

Incidence of Anaphylaxis in Hospitalized Patients

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Key Words

Anaphylaxis • Incidence • Hospitalized

Abstract

Background: Only two studies have analyzed the incidence of anaphylaxis during admission to hospital. We have analyzed the incidence of anaphylaxis among hospitalized patients and determined the timing of and risk factors for episodes of anaphylaxis. **Methods:** Our study was performed between 1999 and 2005. We used the definition of anaphylaxis of the NIAID-FAAN symposium. Cases of anaphylaxis were extracted from an official database of discharge diagnoses coded according to the *International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM), Sixth Edition*. Specific and generic codes related to anaphylaxis were chosen. This strategy revealed 83.3% (95% confidence interval, CI, 47–99%) of all episodes of anaphylaxis in a pilot study. The incidence of episodes of anaphylaxis and the hazard ratios were calculated for the different variables. **Results:** We observed a crude cumulative incidence of 1.5 episodes of anaphylaxis (95% CI, 0.9–1.9) in 5,000 admissions. The cumulative incidence according to the Standardized European Population was 1.6 cases in 5,000 admissions (95% CI, 0.8–2.3). Cox regression analysis showed that anaphylaxis

occurs mainly in young people (0.97; 95% CI, 0.95–0.99) and its incidence differs according to the clinical unit. The Vascular Surgery Unit had the highest incidence rate (hazard ratio 7.7; 95% CI, 2.1–28.6). Males had a lower risk of suffering from anaphylaxis than females (0.5; 95% CI, 0.2–0.9). **Conclusions:** Anaphylaxis is a very rare event among hospitalized patients. Female gender, young age and admission to the Vascular Surgery Unit favored the occurrence of episodes of anaphylaxis among hospitalized patients.

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Introduction

Anaphylaxis is a potentially life-threatening event [1] whose incidence is believed to be rising [2, 3]. Published series are usually based on data from emergency departments, outpatient allergy clinics and health maintenance organizations [4–9]. By contrast, few reports [10–12] have analyzed the incidence of anaphylaxis during admission to hospital. Most studies analyze patients who have been admitted after attending the emergency room due to an episode of anaphylaxis [13–22].

Anaphylaxis during hospitalization is particularly interesting as patients receive many drugs to treat the acute

condition that led to admission (in our hospital, patients receive an average of 10–11 drugs). To our knowledge, only two groups of researchers have assessed anaphylaxis during admission [10, 11]. Their results reveal a very low incidence of anaphylaxis (1.0–2.0 cases per 5,000 admissions) [10, 11], although both studies limited their results to the incidence of drug-induced anaphylaxis. In addition, they provide little information on risk factors that favor anaphylaxis during admission.

Our primary objective was to ascertain the incidence of anaphylaxis – including cases of anaphylaxis not induced by drugs – among hospitalized patients. We also investigated whether anaphylaxis occurred at critical moments, and attempted to determine risk factors for anaphylaxis in admitted patients.

Material and Methods

Setting

Hospital Universitario Fundación Alcorcón (HUFA), Alcorcón (Madrid, Spain) is a tertiary public hospital with 450 beds. It is the reference center for 250,000 people in the southwest metropolitan area of the Autonomous Community of Madrid. All medical and many surgical specialties, except for highly specialized interventions (e.g. neurologic or cardiologic surgery), have been available at our hospital since it opened in 1998.

Selection of Patients

Between January 1, 1999, and December 31, 2005, a total of 114,626 patients were admitted to our hospital (63,963 women and 50,650 men; 13 unknown). Age was 27, 58, and 73 years at the 25th, 50th, and 75th percentiles, respectively. Cases of anaphylaxis were extracted from an official database of discharge diagnoses (Minimal Basic Data Set) used in all public hospitals in the Autonomous Community of Madrid and coded according to the *International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM), Sixth Edition*. The primary and secondary discharge diagnoses were chosen and the different types of codes selected (table 1) were as follows: specific and generic codes related to allergy, urticaria, angioedema and specific causes of anaphylaxis (as recommended by Clark et al. [23]); codes related to adverse reactions to drugs, and finally codes related to symptoms or signs of acute allergic reaction (e.g. urticaria, edema, flushing).

This strategy was tested in a pilot study. We selected and exhaustively reviewed information on patients admitted during two separate months (March 2004 and August 2005) with a large number of anaphylaxis codes in order to find cases of anaphylaxis. We aimed to obtain a sufficiently large number of cases so that the confidence interval was not too wide, as our estimates of the number of cases that would be obtained in the final study were very low. The number of cases retrieved in this way was compared with the number of episodes of anaphylaxis retrieved through a search using the *ICD-9-CM* codes. Only 1 case in 6 was not detected using *ICD-9-CM* codes, with the result that 83.3% (95%

Table 1. *ICD-9-CM* codes used to identify cases of anaphylaxis

CODE	Description
708	Urticaria
782.3	Edema
782.62	Flushing
785.50	Shock, unspecified
785.59	Other shock
995.0	Other anaphylactic shock
995.1	Angioneurotic edema
995.2	Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered
995.3	Allergy, unspecified
995.4	Shock due to anesthesia
995.6	Anaphylactic shock due to adverse food reaction
998.0	Postoperative shock
999.4	Anaphylactic shock due to serum
999.5	Other serum reaction
999.8	Other infusion and transfusion reaction
E879.*	Other procedures, without mention of misadventure at the time of procedure, as the cause of abnormal reaction of patient, or of later complication
E905.3	Hornets, wasps, and bees
E930–E949	Drugs, medicinal and biological substances causing adverse effects in therapeutic use (E930–E949)
V14.0	Personal history of allergy to medicinal agents
V15.01–V15.05	Food allergy to peanuts, allergy to milk products, allergy to seafood, allergy to other foods
V15.06	Allergy to insects
V15.07	Allergy to latex
V15.08	Allergy to radiographic dye
V15.09	Other allergy, other than to medicinal agents

confidence interval, CI, 47–99%) of all cases of anaphylaxis during this period were identified using this strategy.

Data on drug consumption during admission were obtained from the Pharmacy Service using the software package FarmaTools™.

The study was observational, analytical, longitudinal, and retrospective and was approved by the Ethics Committee for Medical Research of our institution.

Inclusion and Exclusion Criteria

We used the definition of anaphylaxis of the NIAID-FAAN symposium, which states that anaphylaxis is likely to occur when several criteria are satisfied [24]: (1) presence of skin symptoms or signs together with respiratory involvement or signs of organic dysfunction or hypotension, or (2) involvement of at least two organs or systems after recent exposure to an allergen, or (3) signs of organ dysfunction or hypotension after exposure to a known allergen. Although participants in this symposium believed that these criteria accurately identify anaphylactic reactions in more than 95% of cases, it was agreed that these criteria need to be tested in a prospective multicenter clinical survey in order to establish their utility and determine whether there was a need for further refinement.

Any signs and symptoms mentioned were documented as being present and assumed absent if they were not reported or reported as not present. After applying the selected codes to the admissions recorded from January 1, 1998, to December 31, 2005, we detected 13,689 admissions with these codes. We followed Brown's criteria [25] to establish the severity of anaphylaxis.

As it was not possible to carry out an allergologic evaluation of all the cases found at the outpatient clinic (almost half of the patients were not referred and almost half did not request an allergology work-up), the etiologic agent was established using only hospital records and the experience and criteria of two allergy researchers (coauthors of the present study), who analyzed the records independently and reached a consensus in cases of disagreement. We present the results from the allergy work-up of patients who attended the Allergy Outpatient Clinic. The researchers made their assessment with no knowledge of the results or the final clinical diagnoses.

The exclusion criteria were as follows: anaphylaxis occurring in the community and resulting in hospital admission; anaphylaxis while in the Emergency Department, even if this event caused an admission; anaphylaxis occurring during surgery; anaphylaxis experienced by patients attending outpatient clinics of our hospital, and anaphylaxis occurring in patients who come to our hospital to receive specific medication (day hospital, cancer treatment). Anaphylaxis episodes occurring immediately before and after surgery were recorded. However, episodes due to general anesthesia were not recorded, because these adverse effects are not usually recorded in the computerized clinical records of our hospital.

In our hospital, all clinical records and notes are recorded using a digital clinical application (Selene, Siemens), which automatically assigns a clinical note to a physician, clinical unit, and care section (outpatient clinic, hospital ward, or emergency department) depending on the role of the physician who enters the data in the system. Consequently, only notes from hospital wards were chosen to select patients who experienced anaphylaxis episodes during admission.

Statistical Analysis

We report cumulative crude and standardized incidence (according to the distribution of ages in the standard European population) and incidence rates, with their respective 95% CIs using Poisson estimates. The risk of producing anaphylaxis attributable to each drug was ascertained using the following calculation: number of anaphylaxis episodes due to a drug divided by the total number of doses of this drug prescribed in the HUFA during the study period (referenced per 1 million doses). In order to stratify the risk of anaphylaxis due to each drug, an arbitrary logarithmic scale was established according to the number of cases per million doses from <100 (low risk) to >1,000 (high risk). Bivariate analysis was performed using the χ^2 test and score rates trend test. The κ -index was used to assess the concordance between the clinical units where the episodes occurred and the discharge units. Survival analysis was carried out using Kaplan-Meier curves and the log-rank test. Finally, all variables used in the different bivariate analyses were adjusted using a Cox regression model. The principal variable was occurrence (or not) of an episode of anaphylaxis during admission, and the principal covariables were gender, age, unit of discharge, complexity of the illnesses attended during admission (rweight), and length of stay.

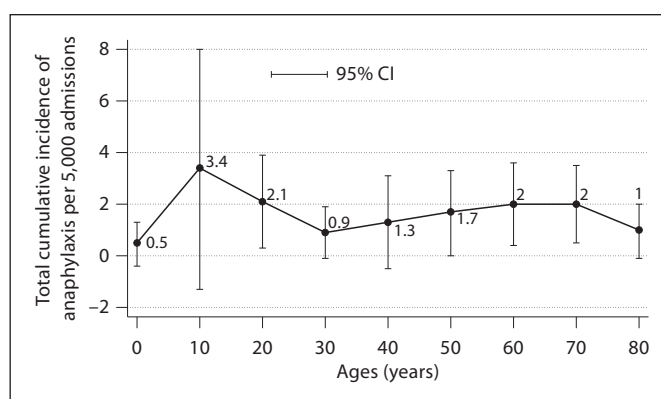


Fig. 1. Cumulative incidence of anaphylaxis per 5,000 admissions [1.5 (0.9–1.9)] to Hospital Universitario Fundación Alcorcón (by age group).

Results

General Incidence and Incidence According to Age and Gender

Using the definition of the NIAID-FAAN symposium [17], we identified 34 cases (20 women and 14 men), with a crude cumulative incidence of 1.5 cases per 5,000 admissions (95% CI, 0.9–1.9), while the standardized European cumulative incidence was very similar, 1.6 cases per 5,000 admissions (95% CI, 0.8–2.3). Therefore, the incidence rate (cases per 5,000 admission days) was 0.2 (95% CI, 0.2–0.3). Incidence rates were very similar in males and females [0.19 per 5,000 admission days (95% CI, 0.11–0.33) and 0.24 per 5,000 admission days (95% CI, 0.16–0.38), respectively].

There was a statistically significant decreasing trend ($p = 0.0006$) – adjusted for medical unit at discharge – in the number of episodes of anaphylaxis as age increased (relative risk, 0.96; 95% CI, 0.94–0.98) (fig. 1).

Incidence According to Unit at Discharge

The discharge data in this study are from the unit of discharge, which may not be the unit where the episode of anaphylaxis occurred, as patients were attended in different units during admission. Nevertheless, there was an excellent correlation between the unit where the event happened and the discharge unit (agreement 88.2%; κ -index 0.9; $p < 0.0001$). We noticed that 8 units did not report episodes of anaphylaxis. The units with the highest number of episodes of anaphylaxis were internal medicine (8 episodes) and general and digestive surgery (8 episodes). However, among units reporting episodes, the

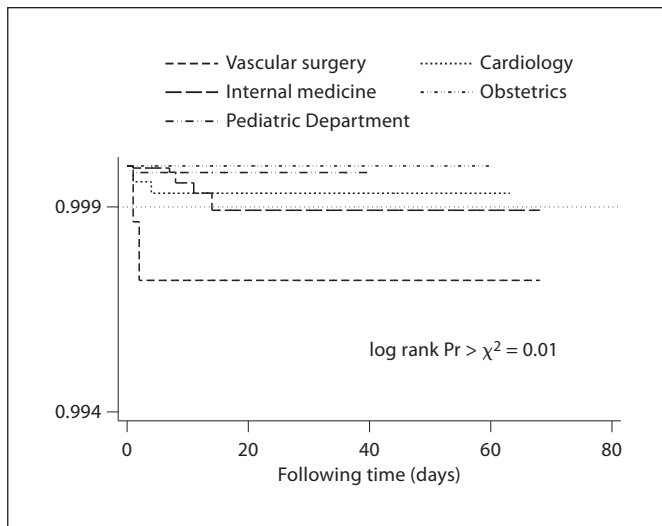


Fig. 2. Survival curves (cumulative probability of not experiencing anaphylaxis) in different clinical units of Hospital Universitario Fundación Alcorcón.

units with the highest incidence rates (per 5,000 admission days) were vascular surgery (1.2; 95% CI, 0.4–3.3) and ophthalmology (2.0; 95% CI, 0.5–8.0), while the lowest rates were observed in internal medicine (0.2; 95% CI, 0.1–0.4), pediatrics (0.2; 95% CI, 0.05–1.3), and orthopedic surgery (0.1; 95% CI, 0.05–0.6). The log-rank test revealed differences in the cumulative probability of anaphylaxis between the different units ($p = 0.01$) (fig. 2).

Timing of Anaphylaxis Episodes

Episodes of anaphylaxis occurred until the 46th day of admission, although 75% of episodes occurred within the first 4 days. The highest numbers of episodes occurred on the first day of admission (17 episodes) and the second day (5 episodes). Incidence rates (anaphylaxis episodes per 5,000 admissions and day) were higher on day 1 (0.7; 95% CI, 0.4–1.2), day 8 (0.3; 95% CI, 0.1–1.3), and day 11 (0.3; 95% CI, 0.4–2.0) (table 2).

We do not show median survival because only 0.04% of admitted patients experienced anaphylaxis during their stay in our hospital. On the 20th day (twice the average stay in our hospital), the cumulative probability of not sustaining an episode of anaphylaxis was 99.96% (95% CI, 99.88–99.96%)

Multivariate Analysis

A Cox regression model adjusted for complexity of care (rweight) and days of stay (table 3) showed that pa-

Table 2. Number and percentage of episodes of anaphylaxis on each day of admission

Admission day	Frequency	Percentage	Cumulative	Incidence rate per 5,000 admission days	95% CI lower limit	95% CI upper limit
1	18	52.94	52.94	0.7	0.5	1.2
2	5	14.71	67.65	0.2	0.1	0.5
3	2	5.88	73.53	0.1	0.0	0.4
4	1	2.94	76.47	0.1	0.0	0.5
5	1	2.94	79.41	0.1	0.0	0.6
7	1	2.94	82.35	0.1	0.0	1.0
8	2	5.88	88.24	0.3	0.1	1.3
11	1	2.94	91.18	0.3	0.0	2.2
14	1	2.94	94.12	0.1	0.0	0.4
16	1	2.94	97.06	0.1	0.0	0.4
46	1	2.94	100.00	0.3	0.0	2.2

Table 3. Hazard ratios of different variables (clinical units, gender, age, stay, and complexity of admission) to suffer from anaphylaxis episodes using Cox regression

	Hazard ratio	p	95% CI lower limit	95% CI upper limit
Vascular surgery	7.7	0.002	2.1	28.6
Cardiology	2.2	0.3	0.5	8.7
General and digestive surgery	0.9	0.9	0.3	3.2
Dermatology	0.0			
Digestive	0.9	1.0	0.1	8.0
Gynecology	0.5	0.4	0.1	2.6
Hematology	0.0			
Nephrology	1.7	0.6	0.2	14.0
Pneumology	2.0	0.4	0.4	10.1
Neurology	0.0			
Obstetrics	0.0			
Ophthalmology	4.0	0.1	0.7	21.6
Oncology	2.2	0.4	0.4	11.0
Ear, nose, and throat	0.6	0.6	0.1	5.4
Pediatrics	0.1	0.1	0.0	1.4
Psychiatry	0.0			
Orthopedic surgery	0.5	0.5	0.1	2.8
Urology	0.0			
Male	0.5	0.05	0.2	1.0
Age groups in intervals of 10 years	1.0	<0.001	1.0	1.0
5–9 days of stay	0.9	0.8	0.3	2.3
10–14 days of stay	0.9	0.9	0.2	3.8
15–19 days of stay	2.5	0.2	0.6	9.6
20–24 days of stay	1.1	0.9	0.1	9.9
25–29 days of stay	2.2	0.5	0.2	19.9
>30 days of stay	1.0	1.0	0.1	9.6
rweight	0.8	0.9	0.8	1.2

Table 4. Drugs inducing episodes of anaphylaxis in admitted patients and their risk of producing anaphylaxis

Drug	Number of doses administered	Number of anaphylaxis episodes	Cumulative incidence per 1,000,000 doses	95% CI lower limit	95% CI upper limit
Streptokinase	157	1	6,369.4	161.3	35,488.2
Platelets transfusion and frozen fresh plasma	405	1	2,469.1	62.5	13,757.1
Rituximab	514	1	1,945.5	49.3	10,839.8
Carboplatin	1,115	1	896.9	22.7	4,997
Iodinated contrast medium	14,382	6	417.2	153.1	908
Plasma	4,787	1	208.9	5.29	1,163.9
Cefotaxime	22,682	1	44.1	1.12	245.6
Cefazolin	46,897	2	42.6	5.16	154.1
Packed red cell concentrate	28,421	1	35.2	0.891	196
Ceftriaxone	34,771	1	28.8	0.728	160.2
Metamizole	659,537	10	15.2	7.27	27.9
Captopril	74,584	1	13.4	0.339	74.7
Amoxicillin/clavulanic acid	324,283	1	3.08	0.0781	17.2
Acetaminophen	393,252	1	2.54	0.0644	14.2

tients in the vascular surgery unit had a higher risk of anaphylaxis than patients in internal medicine (reference value) (hazard ratio, 7.7; 95% CI, 2.1–28.6). This model also revealed a trend toward fewer episodes of anaphylaxis as age increased (hazard ratio, 0.97; 95% CI, 0.95–0.99), and that males had fewer episodes of anaphylaxis than females (hazard ratio, 0.5; 95% CI, 0.2–0.9).

Clinical Notes

According to the severity criteria of Brown [25], 35.1% of anaphylactic episodes were severe. Drugs were the cause of anaphylaxis in 85.3% of admitted patients, while anaphylaxis to latex and idiopathic anaphylaxis affected the same proportion each (6% or 2 episodes). One patient experienced anaphylaxis caused by food (cow's milk). The most commonly involved drugs were metamizole ($n = 9$) and iodine contrast medium ($n = 6$) (table 4).

However, the drugs with the highest risk of producing anaphylaxis (>1,000 episodes per million doses) were streptokinase, platelet concentrates and rituximab. Iodine contrast medium, plasma and carboplatin had an intermediate risk (100–1,000 episodes per million doses). Finally, many standard nonsteroidal anti-inflammatory drugs and β -lactam antibiotics had a low risk of triggering anaphylaxis (<100 episodes) (table 4). Most drugs had wide confidence intervals, with many overlaps between them, except for streptokinase and iodine contrast medium.

We explored the drugs taken by patients in the Vascular Surgery Unit and other closed units (general and di-

gestive surgery) and the reference unit (Internal Medicine), in order to try to explain the higher risk of experiencing anaphylaxis in the Vascular Surgery Unit. We discovered a higher percentage of anaphylaxis induced by iodinated contrast medium in patients in the Vascular Surgery Unit [2 cases of 4 anaphylaxis episodes (50%)] than by iodinated contrast medium in patients in the General and Digestive Surgery Unit [1 case of 6 (16.7%)] and Internal Medicine Unit [1 case of 5 (20%)].

Only 15 of 34 patients (44.1%) underwent an allergy work-up in the allergy outpatient clinic as many were not referred to the Allergy Unit (only 47.1%). Some allergy tests (skin test, specific IgE, or challenge) were performed in 13 of the cases attended (86.7%). Of these, 10 were positive (76.9%) (table 5). Median time between the episode of anaphylaxis and availability of the results of testing was 1.6 months (interquartile range, 0.3–5.4 months). A 100% concordance was observed between the diagnosis by the two allergy researchers (with data from the hospital wards) and the final diagnosis made by allergists from the allergy outpatient clinic (recorded in the clinical reports).

Discussion

Our most remarkable findings were a low incidence of anaphylaxis among admitted patients (1.5 in 5,000 admitted patients) and that the episodes were mainly due to drugs and the most commonly affected group were young people.

Table 5. Results of allergy work-up in patients who attended the Allergy Outpatient Clinic of HUFA

	Tests performed over total number of patients attended at the Allergy Outpatient Clinic (n = 15)		Number of positive tests over total number of each type of test performed at the Allergy Outpatient Clinic		Allergens involved in positive tests
	n	%	n	%	
Skin test	11	73.3	8	72.7	latex, carboplatin, cefazolin (2), cefotaxime, met-amizol (2), cow's milk
Specific IgE	4	26.7	4	100.0	latex (2), cow's milk, penicillin V-amoxicillin
Skin test or specific IgE	13	86.7	10	76.9	
Challenge	3	20.0	1	33.3	cow's milk
Any allergy test	13	86.7	10	76.9	

The cumulative incidence of anaphylaxis was very low when the criteria of the NIAID-FAAN Symposium were applied (1.5 in 5,000 admissions). A low incidence has also been reported in the only two series published to date on anaphylaxis in hospitalized patients. Porter et al. [10] reported an incidence of 2 cases per 5,000 admissions, whereas the International Collaborative Study of Severe Anaphylaxis [11] reported 1 case per 5,000 admissions (these figures are very similar to ours). A Thai series [19] including patients discharged with anaphylaxis codes from *ICD-10* revealed a cumulative incidence of 0.3 episodes of anaphylaxis per 5,000 admissions. The first two studies applied a similar methodology [10, 11] (prospective and research staff actively searching for cases of anaphylaxis in hospitalization wards), whereas the Thai study [19] used a retrospective design as we did. Although the two prospective studies provide an exhaustive list of all cases, our incidence rate, which was even higher than that found in the International Collaborative Study [11], and the high sensitivity of our search strategy lead us to believe that our figures are very close to the real figures in our institution.

In our analysis (adjusted for length of stay and complexity of illnesses attended during admission), a trend toward a decrease in the incidence of anaphylaxis with age and presence of different incidences in different units and in both sexes was noticed. The International Collaborative Study [11] also reported that risk was highest among the youngest patients, although the relation was not linear. In the multivariate analysis, the unit showing a statistically significant difference with the rest of the units was the Vascular Surgery Unit, which had a higher risk than the others. We think that the increased risk ob-

served in vascular surgery was due to a higher proportion of anaphylaxis by iodinated radiologic contrast medium (widely used in vascular surgery). Both in our study and in the International Collaborative Study [12], these agents showed a greater risk of anaphylaxis than the standard antibiotics and nonsteroidal anti-inflammatory drugs used on hospital wards. According to the multivariate model, males had a lower risk of anaphylaxis during admission than females. Similar results are shown by the International Collaborative Study [11] (208 episodes of anaphylaxis per million admissions in females, 150 episodes of anaphylaxis per million admissions in males). Likewise, a higher presence of anaphylaxis in females than in males older than 15 years has been reported in a population-based study [26], and helps to explain the larger presence of anaphylaxis among females in our study, given the predominance of adults (median 58 years). Although our small number of cases should invite caution concerning the external validity of our findings, the results of our multivariate analysis are similar to those reported in other series with similar or different designs [11, 26]. We believe this increases the validity of our results.

ICD-9-CM was created for clinical and administrative purposes [27–29]. Clark et al. [23] conducted a study whose objective was to determine the accuracy of *ICD-9-CM* codes to identify emergency room visits for food and insect sting anaphylaxis. In this study, the only use of *ICD-9-CM* codes for these specific allergic disorders missed 50% of cases of food allergy and 10% of cases of insect sting allergy presenting at the emergency rooms where the study was carried out. The authors concluded that ‘clinical studies identifying patients with allergy

should include both *ICD-9-CM* codes specific to the allergy of interest and more general allergy codes' [23]. Our criteria for choosing *ICD-9-CM* codes are similar to those recommended by Clark et al. [23], although we added others for angioedema and urticaria, symptoms which describe anaphylaxis episodes, and, finally, codes which classify adverse reactions to drugs. With this strategy, we obtained 83.3% sensitivity for identification of anaphylaxis episodes in a 2-month pilot study. To our knowledge, no epidemiologic study using *ICD-9-CM* codes to codify cases of anaphylaxis has explored the sensitivity of their strategy.

Episodes of anaphylaxis tended to occur in the first 5 or 6 days: 51.5% of episodes occurred on the first day and 75% of the episodes occurred during the first 5 days of admission. In the International Collaborative Study [11], the results were very similar: 57% occurred during the first 2 days of admission and 75% occurred during the first 5 days of admission. Rates of anaphylaxis were higher on the 1st, 8th and 11th day.

Only 44.1% of patients in our series underwent an allergy work-up. The results were positive in 76.9% of the 13 patients who underwent testing (table 5). All the patients had positive skin test results or specific IgE results without having to undergo challenge with the responsible allergen to reach the final diagnosis, except for a child with cow's milk allergy. This large percentage of positive results can probably be explained by the short time between the episode of anaphylaxis and the availability of results (median 1.6 months). Many negative challenge test results were recorded during the evaluation of 2 cases of idiopathic anaphylaxis. A 100% concordance was observed between the diagnosis by the two allergists (with data from the hospital wards) and the final diagnosis made by allergists from the allergy outpatient clinic (recorded in the clinical reports). Both diagnoses were made blind. In a logistic regression model (data not shown), several variables, such as severity of anaphylaxis, involvement of different organs or systems, and different age groups, were not more frequent in patients attended or not attended at the allergy outpatient clinic. Therefore, it is possible that, for patients in our series not attended at the Allergy Outpatient Clinic, the final diagnosis of the anaphylaxis episodes had not changed, even after a hypothetical evaluation in the Allergy Outpatient Clinic. Thus, the etiologic agent was identified only using hospital records and the experience and criteria of the 2 allergists who analyzed the clinical records.

Patients not attended at the Allergy Outpatient Clinic did not undergo additional testing, as the approved study

design was observational. In addition, although patients had attended for evaluation, the delay between the episode and evaluation could have been so great that it could have affected the sensitivity of in vitro and in vivo tests; test sensitivity is known to decrease over time, and many authors recommend that tests should be performed within 1 year of the reaction [30].

In our series, drugs were the most frequent and almost only cause of anaphylaxis (85%) in admitted patients. The two series of anaphylaxis in admitted patients published to date are series whose objective was to study anaphylaxis by drugs during admission [10–12]. It is logical to expect the incidence of anaphylaxis by drugs to be high, given the amounts administered during the initial phase to patients admitted with acute and severe illnesses.

Metamizole and iodinated contrast medium were the most commonly involved drugs in almost all age groups and in the group overall. β -Lactam antibiotics (particularly cephalosporins) have also been reported to be a frequent cause of anaphylaxis. In the series of Porter and Jick [10], the most frequent causes of anaphylaxis were hematologic products, asparaginase, and several other drugs whose use has decreased during the two last decades. In the International Collaborative Study of Severe Anaphylaxis [12], the most frequent causes of anaphylaxis were metamizole (12 cases), diclofenac (7 cases), parenteral and oral cephalosporins (6 cases), amoxicillin/ampicillin (5 cases), hematologic products (13 cases), and ionic and nonionic iodinated radiologic contrast medium (61 cases, although in both inpatients and outpatients). Thus, our results are closer to those of the International Collaborative Study of Severe Anaphylaxis [12] than to those of Porter and Jick [10], which was carried out over 30 years ago.

The drugs responsible for the highest absolute number of episodes of anaphylaxis in our study did not always carry the highest risk of causing anaphylaxis. Although differences between risks for each drug were wide, the small number of events meant that overlaps between confidence intervals were observed (except for streptokinase and iodine contrast medium). Nevertheless, we observed the risk of anaphylaxis to be very similar to the risks reported in the International Collaborative Series [12], in which plasma, streptokinase, and snake antivenom carried a risk of more than 100 episodes per 100,000 people exposed. The risk of anaphylaxis with blood products, dextran, pentoxifylline, or iodinated radiologic contrast medium was intermediate (30–100 episodes). Finally, many usual antibiotics and nonsteroidal anti-inflammatory drugs had risks in the range of 5 to 15 episodes per 100,000 persons exposed.

Caution must be exercised when extrapolating the findings of our study to other hospitals with different levels of complexity and different drug use profiles. Another limitation of our study could be its retrospective design. However, many authors [3] find that the quality of hospital data is good, probably because hospitalized patients are attended by a range of health professionals during their stay (physicians of several specialties, pharmacists, nurses), who write up notes only a few moments after clinical events have taken place. Likewise, our findings are very similar to those published by other prospective reports [10, 11]; therefore, the influence of the retrospective design on the results of our study is probably very low. As mentioned above, the small number of cases also limits our study.

The fact that the unit to which the episode of anaphylaxis was assigned was not always the unit where the episode occurred is also a limitation (the only available data were from the discharge unit). However, we detected a good concordance between the unit where episode of anaphylaxis occurred and the discharge unit, and the discharge unit helped to define a clinical profile of patients who experienced an episode of anaphylaxis.

We conclude that the *ICD-9-CM* codes chosen showed high sensitivity in the search for cases of anaphylaxis among admitted patients. In our hospital, anaphylaxis is an unusual event (1.5 per 5,000 admitted patients). It occurs mainly in young people and women, and its incidence varies with the unit, the highest incidence rate being observed in the Vascular Surgery Unit, probably due to the widespread use of iodinated radiologic contrast media, which carry a greater risk of anaphylaxis than other more widely used drugs. Finally, drugs cause almost all cases of anaphylaxis among admitted patients.

Acknowledgements

This study was supported by grant number PI 051744 from the Fondo de Investigación Sanitaria (Spanish Ministry of Research and Technology) and a grant from the Fundación Mutua Madrileña (official announcement 2005). The authors thank Thomas O'Boyle for proofreading the manuscript.

References

- Clark S, Camargo CA: Epidemiology of anaphylaxis. *Immunol Allergy Clin N Am* 2007; 27:145–163.
- Gupta R, Sheikh A, Strachan DP, Anderson HR: Time trends in allergic disorders in the UK. *Thorax* 2007;62:91–96.
- Simons FE, Sampson HA: Anaphylaxis epidemic: fact or fiction? *J Allergy Clin Immunol* 2008;122:166–168.
- Stewart AG, Ewan PW: The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *QJM* 1996;89:859–864.
- Sheikh A, Alves B: Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy* 2001;31:1571–1576.
- Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS; Vaccine Safety Datalink Team: Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;113:536–542.
- Helbling A, Hurni T, Mueller UR, Pichler WJ: Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004;34:285–290.
- Webb L M, Lieberman P: Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006;97:39–43.
- Novembre E, Cianferoni C, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, Giovane A, Vierucci A: Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;101:1–8.
- Porter J, Jick H: Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977;i:587–588.
- The International Collaborative Study of Severe Anaphylaxis: An epidemiologic study of severe anaphylactic and anaphylactoid reaction among hospital patients: methods and overall risks. *Epidemiology* 1998;9:141–146.
- Kaufman DW, Judith P, Kelly JP: The International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoeconomics* 2003;12:195–202.
- Wilson R: Upward trend in acute anaphylaxis continued in 1998–9. *BMJ* 2000;321:1021–1022.
- Sheikh A, Alves B: Hospital admissions for acute anaphylaxis: Time trend study *BMJ* 2000;320:1441.
- Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, Vierucci A: Clinical features of acute anaphylaxis in patients admitted to a university hospital. *Ann Allergy Asthma Immunol* 2001;87:27–32.
- Sheikh A, Alves B: Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy* 2001;31:1571–1576.
- Gupta R, Sheikh A, Strachan D, Anderson R: Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. *BMJ* 2003;327:1142–1143.
- Thong YHB, Leong KP, Tang CY, Chang HH: Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 2003;90:342–347.
- Jirapongsananurul O, Bunsawansong W, Piyaanee N, Visitsunthorn N, Thongnarm T, Vichyanond T: Features of patients with anaphylaxis admitted to a university hospital. *Ann Allergy Asthma Immunol* 2007;98:157–162.

- 20 Mulla ZD, Simon MR: Hospitalizations for anaphylaxis in Florida: epidemiologic analysis of a population-based dataset. *Int Arch Allergy Immunol* 2007;144:128–136.
- 21 Poulos LM, Waters AM, Correll PK, Loblay R, Marks GB: Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007;120:878–884.
- 22 Yang MS, Lee SH, Kim TW, Kwon JW, Lee SM, Kim SH, Kwon HS, Park CH, Park HW, Kim SS, Cho SH, Min KU, Kim YY, Chang YS: L. Epidemiologic and clinical features of anaphylaxis in Korea. *Ann Allergy Asthma Immunol* 2008;100:31–36.
- 23 Clark S, Gaeta TJ, Kamarthi GS, Camargo CA: ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006;16:696–700.
- 24 Sampson HA, Munoz-Furlong A, Campbell RL, 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;117:391–397.
- 25 Brown GA: Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371–376.
- 26 Simons FE, Peterson S, Black CD: Epinephrine dispensing for the out-of-hospital treatment of anaphylaxis in infants and children: a population-based study. *Ann Allergy Asthma Immunol* 2001;86:622–626.
- 27 Guevara RE, Butler JC, Marston BJ, Plouffe JF, File TM Jr, Breiman RF: Accuracy of ICD-9-CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. *Am J Epidemiol* 1999;149:282–289.
- 28 Benesch C, Witter DM Jr, Wilder AL, Duncan PW, Samsa GP, Matchar DB: Inaccuracy of the International Classification of Diseases (ICD-9-CM) in identifying the diagnosis of ischemic cerebrovascular disease. *Neurology* 1997;49:660–664.
- 29 Buchbinder R, Goel V, Bombardier C: Lack of concordance between the ICD-9 classification of soft tissue disorders of the neck and upper limbs and chart review diagnosis: one steel mill's experience. *Am J Ind Med* 1996;29:171–182.
- 30 Brockow K, Romano A: Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des* 2008;14:2778–2791.

Fig. 1: long-term protocol

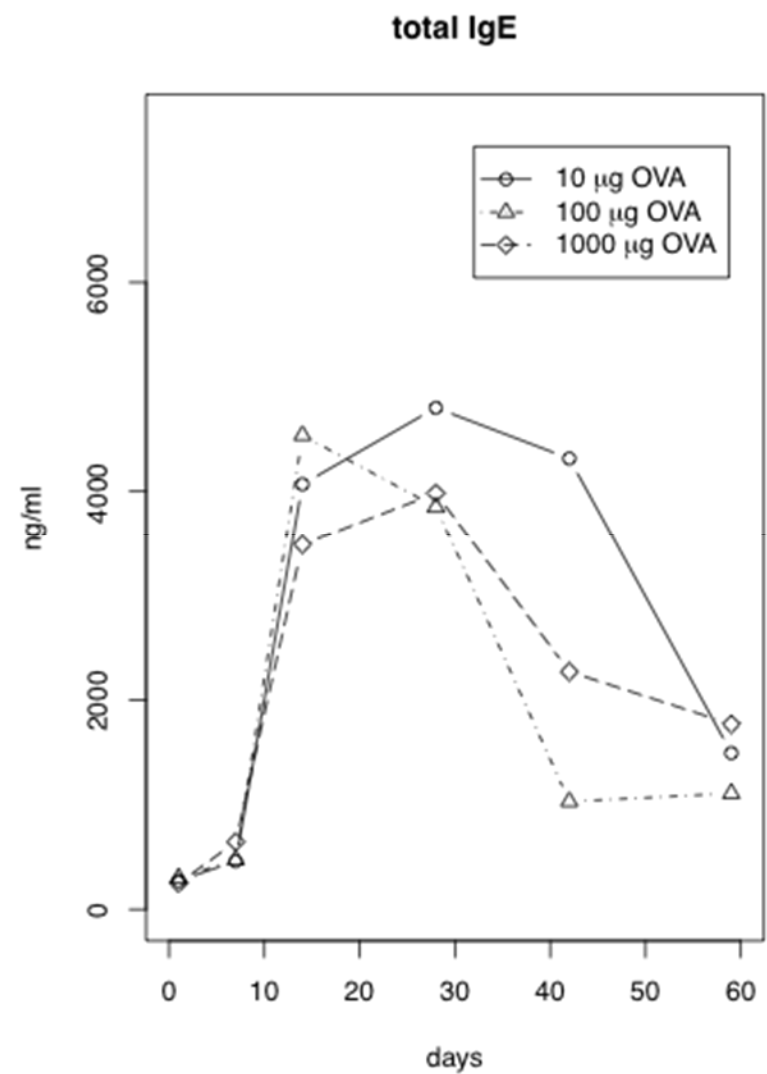
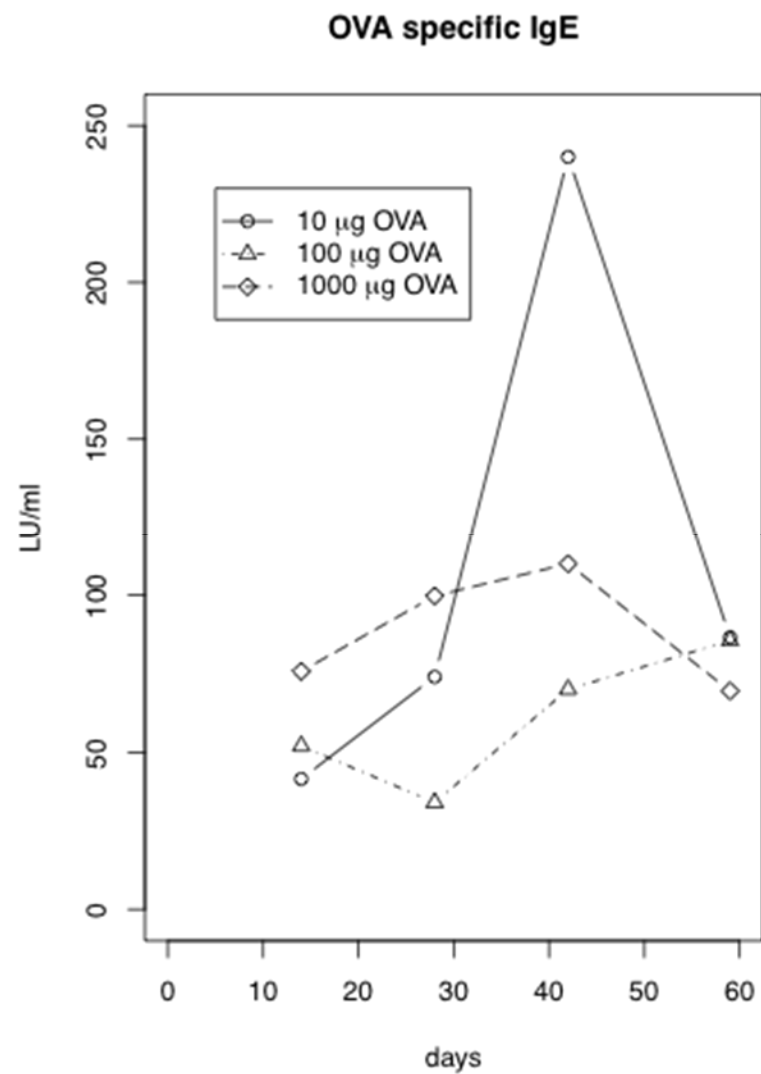


Fig. 2a: short-term protocol

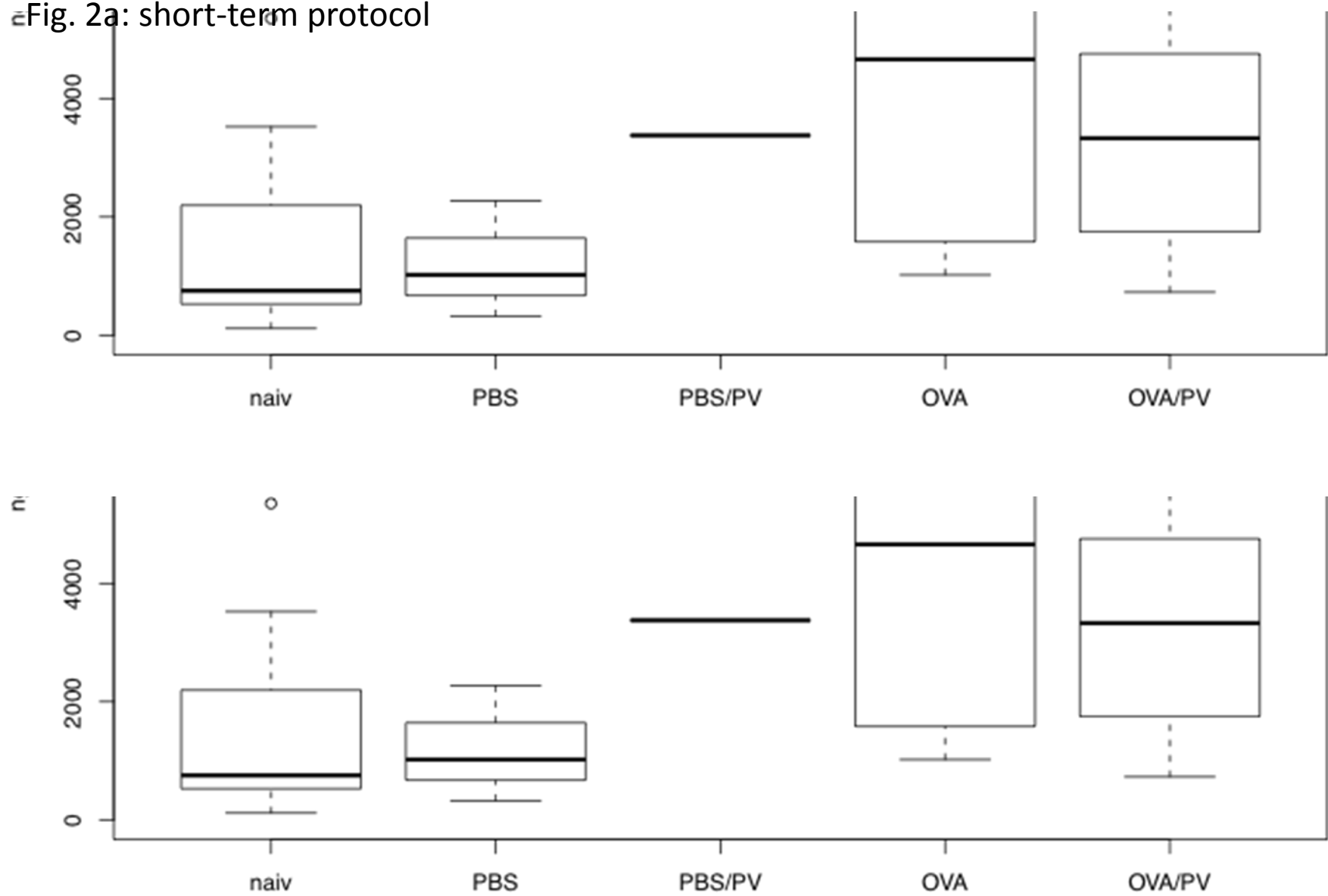


Fig. 2b: short-term protocol

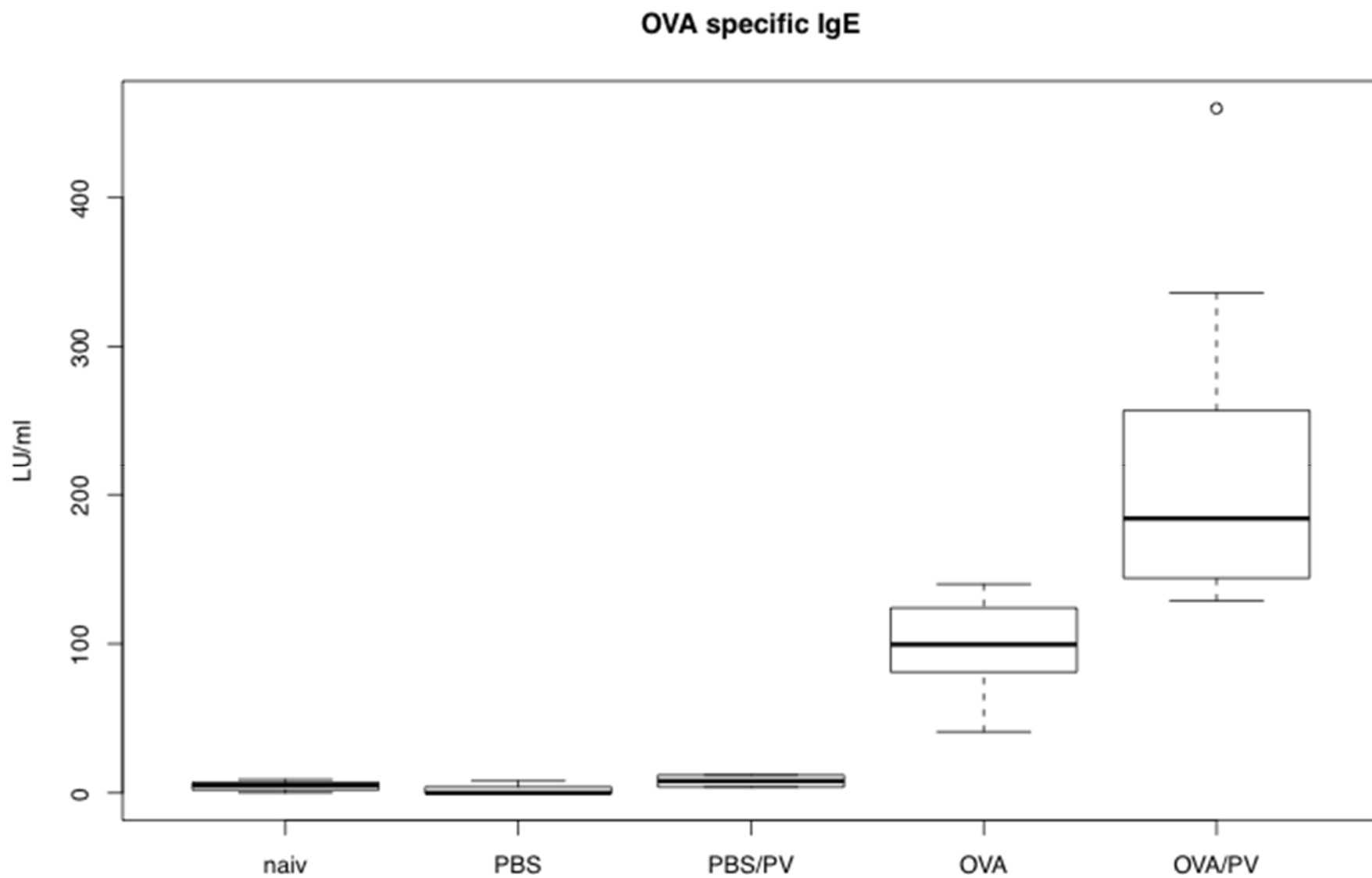


Figure 1: Immunoglobulin titers in OVA-sensitized BN rats: long-term protocol

Animals were sensitized by intraperitoneal injection of OVA (10 µg, 100 µg, or 1000 µg) once every second week for a total of 12 weeks (*long-term protocol*). The allergen of the first injection was absorbed to 2 mg aluminum hydroxide (AL) and *B. pertussis* whole body vaccine (PV) (2×10^6 PV, E. von Behring, Marburg, Germany). Blood samples were taken at indicated time points. Serum levels of allergen-specific IgE and total IgE were measured by ELISA.

Figure 2 a and b: Immunoglobulin titers in OVA-sensitized BN rats: short-term protocol

Animals were sensitized by intraperitoneal injection of 10 µg OVA on days 1, 5 and 10 (*short-term protocol*). To assess the effect of adjuvants on sensitization, the allergen of the first injection was absorbed to 2 mg aluminum hydroxide (AL) and/or *B. pertussis* whole body vaccine (PV) (2×10^6 PV, E. von Behring, Marburg, Germany). Blood samples were taken at day 24. Serum levels of total IgE (figure 2a) and allergen-specific IgE (figure 2b) were measured by ELISA.

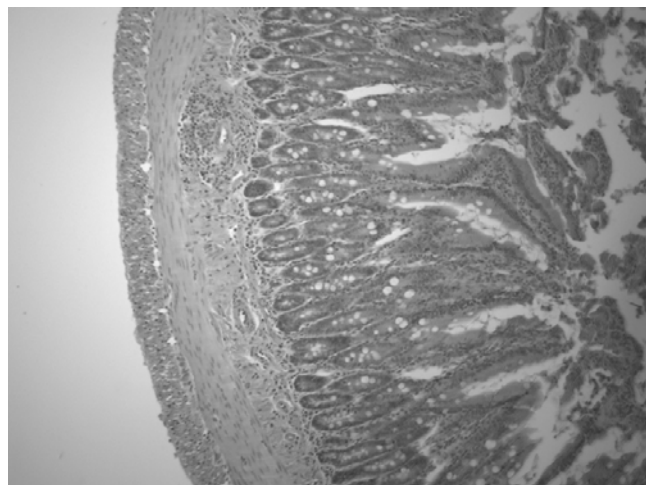
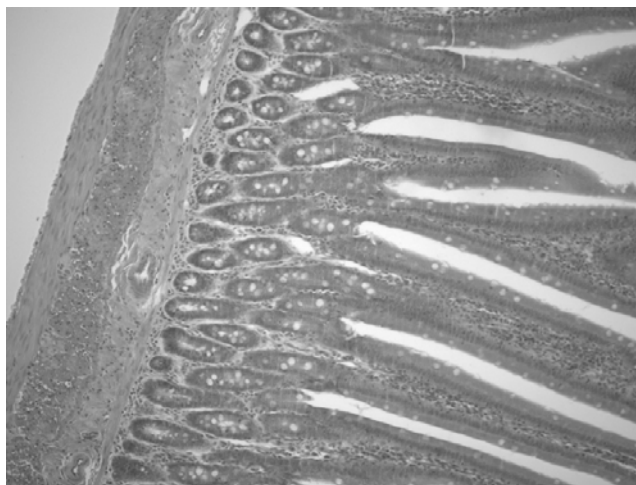
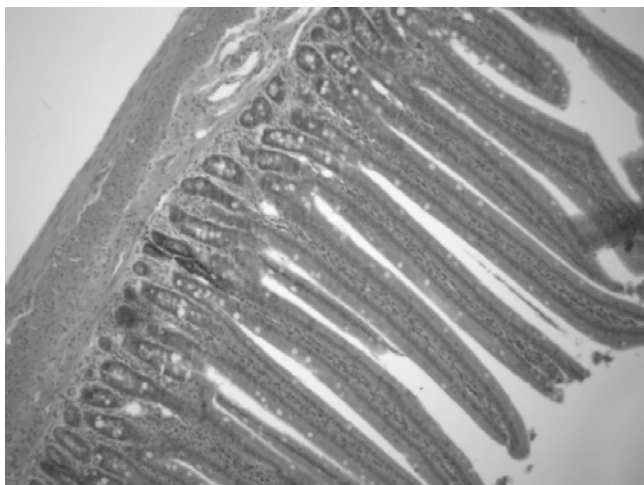


Fig. 3

Figure 3: Intestinal changes upon local allergen challenge

BN were sensitized by intraperitoneal injection of 10 µg OVA on days 1, 5 and 10 (*short-term protocol*). Allergen was absorbed to aluminium hydroxide (2 mg AL) and pertussis whole body vaccine (2x10⁶ PV, E. von Behring, Marburg, Germany) at the first injection timepoint. Sensitized animals according to the short-term protocol were challenged locally by gavage feeding of 500 µg OVA (in 1 ml PBS) twice, on days 20 and 21 (*two challenges*) **(3a)**, or on ten consecutive days, beginning on day 20 (*repeated challenges*) **(3c)**. The negative control groups were sham-sensitized and challenged with PBS according to the same protocols **(3b)**. All animals were sacrificed and analyzed 24 h after the last allergen challenge. Intestinal tissue was fixed in 4% formalin, dehydrated, mounted in paraffin, sectioned, and stained with hematoxylin-eosin (HE) or periodic acid-Schiff (PAS) reaction by using a standard protocol.