203/1. Approval was also obtained from the Data Protection Agency (journal no. 03957 and ID no. HGH-2015–026).

Patients were identified using the search function of the Critical Information System (Daintel, Denmark), which was the electronic health record used in the intensive care units. Because anaphylaxis is a rare occurrence, we chose to collect data from the longest time period possible from the introduction of the Critical Information System. Patients were included if they, as primary or secondary diagnoses, had either of the International Classification of Diseases, Tenth Revision diagnoses: anaphylaxis without specification DT782 or anaphylaxis by proper administration of the drug DT886.

DT782 and DT886 were the only two relevant diagnosis codes available for coding in the Critical Information System.

To retrospectively verify the clinical diagnosis of anaphylaxis, the medical records were reviewed by one investigator (S.H.), using a standardized data registration form. All parts of the notes were examined, including physician's notes, nursing notes, and the intensive care unit observation charts with recordings of heart rate, blood pressure, oxygen saturation, respiratory rate, and other ventilator parameters in patients on mechanical ventilation. Electronic medication records were reviewed to identify given interventions. The definition of anaphylaxis used in this study was based on the criteria widely used in international guidelines[11] (table 1). Only patients fulfilling these criteria were included for further analysis of a possible biphasic allergic reaction. Patients were excluded if their disease course was so complicated that the symptoms identifying a biphasic allergic reaction were impossible to detect.

Table 1. Clinical Criteria for Diagnosing Anaphylaxis

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.*, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
(b) Reduced BP or associated symptoms of end-organ dysfunction (*e.g.*, hypotonia [collapse], syncope, incontinence)

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Study Variables

Data collection for initial reaction and admission to intensive care unit included data on demographics: age and sex; symptoms: hypotension, tachycardia, bradycardia, dyspnea, low oxygen saturation, stridor, wheezing, laryngeal edema, cyanosis, angioedema, rash, urticaria, pruritus, erythema, mucosal swelling, syncope, dizziness, nausea, diarrhea, abdominal pain, vomiting; suspected trigger: medication, venom, food, *etc.*; treatment: dose and route of administration of systemic epinephrine, antihistamines, corticosteroids, epinephrine inhalation, and IV fluids. It was also noted whether the patient required intubation and mechanical ventilation; as well as duration of admission to the intensive care unit and discharge destination; and 7 days follow-up after discharge was performed in the electronic health record to ensure that there was no further contact with a hospital.

Identification of Possible Biphasic Allergic Reactions

To ensure that all potential biphasic allergic reactions were identified, very broad criteria were used for initial inclusion. Any charts or notes reporting one or more of the symptoms listed in the Study Variables section, occurring after the initial reaction, were selected. In addition, any potential intervention for anaphylaxis (IV or inhaled epinephrine, antihistamine, and steroids), and time delay between the initial reaction and onset of symptoms were identified. Overall

outcome (*i.e.*, survival or death) was registered 7 days after the reaction. Information on subsequent allergy investigations were not available for any of the cases. All incidents identified on the initial wide screening were analyzed. They were included, if they fulfilled the following definition of a biphasic allergic reaction: a new reaction occurring within 1 to 72 h after the initial symptoms have resolved, without further exposure to the triggering cause.

If the definition was fulfilled, the available information was carefully reviewed to determine if there were other more likely explanations for the patients symptoms. If this was not the case, it was planned to classify biphasic allergic reaction according to severity: mild reactions: skin symptoms only; or severe reactions: anaphylaxis fulfilling the definition of anaphylaxis in table 1.

Statistical Analysis

This study is a descriptive study and descriptive statistics were reported using frequency counts (%) for categorical data, and median and interquartile range for continuous data in Microsoft Excel for Mac 2011 version 14.7.7.
To estimate the uncertainty in the event rates of biphasic allergic reaction, the 95% CI was given by the normal approximation method of CI for single proportion of a binomial outcome.

Results

A total of 14,919 patients were admitted to the five intensive care units over the study period January 1, 2011, to December 31, 2014. Two of these intensive care units only used the Critical Information System electronic health records for a shorter period (one from October 1, 2013, and one from December 1, 2011), and data from these hospitals were registered from these dates only.

Of the 100 patients with at least one of the diagnosis codes for anaphylaxis who were included in the study, 17 were excluded after review of the notes: 15 did not fulfill the definition of anaphylaxis, and it was not possible to assess a biphasic allergic reaction for two because of a complicated course of disease (fig. 1).

After the exclusions, 83 incidents of anaphylaxis in 82 patients (four of them children) were included for further analysis. The incidence of intensive care unit admission for anaphylaxis was 83 of 14,919 (0.6%) for the total study population over the entire study period. There were 46 (56%) female and 36 (44%) male patients, with a median age of 54 yr (interquartile range, 41 to 64). The median duration of intensive care unit stay was 19 h (interquartile range, 9 to 26). Patients with longer duration of stay typically had several comorbidities and had been hospitalized before the anaphylactic reaction.

Medication was the most common cause of anaphylaxis with antibiotics causing the majority of reactions, followed by x-ray contrast media and chemotherapy. Several antibiotics were suspected triggers: penicillin, piperacillin/tazobactam, cefuroxime, sulfamethizole, amoxicillin/clavulanic acid, trimethoprim, moxifloxacin, meropenem, vancomycin, and metronidazole. Three types of chemotherapy were suspected triggers: cetuximab, docetaxel, and carboplatin. Iodinated contrast agents were suspected triggers in 8 patients. Skin symptoms were reported in the majority of patients and just more than 50% had either respiratory, circulatory or both symptoms. A small group of patients had gastrointestinal symptoms and the suspected trigger was medication for nine patients, while three had food and two had venom as suspected triggers. Almost all patients received antihistamines and corticosteroids, and approximately 66 of 83 (80%) were treated with epinephrine (table 2).

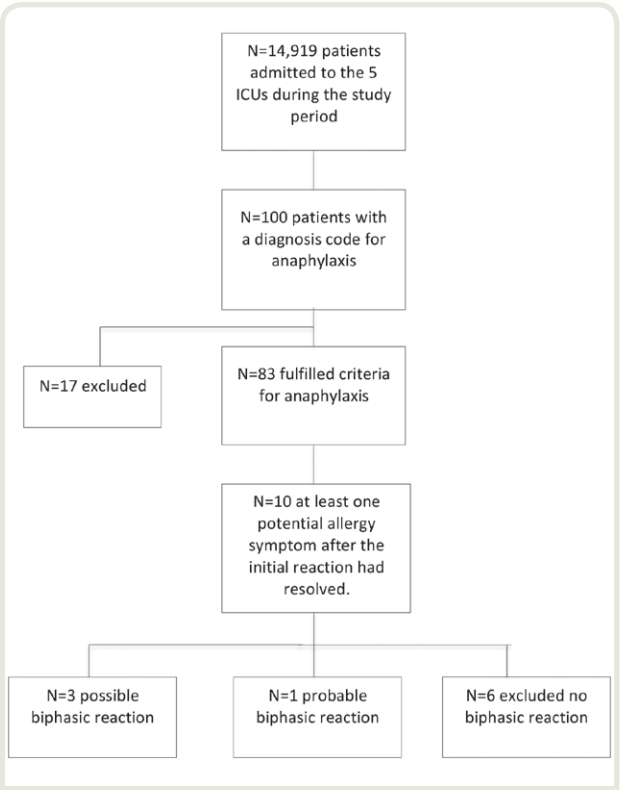

Fig. 1. Overview of the inclusion of patients. ICU, intensive care unit.

Identification of Potential Biphasic Reactions

Of the 82 patients with 83 initial reactions fulfilling the criteria for anaphylaxis, 10 developed at least one new symptom after the initial reaction and thus fulfilled the initial broad criteria used to identify potential cases of biphasic allergic reaction. On detailed review of the cases it was clear that not all fulfilled the definition of a biphasic allergic reaction, and in six patients a biphasic allergic reaction

Table 2. Suspected Triggers, Symptoms, and Treatment of the Initial Anaphylactic Reaction

	N	%
Suspected trigger		
Medication	58	70
Antibiotic	26	45
Contrast media	8	14
Chemotherapy	7	12
Others	17	29
Food	13	16
Venom	10	12
Allergy test	1	1
Unknown	1	1
Symptoms		
Skin	69	83
Circulatory	48	58
Respiratory	45	54
Gastrointestinal	14	17
Treatment		
Antihistamine	82	99
Corticosteroids	80	96
Epinephrine	66	80

was ruled out. One patient had recurrence of urticaria after more than 72 h, and one was reexposed to a possible trigger. Two patients had no asymptomatic period and were instead defined as having a protracted reaction. Two other patients had transient hypotension without any other symptoms or clinical deterioration, and no treatment was given.

The four cases where a biphasic allergic reaction could not be excluded were all mild reactions with skin symptoms only; thus, there were no cases of biphasic anaphylaxis. After detailed review, three cases were concluded to be possible biphasic allergic reaction and one case was concluded to be a probable biphasic allergic reaction (see fig. 1 for overview and appendix for description of the four cases). If all four cases are included, the incidence of biphasic allergic reaction in this study is 4 of 83 (4.8%; 95% CI, 1.6 to 12.5), and if only the probable case is included, the incidence is 1 of 83 (1.2%; 95% CI, 0.1 to 7.4). The mean symptom-free period was 14 h (range, 8 to 36 h) for all four possible and probable biphasic allergic reactions. One reacted to an allergy skin prick test, one to a bee sting, one to cetuximab and the last one reacted to either food or medication.

Discussion

We observed 83 cases of anaphylaxis, giving an incidence rate of intensive care unit admission for anaphylaxis of 83 of 14,919 (0.6%) for five general intensive care units during 2011 to 2014.

There were no cases of life-threatening biphasic allergic reactions fulfilling the definition of anaphylaxis as defined in table 1, and there were no deaths resulting from biphasic allergic reaction.

It was concluded that a mild biphasic allergic reaction may have occurred in 4 of 83 cases (4.8%). However, three cases had other possible explanations, thus only one case of a probable biphasic allergic reaction was observed, and the true incidence could be argued to be 1 of 83 (1.2%). Several studies have reported incidences around 4 to 5%,[12–18] while others found a higher incidence.[19–24] More recent larger studies of other patient groups have found incidences closer to 1.2%,[25–27] or even lower.[28] There is so far still conflicting evidence on the incidence of biphasic allergic reaction in the literature, and there are no previous studies of biphasic allergic reaction after admission to intensive care unit after anaphylaxis.

Common for all four cases was that they were mild, without life-threatening symptoms and all resolved on treatment with antihistamines and steroids. If these patients had been discharged, patients would not have experienced severe consequences, and the symptoms could have been managed at home after relevant information and reassurance was provided.

The great variation in the reported incidence of biphasic allergic reaction is likely due to varying definitions and inclusion criteria. Some studies include only severe cases (*e.g.*, fulfilling definition of anaphylaxis), and others include all cases ranging from mild to severe without determining their clinical importance. It is difficult to assess cases retrospectively and other investigators must have faced these difficulties too. It is clinically difficult to identify biphasic allergic reaction for several reasons: there is no International Classification of Diseases, Tenth Revision code for a biphasic allergic reaction; there are no well-defined guidelines giving physicians criteria to identify biphasic allergic reaction; and it is difficult to differentiate between protracted, new, and biphasic reactions. Relevant differential diagnoses should also be considered, such as hyperventilation/anxiety or circulatory compromise as a result of septicemia, which are all relevant in some of the cases in this study.

It seems that there is a decrease in the incidence of biphasic allergic reaction over time, which might be explained by better diagnosis and treatment of anaphylaxis in recent years. Almost 66 of 83 (80%) of the patients in this study were treated with epinephrine, which may contribute to a low incidence of biphasic allergic reaction.

All four patients with possible or probable biphasic allergic reaction received epinephrine at the initial reaction. Three out of four patients received more than one dose of epinephrine, and two received both intramuscular and IV administration. Several studies have reported that patients with biphasic allergic reaction often have been treated with larger doses of epinephrine in the initial phase, which has been interpreted as a sign of a more severe initial reaction increasing the risk of biphasic allergic reaction.[19,21,23,26] Conversely, one study found that less epinephrine was administered in patients with biphasic allergic reaction,

suggesting that inadequate treatment of the initial reaction increased the risk of a biphasic allergic reaction.[20]

An interesting suggestion for the mechanism behind some biphasic allergic reaction is that continuous exposure to the allergen (*e.g.*, food in the stomach) might increase the risk of developing biphasic allergic reaction. In our study, almost all patients admitted to the intensive care unit had IV medication as possible trigger—and not oral medication—which may also explain the low incidence of biphasic allergic reaction identified in this study. Only 13 of 83 (16%) of the patients admitted to the intensive care unit had anaphylaxis triggered by food.

In this study, admission to the intensive care unit was used as a proxy for severe reactions, however, the incidence of biphasic allergic reaction in this study was not higher than the incidence reported in recent studies in non–intensive care unit patients. While this may be due to better treatment of the initial reaction, the close observation in the intensive care unit setting provides optimal conditions to discover a biphasic allergic reaction compared to a general medical department. This decreases the risk of reactions being overlooked.

It has been suggested that treatment with antihistamines and corticosteroids play a role in preventing biphasic allergic reaction, but findings are inconsistent in the literature.[21,29–31] One study found patients with biphasic allergic reaction more likely to have received corticosteroids for their initial reaction,[26] while others found a significantly lower use of corticosteroids and H1-antihistamines.[16,20]

In this study, all four patients received antihistamines and corticosteroids for the initial reaction, but there is no record of continued treatment in the subsequent days.

All four possible and probable biphasic allergic reactions, in our study, responded to a combination of corticosteroids and antihistamines. While there is no evidence for a preventative effect of antihistamines and/or corticosteroids, there is no evidence to the contrary. Future studies should investigate the role of antihistamines and corticosteroids in the days after anaphylaxis in preventing recurrence of skin symptoms, once the effect of initial treatment with antihistamines ceases.

The symptom-free period before a biphasic allergic reaction differs greatly in the literature. Some studies have found results similar to this study with a mean symptom-free period of 14 h.[19,32] It is conceivable that the true duration is shorter, because the estimated time for the two patients who developed symptoms at home (19 h in patient number 67 and 36 h in patient number 81) is based on time to readmission and not time of onset of symptoms.

Information on how long these two patients waited before seeking hospital and the waiting time before seeing a doctor is not available.

The symptom-free period has implications for the recommended observation time after anaphylaxis. It is important for optimal patient safety to identify an interval, long enough to catch the few patients at risk of biphasic allergic reaction, while avoiding unnecessary hospitalization of the majority of patients not at risk.

Our study is too small to conclude on optimal observation time, but in deciding on the observation time, it is important to carry out a risk assessment of the patients comorbidity, social circumstances, severity of symptoms and response to treatment at the initial reaction.

There are several limitations to our study. Data were collected retrospectively and it is likely that some relevant patients may have been overlooked. In addition, anaphylaxis is a clinical diagnosis, which may be difficult to validate retrospectively from available health records, even if a standardized definition is used.

In the intensive care unit setting, the clinical picture may be very complex and we excluded two patients because of difficulties in assessing the clinical situation retrospectively. Also, even though we had a 7-day follow-up, it is possible that patients were admitted to a hospital in another region in Denmark. Thus, in theory, we may have excluded or overlooked patients with true biphasic allergic reaction. Also, because of the retrospective nature of the study, we did not have access to information about subsequent allergy investigations and thus, cannot confirm that the reactions were allergic anaphylaxis.

Last, this study investigated only patients admitted to the intensive care unit, which limits observations to this population and findings may not be directly extrapolated to other populations.

Conclusions

In this study, we observed a low incidence of biphasic reactions in patients admitted to an intensive care unit after anaphylaxis, a rate equivalent to that reported in other patient groups and settings. All cases of biphasic allergic reaction were mild and responded to antihistamine and corticosteroids. There were no cases of biphasic anaphylaxis requiring epinephrine, and no deaths.

This finding could have implications for the management of patients after anaphylaxis and highlights the need for an evaluation of recommended observation times and treatment after anaphylaxis, for which there is currently no consensus.

Competing Interests

The authors declare no competing interests.

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References

1. Brown SG, Stone SF, Fatovich DM, Burrows SA, Holdgate A, Celenza A, Coulson A, Hartnett L, Nagree Y, Cotterell C, Isbister GK: Anaphylaxis: clinical patterns, mediator release, and severity. J Allergy Clin Immunol 2013; 132:1141–9.e5
2. Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, Lieberman P, Lockey RF, Muraro A, Roberts G, Sanchez-Borges M, Sheikh A, Shek LP, Wallace DV, Worm M: International consensus on (ICON) anaphylaxis. World Allergy Organ J 2014; 7:9
3. Jeppesen AN, Christiansen CF, Frøslev T, Sørensen HT: Hospitalization rates and prognosis of patients with anaphylactic shock in Denmark from 1995 through 2012. J Allergy Clin Immunol 2016; 137:1143–7
4. Douglas DM, Sukenick E, Andrade WP, Brown JS: Biphasic systemic anaphylaxis: an inpatient and outpatient study. J Allergy Clin Immunol 1994; 93:977–85
5. Popa VT, Lerner SA: Biphasic systemic anaphylactic reaction: three illustrative cases. Ann Allergy 1984; 53:151–5
6. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, Ellis A, Golden DB, Greenberger P, Kemp S, Khan D, Ledford D, Lieberman J, Metcalfe D, Nowak-Wegrzyn A, Sicherer S, Wallace D, Blessing-Moore J, Lang D, Portnoy JM, Schuller D, Spector S, Tilles SA: Anaphylaxis–a practice parameter update 2015. Ann Allergy Asthma Immunol 2015; 115:341–84
7. Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL: Time of Onset and Predictors of Biphasic Anaphylactic Reactions: A Systematic Review and Meta-analysis. J Allergy Clin Immunol Pract 2015; 3:408–16.e1–2
8. Brady WJ Jr, Luber S, Carter CT, Guertler A, Lindbeck G: Multiphasic anaphylaxis: an uncommon event in the emergency department. Acad Emerg Med 1997; 4:193–7
9. Oya S, Nakamori T, Kinoshita H: Incidence and characteristics of biphasic and protracted anaphylaxis: evaluation of 114 inpatients. Acute Med Surg 2014; 1:228–33
10. Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, Santos AF, Zolkipli ZQ, Bellou A, Beyer K, Bindslev-Jensen C, Cardona V, Clark AT, Demoly P, Dubois AE, DunnGalvin A, Eigenmann P, Halken S, Harada L, Lack G, Jutel M, Niggemann B, Ruëff F, Timmermans F, Vlieg-Boerstra BJ, Werfel T, Dhami S, Panesar S, Akdis CA, Sheikh A; EAACI Food Allergy and Anaphylaxis Guidelines Group: Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014; 69:1026–45
11. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW: 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. J Allergy Clin Immunol 2006; 117:391–7
12. Civelek E, Erkoçoğlu M, Akan A, Özcan C, Kaya A, Vezir E, Giniş T, Azkur D, Toyran M, Tokaç M, Kocabaş CN: The Etiology and Clinical Features of Anaphylaxis in a developing country: A nationwide survey in Turkey. Asian Pac J Allergy Immunol 2017; 35:212–9
13. Lee S, Bellolio MF, Hess EP, Campbell RL: Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. J Allergy Clin Immunol Pract 2014; 2:281–7
14. Manivannan V, Hess EP, Bellamkonda VR, Nestler DM, Bellolio MF, Hagan JB, Sunga KL, Decker WW, Li JT, Scanlan-Hanson LN, Vukov SC, Campbell RL: A multifaceted intervention for patients with anaphylaxis increases epinephrine use in adult emergency department. J Allergy Clin Immunol Pract 2014; 2:294–9.e1
15. Noone S, Ross J, Sampson HA, Wang J: Epinephrine use in positive oral food challenges performed as a screening test for food allergy therapy trials. J Allergy Clin Immunol Pract 2015; 3:424–8
16. Rohacek M, Edenhofer H, Bircher A, Bingisser R: Biphasic anaphylactic reactions: occurrence and mortality. Allergy 2014; 69:791–7
17. Smit DV, Cameron PA, Rainer TH: Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. J Emerg Med 2005; 28:381–8
18. Vezir E, Erkoçoğlu M, Kaya A, Toyran M, Özcan C, Akan A, Azkur D, Giniş T, Civelek E, Kocabaş CN: Characteristics of anaphylaxis in children referred to a tertiary care center. Allergy Asthma Proc 2013; 34:239–46
19. Brazil E, MacNamara AF: "Not so immediate" hypersensitivity–the danger of biphasic anaphylactic reactions. J Accid Emerg Med 1998; 15:252–3

20. Ellis AK, Day JH: Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann Allergy Asthma Immunol 2007; 98:64–9
21. Mehr S, Liew WK, Tey D, Tang ML: Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009; 39:1390–6
22. Stark BJ, Sullivan TJ: Biphasic and protracted anaphylaxis. J Allergy Clin Immunol 1986; 78(1 Pt 1):76–83
23. Alqurashi W, Stiell I, Chan K, Neto G, Alsadoon A, Wells G: Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. Ann Allergy Asthma Immunol 2015; 115:217–23.e2
24. Sricharoen P, Sittichanbuncha Y, Wibulpolprasert A, Srabongkosh E, Sawanyawisuth K: What clinical factors are associated with biphasic anaphylaxis in Thai adult patients? Asian Pac J Allergy Immunol 2015; 33:8–13
25. Järvinen KM, Amalanayagam S, Shreffler WG, Noone S, Sicherer SH, Sampson HA, Nowak-Wegrzyn A: Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. J Allergy Clin Immunol 2009; 124:1267–72
26. Lee J, Garrett JP, Brown-Whitehorn T, Spergel JM: Biphasic reactions in children undergoing oral food challenges. Allergy Asthma Proc 2013; 34:220–6
27. Nagano C, Ishiguro A, Yotani N, Sakai H, Fujiwara T, Ohya Y: [Anaphylaxis and biphasic reaction in a children hospital]. Arerugi 2013; 62:163–70
28. Grunau BE, Li J, Yi TW, Stenstrom R, Grafstein E, Wiens MO, Schellenberg RR, Scheuermeyer FX: Incidence of clinically important biphasic reactions in emergency department patients with allergic reactions or anaphylaxis. Ann Emerg Med 2014; 63: 736–44.e2
29. Lee JM, Greenes DS: Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000; 106:762–6
30. Lertnawapan R, Maek-a-nantawat W: Anaphylaxis and biphasic phase in Thailand: 4-year observation. Allergol Int 2011; 60:283–9
31. Poachanukoon O, Paopairochanakorn C: Incidence of anaphylaxis in the emergency department: a 1-year study in a university hospital. Asian Pac J Allergy Immunol 2006; 24:111–6
32. Ko BS, Kim WY, Ryoo SM, Ahn S, Sohn CH, Seo DW, Lee YS, Lim KS, Kim TB: Biphasic reactions in patients with anaphylaxis treated with corticosteroids. Ann Allergy Asthma Immunol 2015; 115:312–6

Appendix: Description of the Four Possible/ Probable Biphasic Allergic Reactions

Patient Number 9: Possible Biphasic Allergic Reaction

A 51-yr-old female reacted during an allergy skin test. At the initial reaction she developed redness, flushing, rash, angioedema, tightness in the throat, and dyspnea. She was treated with 0.3 mg intramuscularly epinephrine × 2, 2 mg clemastin, and 80 mg prednisolone. 8 h later, she developed dyspnea and light chest tightness during a toilet visit, the doctor treated her with 1 mg clemastin and 40 mg methylprednisolone. She was observed in an intensive care unit for 25 h and discharged home.

Conclusion: Symptoms might be due to hyperventilation and anxiety. Biphasic allergic reaction not very likely, but cannot be ruled out.

Patient Number 81: Possible Biphasic Allergic Reaction

A 57-yr-old female was admitted to an intensive care unit after a bee sting caused angioedema, urticaria and hypotension (88/52). She was treated with unknown amount of methylprednisolone, clemastin, and 0.1 mg epinephrine intravenously. She was observed for 6 h in the intensive care unit and then discharged to home with 25 mg promethazine for after treatment. It is unclear whether the patient was still symptomatic with urticaria and angioedema, or asymptomatic when she was discharged. After 36 h, she presented at the emergency department with increasing edema, urticaria, and an itching arm. She was observed for a few hours and discharged with 50 mg prednisolone × 1 and 10 mg cetirizine × 1 for 3 days.

Conclusion: Biphasic allergic reaction cannot be ruled out but protracted reaction more likely.

Patient Number 67: Possible Biphasic Allergic Reaction

A 32-yr-old male developed anaphylaxis as a result of either food or medication. At the initial reaction, he had urticaria, itching, redness, and tightness in his throat. He was treated with 0.3 mg epinephrine intramuscularly, an unknown amount of intravenously epinephrine and epinephrine inhalation, 10 mg by mouth cetirizine, 4 mg clemastin intravenously, and 80 mg methylprednisolone. He was observed for 4 h in the intensive care unit and discharged to another department, from which he was discharged home almost immediately. He was readmitted 19 h after the initial reaction. The second reaction leading to readmission occurred after intake of another type of medication. His symptom was urticaria. He was treated with 2 mg intravenously clemastin, and 80 mg intravenously methylprednisolone. After the second discharge, he was treated with 50 mg prednisolone × 1 and 10 mg cetirizine × 1 for 3 days.

Conclusion: Biphasic allergic reaction cannot be ruled out but it is likely, that the patient was exposed to new potential allergen.

Patient Number 42: Possible Biphasic Allergic Reaction

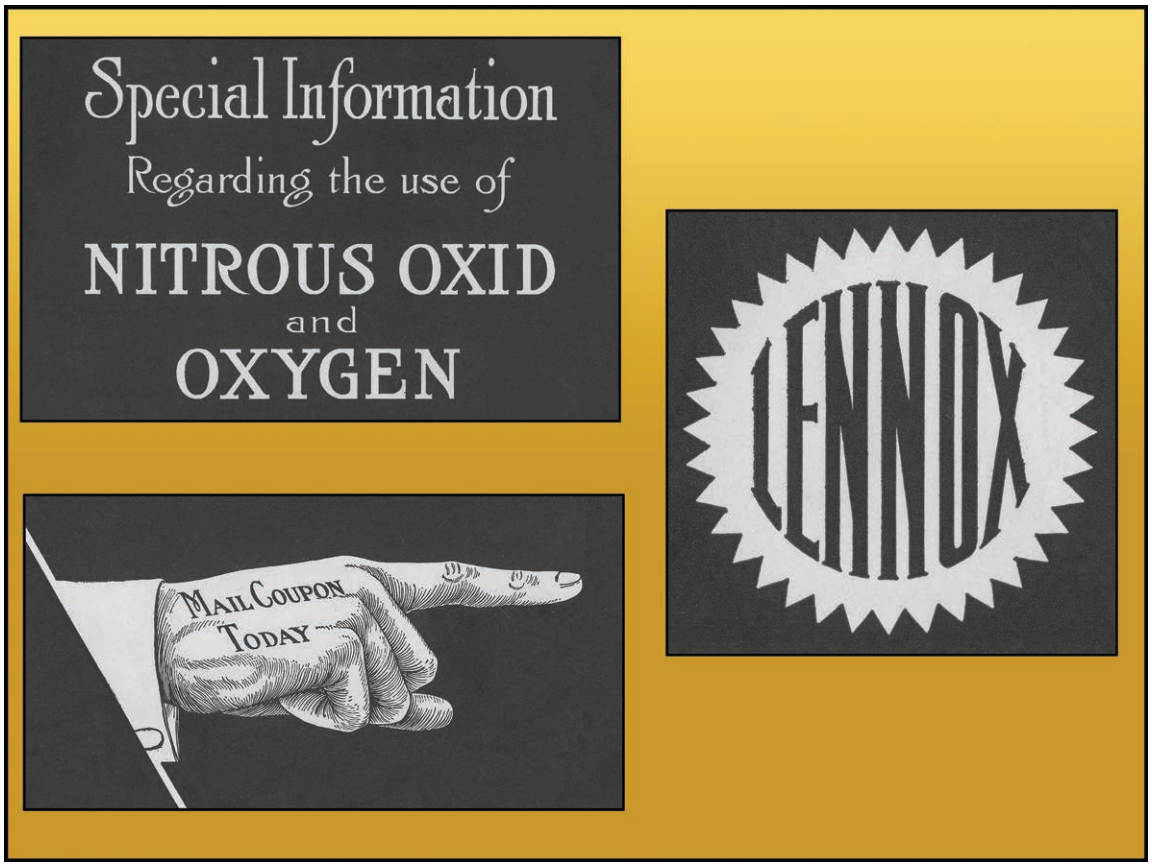
A 69-yr-old male developed anaphylaxis after cetuximab treatment with the following symptoms: flushing, dizziness,

and hypotension (55/30). He was treated with 0.5 mg intramuscularly plus 5 mcg intravenously epinephrine, 2 mg intravenously clemastin, and 2 × 40 mg methylprednisolone. He was observed in the intensive care unit for 6 h and discharged to another medical department. After approximately 8 h, he got urticaria on his elbows and knees, and was treated with unknown type of antihistamines and 40 mg methylprednisolone.

Conclusion: Likely biphasic allergic reaction, no other plausible explanation.

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Pointers on Dating Lennox's Laughing Gas Advertising



From Cleveland, Ohio, the Lennox Chemical Company printed a sunburst logo (*right*) on the firm's advertising cards informing clinicians (*upper left*) about the "use of nitrous oxid and oxygen." Since the "oxid" spelling was largely abandoned by the mid-1920s, when was the earliest such a card might have been printed? By 1917 the Lennox Chemical Company was operated by the firm listed on this card in fine print, the Bishop-Babcock-Becker Company (BBB). Curiously, BBB was directory-listed as a manufacturer of "Nitrous Oxide and Oxygen, Carbonic Acid Gas, Epsom Salts and Soda Water Flavors." So, the same company supplying components for soda fountains and taverns in Cleveland, BBB, was also supplying the city's clinicians with nitrous oxide. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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