A Unique Case of Angioedema With Anti-C1 Inhibitor Antibodies and Normal C1 Inhibitor Levels

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Angioedema with acquired C1-inhibitor deficiency (C1-INH-AAE) is a rare disease whose prevalence is estimated to be 1:500 000 [1]. Fewer than 200 cases have been reported in the literature. C1-INH-AAE manifests as recurrent episodes of nonpitting angioedema lasting 24-72 hours and involving mainly the face, tongue, uvula, and upper airways. Patients do not have a family history of angioedema, and onset of symptoms is usually after the age of 40 years [2].

The suspected diagnosis is confirmed by a C1-INH function <50% of normal. Moreover, C4 levels are reduced in almost all patients, and anti-C1-INH antibodies and low C1q plasma levels are detected in >70% of cases. C1-INH antigen levels are <50% in most patients, even if the presence of a cleaved form of C1-INH yielding apparently normal C1-INH protein levels is reported in 20% of patients [3,4].

In some cases, it is difficult to differentiate C1-INH-AAE from idiopathic nonhistaminergic angioedema (InH-AAE). This condition comprises nonfamilial, nonhereditary forms in which known causes have been excluded and recurrences persist despite antihistamine treatment [5].

We report the case of a patient affected by recurrent angioedema with anti-C1-INH antibodies and normal C1-INH functional and antigen levels.

An 80-year-old woman came to our outpatient department in 2011 because of recurrent attacks of angioedema without wheals.

Her symptoms began in 2001 (aged 66 years) with an episode of peripheral edema without wheals or pruritus involving the upper arms and lasting 3 days. Shortly after onset, she experienced upper airway edema, which was treated with methylprednisolone 60 mg IV, chlorpheniramine 10 mg IM, ranitidine 50 mg IV, and epinephrine 0.5 mg IM, although no clear benefit was observed.

During the following years, she experienced angioedema without wheals that generally affected peripheral sites (about 1 episode per month). The frequency of attacks decreased progressively until 2011, when she had a severe laryngeal attack requiring admission to the emergency department. The attack took 3 days to resolve, despite treatment with standard therapy for histaminergic angioedema including methylprednisolone, chlorpheniramine, and epinephrine.

The patient was subsequently referred to the Center for Diagnosis and Treatment of Angioedema at the University of Naples Federico II. Her past clinical history was unremarkable except for arterial hypertension, which had been treated with irbesartan and hydrochlorothiazide for about 1 year. None of her relatives had ever experienced angioedema.

The patient underwent diagnostic tests, which excluded infection and autoimmune and allergic diseases. Since her history was typical of bradykinin-mediated angioedema, we measured levels of antigenic and functional C1-INH, C4, and C1q, all of which were normal. Nevertheless, because of her age and clinical history, we strongly suspected C1-INH-AAE. In some patients, at disease onset, C1-INH deficiency and consumption of complement components are only evident during angioedema attacks and not during the intercritical period. Therefore, we investigated anti-C1-INH antibodies using semiquantitative ELISA. We detected anti–C1-INH IgG in 2 subsequent determinations, but not anti-C1-INH IgM or IgA. Total serum IgG levels were within normal limits, thereby excluding false-positive results. Based on clinical data and on the presence of these antibodies, we classed this patient as C1-INH-AAE, that is, a patient at risk of lymphoproliferative disorders [6]. Consequently, she has since undergone tests every 6 to 8 months to rule out underlying autoimmune and lymphoproliferative diseases and monoclonal gammopathy of undetermined significance.

Because her attacks were infrequent, we prescribed off-label treatment with icatibant 30 mg SC on demand [7]. We trained the patient and her daughter to administer the drug; therefore, treatment was usually administered at home, except in 2 cases involving the upper airways, when she was treated with icatibant in the emergency department. To date, she has experienced 12 attacks involving peripheral sites or the upper airways and face. These attacks were treated with icatibant. Symptoms began to resolve after about 20 minutes and disappeared completely after 8-20 hours. In 1 case, the patient administered 2 syringes of icatibant for the same attack, possibly because she treated the attack more than 6 hours after the onset of angioedema. No adverse events were reported.

We evaluated complement components twice yearly during 3 years of follow-up, and values remained normal.

We recently retested the patient and confirmed the presence of anti-C1-INH IgG.

A limitation in this case report is that C1-INH and C1q were never evaluated during the attacks [8]. However, C4 was measured during the only attack that required hospitalization and was found to be within the normal range.

Given the patient's clinical history and laboratory data, our diagnosis was InH-AAE with anti-C1-INH antibodies. Key features, including clinical presentation, age at onset, confirmed presence of anti-C1-INH antibodies, and response to icatibant, are reminiscent of C1-INH-AAE. However, the normal findings in the C1-INH functional assay and analysis of C4 and C1q do not allow us to confirm this diagnosis.

We propose 2 hypotheses to explain this unusual form of angioedema. First, the anti-C1-INH antibodies bind to C1-INH, leading to structural alteration of the molecule that precludes binding to factor XII without interfering in binding to C1 esterase, the substrate used for the functional assay of C1-INH activity [9]. Second, the case we report could be a true form of InH-AAE that responds to icatibant in which the presence of anti-C1-INH antibodies is no more than a concomitant laboratory finding with no pathogenic relevance.

We report a unique form of InH-AAE associated with anti-C1-INH antibodies that is clinically consistent with C1-INH-AAE. Our findings underline the importance of further investigating the role of anti-C1-INH antibodies in the pathogenesis of angioedema.

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Conflicts of Interest

Maria Bova and Angelica Petraroli have received sponsorship for educational purposes, have been paid for providing consultancy services, and have taken part in clinical trials sponsored by Shire, Pharming NV, CSL-Behring, and SOBI. Gianni Marone has taken part in clinical trials sponsored by Shire and Pharming NV. Massimo Triggiani has consultancy agreements with and has been an invited speaker for Shire Human Genetic Therapies Inc., ViroPharma, SOBI, and CSL Behring. Stefania Loffredo declares that she has no conflicts of interest.

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Clinical Characteristics of Patients Sensitized to Siberian Hamster

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The Siberian, Russian, or Dzungarian hamster (*Phodopus sungorus*) has gained great popularity with its introduction as a pet [1], probably because it is more sociable and smaller than other hamsters. The Siberian hamster (SH) has a similar appearance to common hamsters such as the European hamster (*Cricetus cricetus*) and the golden hamster (*Mesocricetus auratus*), although it belongs to a different genus. The fact that its main allergen shows no IgE cross-reactivity with allergens from European or golden hamsters [2] hampers diagnosis, because there is currently no standardized commercial extract available for SH. Clinical data on allergy to SH are relatively scarce [3-5]. We describe the clinical characteristics of patients sensitized to SH.

Consecutive patients from the outpatient clinic who had presented symptoms of allergy after exposure to SH were recruited from the outpatient clinic. All patients had kept at least 1 SH at home, mostly in cages, although the animals were free to run around the house. Most cases of allergy were caused by cleaning SH cages. Extracts were derived from hair, urine, and salivary glands and prepared as previously described [2].

Skin prick tests (SPT) with extracts of SH and a battery of common aeroallergens, including cat, dog, and horse extracts, were performed according to the guidelines of the European Academy of Allergy and Clinical Immunology Guidelines [6]. Five nonatopic patients were used as controls. Clinical assessments, spirometry, and fraction of exhaled nitric oxide (FeNO) measurements (NIOX MINO, Aerocrine, Sweden) were carried out at baseline and 6 months later, once the hamsters had been removed from the patients' houses. Three patients underwent a specific nasal challenge (SNC) and two 2 types of specific bronchial challenge (SBC). All asthma medications, antihistamines, and nasal corticosteroids were withheld for at least 1 week before the start of a specific inhalation challenges. SNC was performed as previously described [7] using an extract of SH epithelium. The nasal response was monitored using a visual analog scale (VAS) for nasal congestion, sneezing, and rhinorrhea (recorded on a 100-mm line) and by acoustic rhinometry (SRE 2100; Rhino-Metrics). A decrease in minimal cross-sectional area (MCA), or Vol 5 ≥30% from baseline and an increase in any VAS parameters >20 mm were considered a positive test result [7,8]. A nasal smear was performed at baseline and 24 hours after SNC [8]. One SBC was performed using the tidal volume method, as previously described [9]. The other challenge was carried out inside a 7- m^3 inhalation challenge chamber. Four hamsters were placed inside a cage in the chamber. Airborne particles were measured using a DustTrak (TSI) aerosol monitor (mean, 0.130 mg/m^3). FEV_1 and nasal parameters were measured before exposure and every 10 minutes during the first hour after challenge. FEV_1 was then measured hourly until bedtime, upon awakening, and again the day after. A fall in FEV_1 ≥20% from baseline was considered a positive asthmatic response. The methacholine challenge and induced sputum tests were performed as described elsewhere at baseline and 24 hours after exposure [10].

The statistical analysis was performed using the *t* test for dependent samples. Statistical significance was set at $P<.05$.

The study population comprised 21 SH-allergic patients, of whom 14 (66.7%) were female. The mean (SD) age was 27.2 years (4.3; range, 10-46 years). Fifteen patients (71.42%) reported asthma and rhinoconjunctivitis symptoms while 5 (23.81%) only reported rhinoconjunctivitis. One patient (4.76%) had experienced an anaphylactic reaction owing to an SH bite on a finger and required medical attention at the emergency department. The initial symptoms in most patients (71%) were respiratory symptoms 4 to 12 weeks after their first exposure to SH. Of note, 18 of the 21 patients (85.71%) had previously experienced respiratory symptoms as a result of sensitization to other pets, as follows: cat (10), dog (5), mouse (1), Guinea pig (1), and horse (1) (Table). All patients underwent SPT with these allergens. Eight patients (38.09%) required emergency treatment of asthma before diagnosis. Treatment at baseline is described in the Table. Medication was maintained until patients felt that their symptoms had improved.

The results of SPT were positive to all 3 SH extracts (epithelium, urine, and salivary glands) in all patients. Eleven patients (52.38%) were monosensitized to SH, while 8 patients (38.09%) were also sensitized to Roborovsky hamster (*Phodopus roborovskii*) and 2 patients were sensitized to both SH and European hamster (Table). The results of SPT in control patients were all negative.

Statistically significant differences were observed in mean FEV_1/FVC, FEV_1, and FeNO values at baseline (FEV_1/FVC, 80.7 [9.8]; FEV_1, 2.28 [0.62] L; FeNO, 49.52 [15.10] ppb) and after 6 months without exposure to SH (FEV_1/FVC, 86 [8.1]; FEV_1, 2.72 [0.62] L; FeNO, 22.57 [8.27] ppb), ($P<.0001$). Treatment was also decreased in most patients (Table). Following the removal of the hamsters from their homes, 17 patients (80.95%) with SH allergy experienced an improvement in respiratory symptoms between weeks 4 and 12, whereas 4 patients improved before week 4.

Two patients presented intense rhinoconjunctivitis a few minutes after SNC and a decrease in MCA >30%

Table. Clinical Characteristics of Siberian Hamster–Allergic Patients

Patient	Age, y	Sex	Previous Animal Exposure	Hamster SPT	Symptoms	Exposure Time, wk	FEV_1/FVC Pre, %	FEV_1 Pre, L/% Predicted	FEV_1/FVC Post, %	FEV_1 Post, L/% Predicted	FeNO Pre, L	FeNO Post, L	Imprv, wk	Treatment at Baseline	Treatment Post
1	46	F	Dog	SH/RH	RC/A	8-12	77	2.66/82	78	2.92/90	77	12	8-12	LABA/IC/RB	No
2	43	F	Dog	SH	RC/A	8-12	75	2.45/74	82	2.75/83	75	20	4-8	LABA/IC/RB	Yes
3	27	F	Cat	SH	RC	>12	71	2.76/76	76	3.25/90	71	26	≤4	Anti-H1/nasal cort	No
4	14	M	Dog	SH/RH	RC/A	4-8	93	1.89/81	90	2.02/91	93	18	4-8	LABA/IC/RB/anti-H_1	No
5	42	F	Rabbit	SH	RC/A	4-8	78	1.76/85	81	1.90/92	78	16	4-8	LABA/IC/RB/anti-H_1	No
6	10	F	Horse/cat	SH	RC/A	4-8	70	1.75/73	76	2.24/94	70	17	4-8	LABA/IC/RB/anti-H_1	No
7	43	F	Cat	SH	RC/A	4-8	68	1.90/68	82	2.87/103	68	33	4-8	LABA/IC/RB/anti-H_1	No
8	17	M	Dog	SH	RC	>12	95	2.92/104	97	3.05/117	95	18	≤4	Anti-H_1/nasal cort	No
9	12	M	Guinea pig	SH/RH	RC/A	4-8	85	2.45/75	88	2.57/78	85	23	4-8	LABA/IC/RB/antiH$_1$	No
10	27	M	No	SH	RC/A	4-8	82	2.15/71	90	2.48/82	82	18	4-8	LABA/IC/RB/antiH$_1$	No
11	33	F	Cat	SH/RH	Ax	>12	96	2.77/104	98	2.82/106	96	32	≤4	Adren/IV antiH1/IV cort	Yes
12	23	F	Cat	SH/RH	RC/A	4-8	91	3.66/93	93	3.74/95	91	6	8-12	LABA/IC/RB/anti-H_1	Yes
13	33	F	Cat	SH/RH	RC/A	<4	85	1.93/85	96	2.37/90	85	43	8-12	LABA/IC/RB/anti-H_1	Yes
14	42	F	Dog	SH	RC/A	8-12	82	2.23/70	84	2.90/88	82	19	4-8	LABA/IC/RB/anti-H_1	Yes
15	12	M	Rabbit	SH	RC/A	<4	94	2.35/84	99	2.45/102	94	32	8-12	LABA/IC/RB/anti-H_1	Yes
16	12	F	Cat	SH	RC	>12	77	1.68/70	88	2.45/85	77	18	8-12	Anti-H_1/nasal cort	No
17	11	F	Cat	SH/EH	RC	8-12	63	3.36/74	69	3.86/105	63	22	8-12	Anti-H_1/nasal cort	No
18	27	M	No	SH/EH	RC	4-8	85	2.44/71	85	3.65/100	85	30	≤4	Anti-H_1/nasal cort	No
19	41	F	Cat	SH	RC/A	4-8	79	1.96/69	79	2.85/90	79	21	4-8	LABA/IC/RB/anti-H_1	No
20	39	F	No	SH/RH	RC/A	4-8	82	2.02/70	84	2.66/90	82	28	8-12	LABA/IC/RB/anti-H_1	Yes
21	18	M	Cat	SH/RH	RC/A	4-8	66	0.89/58	91	1.26/82	66	22	8-12	LABA/IC/RB/anti-H_1	Yes
Mean	27.2 (4.3)						80.7 (8.9)	2.28 (0.62) L	86 (8.1)[a]	2.72 (0.62) L[b]	49.52 (15.1)	22.57 (8.27)[b]			

Abbreviations: A, asthma; Adren, adrenaline; Anti-H_1, antihistamines; Ax, anaphylaxis; EH, European hamster; FEV_1, forced expired volume in the first second of inspiration; F, female; FeNO, fraction of exhaled nitric oxide; IC, inhaled corticosteroids; Imprv, improvement time; IV, intravenous; LABA, long-acting bronchodilators; M, male; Nasal cort, nasal corticosteroids; Pre, baseline visit; Post, 6-month visit after removal of SH; RB, relief bronchodilators; RC, rhinoconjunctivitis; RH, Roborovsky hamster; SH, Siberian hamster; SPT, skin prick test.

[a] P=.0007.

[b] P<.0001.

from baseline. Eosinophil counts in nasal smears increased significantly 24 hours after the SNC in both cases. SBC results were positive in 2 cases (1 early asthmatic reaction and 1 dual asthmatic response). An increase in FeNO values (30 vs 55 ppb and 32 vs 45 ppb), an increase in sputum eosinophils (0.69 vs 2.11 and 0.35 vs 2×10^6 L), and a significant decrease in methacholine PC_{20} (0.25 vs <0.125; 2.8 vs 0.6 mg/mL) were observed 24 hours after challenge.

In summary, exposure to SH in sensitized patients can elicit intense respiratory symptoms and even anaphylaxis if patients are bitten. The onset of symptoms was between 4 to 12 weeks after the initial exposure. The importance of avoiding exposure was demonstrated, since the patients reported here showed a clear improvement in symptoms, pulmonary function test results, and FeNO levels after removal of the SH from their homes. As we previously reported [2], it is important to use extracts of SH (urine, epithelium) to demonstrate specific IgE, since SH allergens have no cross-reactivity with European and golden hamsters.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Comparison of Pollen Levels Between 2 Pollen Traps in Salamanca, Spain

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In recent years, an increasing number of aerobiological sampling stations have been installed in urban areas to report airborne pollen content. Several authors have studied the differences in atmospheric pollen levels between cities, which are mainly due to variations in local climatic and geographical conditions and to urban management [1,2]. Other studies in 2 or more areas of the same city showed differences that were attributable to sampler height, variations in vertical movement of air [3], and surrounding vegetation [4].

In the present study, we investigated the airborne pollen content of Salamanca (midwestern Iberian Peninsula [40º 58' N; 5º 40' W], Mediterranean continental climate, 800 m above sea level) by comparing 2 sampling stations located at different heights between February 1, 2007 and February 7, 2008 (372 days). Our objective was to record potential differences in moderate and high pollen concentrations that could cause symptoms in sensitized people.

Aerobiological samples were collected using 2 Hirst type volumetric pollen traps based on the impact principle [5]. Sampler 1, a Burkard 7-day recorder (Burkard Manufacturing Co Ltd) was placed on the roof of a centrally located municipal building 20 m above ground level. The immediate surroundings are characterized mainly by historical buildings and narrow streets with a low number of trees. Sampler 2, a VPPS 2000 (Lanzoni s.r.l.), was placed on the roof of the Faculty of Pharmacy at 30 m above ground level. The building is located on the outskirts of the city near the Tormes River and its riverside forests, 1.5 km west of the first location.

Sampling, slide preparation, and data interpretation were all performed by the same person, who also recorded days with moderate and high pollen levels, following the criteria of the Spanish Aerobiology Network [6]. Total days with moderate and high levels in 2 samplers were obtained when at least 1 type of pollen reached moderate and high concentrations. The Spearman rank correlation coefficient was used to establish the relationship between the daily pollen counts of both samplers. This test was chosen because daily pollen counts are not normally distributed. Statistical analysis was carried out using SPSS Version 12.0.

Table. Aerobiological Data From 2 Samplers During the Study Period and Spearman Rank Correlation Coefficients for Comparison of Levels of the Main Pollen Types

	Sampler 1				Sampler 2				Spearman
	Total Pollen	Peak Value[a]	Peak Day	Days With Moderate/High Levels	Total Pollen	Peak Value[a]	Peak Day	Days With Moderate/High Levels	Correlation Coefficient[b]
Total	31 478	957	June 8	106	28 493	959	March 10	100	0.939
Quercus	9352	689	June 6	38	8368	551	May 13	38	0.845
Poaceae	7764	355	June 30	72	6932	282	June 30	73	0.902
Cupressaceae	4047	550	March 4	26	3728	853	March 10	15	0.700
Plantago	1706	159	July 13	16	1437	106	May 10	13	0.860
Populus	1087	180	March 19	4	1465	322	March 13	6	0.935
Platanus	1017	297	April 16	5	751	117	March 19	7	0.789
Rumex	1012	52	May 11	10	1031	58	May 11	10	0.847
Urticaceae	969	31	June 23	9	950	43	April 29	9	0.799
Olea	678	162	June 8	2	525	107	June 8	2	0.660
Fraxinus	425	51	February 16	1	504	53	March 10	1	0.759
Castanea	410	62	July 8	2	374	60	July 8	1	0.843
Pinus	686	79	June 5	1	236	42	June 6	0	0.646

[a]Pollen grains/m^3
[b]$P<.01$.

The total number of airborne pollen grains counted during the 372 study days was higher in sampler 1 than in sampler 2 (64 and 61 types of pollen, respectively). Boraginaceae, *Pittosporum*, Scrophulariaceae, *Sophora*, and Thymelaeaceae grains were not found in sampler 2, and *Convolvulus*, *Medicago*, and *Philadelphus* grains were not found in sampler 1. The main types of pollen in both samplers were *Quercus*, Poaceae, and Cupressaceae, which together accounted for 67% of the total pollen levels recorded. Sampler 1 showed higher total pollen levels and higher peak values for all but 18 pollen types (mainly *Populus, Fraxinus, Rumex* and Ericaceae). Levels of Cupressaceae pollen grains were higher in sampler 1, although their maximum daily concentration was higher in sampler 2. With respect to the moderate and high daily levels reported for the main pollen types, sampler 1 revealed more days with moderate and high levels in most cases, except for Poaceae, *Populus*, and *Platanus*, for which moderate and high levels were observed on more days in sampler 2 (Table). The number of days with high levels for *Fraxinus, Olea, Rumex,* and Urticaceae was the same for both samplers.

The Spearman rank correlation coefficient revealed high correlations between the total daily counts of the 2 sampling sites, with significant values (P<.01) for the main types of pollen.

Knowledge of atmospheric pollen levels can improve the diagnosis and treatment of pollen allergy. Another study conducted in the same area showed that sensitization was most frequent to Poaceae, followed by *Olea*, Cupressaceae, *Plantago, Artemisia*, and *Platanus* [7]. Few differences were obtained after comparison of the 2 samplers, revealing a close statistical correlation between them, as reported in other southern European cities [8,9]. Small variations recorded in the occurrence of peak days in both samplers and even lower correlation coefficients in some pollen types during the study period could be due to differences in the distribution of urban flora throughout the city. In addition, local differences in the timing of the peak could be significant for some people with pollen allergy [10]. Our results indicate that 1 volumetric sampler is sufficient to record the main airborne pollen types, their atmospheric behavior, and daily high levels in an urban area.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Quail's Egg–Induced Severe Enterocolitis in a Child Tolerant to Hen's Egg: First Reported Case

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Palabras clave: Alergia alimentaria. Huevo de codorniz. Enterocolitis. Niño.

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food hypersensitivity reaction characterized by profuse, repetitive vomiting and diarrhea that may progress to dehydration and shock in 15%-20% of patients. FPIES is usually caused by cow's milk or soy in formula-fed infants whose food contains solids, rice, oat, barley, chicken, turkey, fish, and, rarely, peanut [1]. Case series and reports of FPIES with hen's egg have been triggered by both egg white and yolk [2]. The prevalence of egg allergy is estimated to be between 1.8% and 2% in children younger than 5 years of age [3]. Allergy to quail's egg is a rare condition described only in case reports [4,5].

We report the case of a 3-year-old girl with no history of food allergy who was brought to hospital with repetitive and persistent vomiting, abundant bloody diarrhea, and systemic hypotension (60/40 mmHg). She was severely dehydrated. Stool analysis revealed a high red blood cell count. The complete blood count disclosed the following: hemoglobin, 15.7 g/dL; erythrocytes, 5.6×10^6/µL; white blood cells, 27 650/µL; and platelets, 400 000/µL. No pathogenic bacteria were detected in the stool culture. The patient was discharged after recovery. One week later, she was admitted with the same symptoms, which started 2 hours after consumption of boiled quail's egg on "quail's egg day" in her kindergarten. She had no other food allergy or any known allergic disease before attending the school and had never consumed quail's egg.

Skin prick tests for foods (cereals, hazelnut, peanut, walnut, cacao, tuna fish, chicken, banana, strawberry, tomato, hen's egg, and cow's milk) were performed using commercial extracts (Stallergènes). Positive and negative controls (histamine and saline) were also applied. The result was negative for all allergens, including hen's egg. The results of prick-to-prick testing with uncooked and boiled yolk and white of quail's egg were negative. Serum specific IgE for hen's egg was negative. An oral challenge with quail's egg was performed starting at 1 g. Two hours later, the patient began to vomit repetitively. After 4 hours, she had bloody diarrhea. None of the symptoms recurred when quail's egg was eliminated from her diet during the 1-year follow-up period. The patient tolerates hen's egg.

We present an unusual case of severe quail's egg protein–induced enterocolitis in a hen's egg–tolerant 35-month old girl who was admitted with hypotension, recurrent vomiting, and abundant bloody diarrhea. To our knowledge, this is the first report of life-threatening quail's egg–induced enterocolitis.

Domestic hen (*Gallus domesticus*) and quail (*Coturnix coturnix*) belong to the family Galliformes. The 5 major allergens identified in hen's egg are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4), and albumin (Gal d 5). Most allergenic proteins are contained in egg white (Gal d 1-4) rather than egg yolk (Gal d 5). Ovomucoid is resistant to degeneration by heat and digestive enzymes, thus making it the most allergenic protein, whereas ovalbumin is the most abundant protein [6]. Although clinical and serological cross reactivity between hen's egg protein and proteins of eggs from other birds has been described for IgE-mediated food reactions [7], there is no such description for non–IgE-mediated food reactions including FPIES. IgE-mediated allergy with allergy to other bird's eggs in the absence of IgE-mediated hen's egg allergy has been reported [8].

Data from 2 cohorts of 168 and 38 children with FPIES revealed hen's egg–induced FPIES in 3 and 4 children, respectively [9,2], while in a retrospective study [10], egg was found to be the fifth most commonly involved food in FPIES and responsible for 11% of cases. Onset of FPIES can occur a few days after birth up to 1 year, and the condition usually resolves by 2-3 years of age [6]. In our case, the patient was 35 months old at diagnosis and had consumed quail's egg relatively late. In a report of 4 cases of FPIES with hen's egg, one patient was 48 months old when the initial symptoms started and 54 months at diagnosis [2].

Both determination of specific IgE and skin prick tests are useful for diagnosing IgE-mediated egg allergy, although these approaches have no role in the diagnosis of non–IgE-mediated egg allergy. A complete clinical history is paramount, and an oral food challenge is necessary for confirmation [6]. In support of these observations, in the case we report, the results of prick tests were all negative including tests with quail's egg and hen's egg, and the oral food challenge with quail's egg triggered symptoms of enterocolitis. Quail's egg was eliminated from the patient's diet, and the symptoms did not recur during 1 year of follow-up.

To our knowledge, this is the first report of life-threatening FPIES triggered by quail's egg. Diagnosis was early. As hen's egg–induced FPIES is increasingly reported in the literature, other bird's eggs should be borne in mind, even if no symptoms are detected with ingestion of hen's egg. Although FPIES is mostly seen below 1 year of age, in older children presenting with symptoms such as vomiting, bloody diarrhea, and hypotension of unknown cause, a complete clinical history should be taken to record initiation of symptoms after specific food ingestion and thus rule out allergic etiologies.

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Conflicts of Interest

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Positive Allergy Study (Intradermal, Patch, and Lymphocyte Transformation Tests) in a Case of Isoniazid-Induced DRESS

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Palabras clave: DRESS. Antituberculostáticos. Isoniazida. Test de Transformación Linfocitaria. Pruebas epicutáneas.

Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a rare but severe clinical entity that requires early withdrawal of the causative agent. A high degree of diagnostic suspicion is needed. Several diagnostic criteria have been established based mainly on clinical features, laboratory findings, and the association between administration of the culprit drug and onset of the reaction. The etiologic diagnosis is difficult (many drugs may be involved), the result of the allergy workup is usually negative, and a challenge test is not advisable owing to potentially life-threatening consequences. We present a case of isoniazid-induced DRESS in which the culprit agent was identified by positive results in an intradermal skin test (IDT, delayed reading), patch test, and lymphocyte transformation test (LTT).

A 21-year-old Peruvian man with pulmonary tuberculosis started treatment with ethambutol, isoniazid, pyrazinamide, and rifampicin. He was admitted 1 month later with fever, lymphadenopathy, pruritic rash, facial edema, leukocytosis (40 600/mm^3), atypical lymphocytosis (13 800/mm^3), elevated liver enzyme levels (aspartate aminotransferase, 664 U/L; alanine aminotransferase, 637 U/L), and dyspnea. A few days later, he experienced respiratory failure and required invasive mechanical ventilation in the intensive care unit. Fine-cut computed tomography scans showed features compatible with alveolitis, and skin biopsy revealed mild superficial perivascular dermatitis with the presence of eosinophils. The results of serological tests (for respiratory tract and liver infections and viral infections [human immunodeficiency virus, herpes]) and autoimmunity studies were negative.

Despite discontinuation of the antituberculosis drugs, the patient's condition worsened, and systemic corticosteroids and second-line antituberculosis therapy (ethambutol, streptomycin, and levofloxacin) were started. Three weeks later, the patient's symptoms resolved, and his pulmonologist reintroduced rifampicin cautiously. No adverse events were recorded.

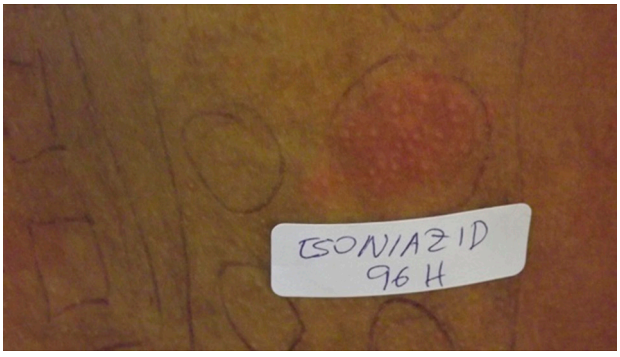

Figure. Positive patch test with isoniazid at 96 hours.

The allergy workup, which was performed 8 months after the onset of symptoms, included skin tests (prick test and IDT with immediate and delayed readings) with isoniazid and pyrazinamide (isoniazid, prick [60 mg/mL] and IDT [0.6 mg/mL]; pyrazinamide, prick as is), patch tests (TRUE Test with solutions of isoniazid 1% in water and pyrazinamide 1% in alcohol), and LTT with isoniazid and pyrazinamide. Tests were positive with isoniazid (delayed IDT test at 72 hours, which remained positive until day 7; patch test [+++] at 96 hours; and LTT at all concentrations tested [1, 5, 10, 50, and 100 mg/mL]) (Figure). The result of the oral challenge test with pyrazinamide was negative.

The diagnosis of DRESS remains mainly clinical [1]. The 2 sets of diagnostic criteria usually adopted are those of the International Registry of Severe Cutaneous Adverse Reactions group and the Japanese consensus group [2,3]. The case discussed here fulfills both sets of criteria.

We present the case of a patient who experienced isoniazid-induced DRESS with positive results in in vivo and in vitro tests. Isoniazid is a very rare cause of DRESS [4-7]. In the case we report, both the patch test and LTT were helpful in the diagnosis of DRESS, in which many drugs are implicated [6,8]. Nevertheless, physicians should be aware of the possibility of life-threatening drug reactions associated with patch testing in DRESS [9]. LTT, an ex vivo technique, seems to be safer, although further studies are needed to establish its sensitivity and specificity, especially in patients with serious conditions, such as DRESS.

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Cost-Effectiveness Analysis of 3 Methacholine Challenge Tests: Importance of Simplified Protocols

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Palabras clave: Asma. Metacolina. Hiperrespuesta. Coste-efectividad.

Methacholine challenge testing is a key tool in the evaluation and management of asthma [1], and several protocols are currently available [2,3]. Given that the cost-effectiveness of these protocols has received little attention, our objective was to compare the effectiveness and cost of 3 common methods of methacholine bronchial challenge.

We evaluated consecutive patients referred to our center for methacholine bronchial challenge owing to suspected asthma in 3 time periods. According to current guidelines, bronchial challenge was performed by the pulmonologist or allergist who attended the patient, and all participants signed the informed consent document.

Between 1992 and 1996, we used the 5-breath protocol of Chai et al [4]. Methacholine was diluted in phenol-buffered saline and administered using a continuous jet nebulizer. In each successive stage, 5 puffs of methacholine were administered (from 0.0625 to 16 mg/dL of solution) [4]. Spirometry was performed 5 minutes after each dose, and the result was considered positive when FEV_1 fell by ≥20%.

In 2000 and 2001, the technique used was the long protocol of the dosimetric method of Chinn et al [5] and, subsequently, García Río et al [6], while in 2013 and 2014 the technique used was the simplified protocol of the dosimetric method [5], which was later amplified by Perpiñá et al [3]. The difference between the methods lies in the number of doses administered, namely, 9 in the long protocol and 5 in the simplified protocol. A

Table, A. General Characteristics of the Study Patients

	Five-Breath Method[a]	Long Protocol of the Chinn Dosimeter Method[b]	Simplified Protocol of the Chinn Dosimeter Method[c]	*P* Value
Time period	1992-1996	2000-2001	2013-2014	-
No.	1276	245	303	-
Gender				.396
Women, %	63.3	62.9	62.7	
Men, %	36.7	37.1	37.3	
Age, y	32 (15)	36 (18)	38 (15)	.081
Height, cm	162 (9)	163 (9)	163 (10)	.625
Weight, kg	73 (14)	74 (13)	72 (15)	.539
BMI, kg/m^2	28.1 (5.4)	27.8 (6.3)	27.7 (5.9)	.368
Current smokers, %	26	22.0	20.8	.352
Baseline FVC, L	3.50 (1.03)	3.47 (0.98)	3.50 (1.04)	.369
Baseline FVC, % predicted	105 (14)	105 (15	106 (17)	.249
Baseline FEV_1, L	2.50 (0.87)	2.46 (0.89)	2.47 (0.82)	.317
Baseline FEV_1, % predicted	99 (12)	97 (5)	100 (15	.366
Baseline FEV_1/FVC	0.80 (0.06)	0.78 (0.04)	0.79 (0.06)	.631
Asthma suspicion by				.344
Wheezing, %	58.2	53.1	57.1	
Persistent cough, %	22.5	24.5	24.2	
Previous AHR, %	12.4	14.7	12.2	
Dyspnea, %	6.9	7.8	6.3	
Maximum fall in FEV_1, %	16.5 (18.4)	14.0 (11.8)	14.2 (10.5)	.272
Severity of AHR				.103
Mild, %	-	63.7	73.6	
Moderate-severe, %	-	36.3	24.3	

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; AHR, airway hyperresponsiveness.
[a]Chai et al [4].
[b]Chinn et al [5,6].
[c]Chinn et al [3,5].

Table, B. Cost Analysis of the Methacholine Challenge Tests Evaluated

Protocol	Five-Breath Method[a]	Long Protocol of the Chinn Dosimeter Method[b]	Simplified Protocol of the Chinn Dosimeter Method[c]
Period	1992-1996	2000-2001	2013-2014
Estimated working time and methacholine consumption			
Test duration, min	90	120	80
No. scheduled test/day	1	2	3
Physician, min	28 min (prior rating, 5 min; availability during the test [20% of the time]:,18 min; report, 5 min)	32 min (prior rating, 5 min; availability during the test [20% of the time], 24 min; report, 3 min)	24 min (prior rating, 5 min; availability during the test [20% of the time], 16 min; report, 3 min)
Pharmacist, min	0.75 min (build 5 + 1 vials 4 weeks, 15 min; 1 test/day, 20 days = 20 tests, 15/20 = 0.75 min per test)	0.75 min (prepare 9 + 1 vials 4 weeks, 30 minutes; 2 tests/day, 20 days = 40 tests, 30/40 = 0.75 min per test)	0.16 min (prepare 3 + 1 vials 4 weeks, 10 min; 3 tests/day, 20 days = 60 tests, 10/60 = 0.16 min per test).
Nurse, min	86 min (explain procedure, 3 min; puffs [5 + 1], 12 min; standby time [5 + 1], 18 min; spirometry [7], 35 min; bronchodilator and spirometry, 15 min; observation, 3 min)	113 min (explain procedure, 3 min; puffs [9 + 1], 10 min; standby time [9 + 1], 20 min; spirometry [11], 55 min; bronchodilator and spirometry, 15 min; observation, 10 min)	74 min (explain procedure, 3 min; puffs [5 + 1], 6 min; standby time [5 + 1], 12 min; spirometry [7], 35 min; bronchodilator and spirometry, 15 min; observation: 3 min)
Nursing assistant, min	19 min (measurement of height and weight, 3 min; place mouthpiece and filter, 1 min; solutions management, 10 min; cleaning equipment, 5 min)	24 min (measurement of height and weight, 3 min; place mouthpiece and filter, 1 min; solutions management, 10 min; cleaning equipment, 10 min)	13 min (measurement of height and weight, 3 min; place mouthpiece and filter, 1 min; solutions management, 5 min; cleaning equipment, 4 min)
Secretary, min	7 min (appointment and copy report)	2 min (appointment)	2 min (appointment)
Volume of the solutions prepared with 1 methacholine vial, mL	9	3	12
Reqired solutions volume, mL	2.5	4.5	2.5
Used methacholine vials	0.28	1.5	0.21
Cost of methacholine	€15.00	€80.50	€11.30
Cost analysis			
Personnel cost			
Physician (€0.55/min)	15.40	17.60	13.20
Pharmacist (€0.55/min)	0.41	0.41	0.09
Nurse (€0.36/min)	30.96	40.68	26.64
Nursing assistant (€0.27/min)	5.13	6.48	3.51
Secretary (€0.27/min)	1.89	0.54	0.54
TOTAL	53.79	65.71	43.98
Material/equipment Cost			
Equipment amortization	€5.22 (230 studies per year × 5 years = 1150 possible feasibility studies; equipment cost = €6000; €6000/1150 studies = €5.22 p per test)	€3.91 (460 studies per year × 5 years = 2300 possible feasibility studies; equipment cost = €9000; €9000/2300 studies = €3.91 per test)	€2.61 (690 studies per year × 5 years = 3450 possible feasibility studies; equipment cost = €9000; €9000/3450 studies = €2.61 per test)
Amortization of material (tweezers, nebulizers)	€0.09 (€100/1150 studies)	€0.08 (€180/2300 studies)	€0.03 (€100/3450 studies)
Consumables	€0.45 (mouthpiece/filter)	€0.45 (mouthpiece/filter)	€0.45 (mouthpiece/filter)
Methacholine vials cost	€15.00	€80.50	€11.30
TOTAL	€20.76	€84.94	€14.39
General cost (water, electricity, laundry, maintenance, property expenses)[d]	€11.25 (90 min × € 0.125)	€15 (120 min × €0.125]	€10 (80 min × €0.125)
TOTAL	€85.80	€165.65	€68.37
Methacholine challenge test results			
N	1276	245	303
Positive challenge, %	33.0	31.4	34.0
PD_{20}, mg	47 (34) CU	0.702 (0.681)	0.807 (0.567)

[a]Chai et al [4]. [b]Chinn et al [5,6]. [c]Chinn et al [3,5]. [d]€64 827 per year (minus staff costs) = €64 827/12 = €5402 per month; €5402/43 200 min in a month = €0.125 per minute

dosimeter (APS, Viasys) was used in both cases to nebulize the doses of methacholine that correspond to each step. Spirometry was performed 90-120 seconds after each nebulization, and the test was interrupted if a fall in FEV_1 ≥20% was recorded. In both cases, the PD_{20} (dose which causes a 20% fall in FEV_1) was determined [3].

Costs were estimated taking into account the duration of the protocol, which was based on data from daily practice (considering the average time to perform at least 20 tests and the distribution of responsibilities between the health professionals from our center). The Table shows the test duration and timing of the tasks assigned to the physician, pharmacist, nurse, nursing assistant, and secretary at the completion of each challenge test according to the different protocols evaluated. Secretary times are lower in the dosimetric method [3,5,6] than in the 5-breath method [4], since the report is automatically generated. Given these working times, wage costs were determined directly from the salaries of personnel assigned to our laboratory in 2013. According to data provided by the Analytical Accounting Service of our center and taking into account that the working week in our autonomous community was 37.5 hours, with 46 weeks per year, it was estimated that the cost per minute of the physician, nurse, nursing assistant/administrative personnel was €0.55, €0.36, and €0.27, respectively.

The number of vials of methacholine used in each protocol was calculated based on the volume of methacholine solution that can be prepared from a vial and the volume of solution required. As the current price of 6 vials of methacholine (Provocholine) amounts to €321.99, the purchase cost of methacholine was determined. Moreover, the amortization of consumables and lung function testing equipment was estimated for the medium term and according to the market price. Finally, general costs (eg, water, electricity, laundry, maintenance, electricity, and property expenses) were established according to the report made in 2013 to our hospital functional group by the Analytical Accounting Service.

We evaluated 1824 patients (1276 in the first period, 245 in the second, and 303 in the third), with a predominance of women in all groups. No differences in anthropometric characteristics, smoking habit, baseline lung function, or indications for bronchial challenge were detected between the 3 periods analyzed. Similarly, the minimum FEV_1 reached after the methacholine bronchial challenge was similar across the 3 periods. No differences in PD_{20} or severity of airway hyperresponsiveness were detected between the long and short protocols of the dosimetric method [3,5,6] (Table, A).

Personnel costs were higher in the long protocol (€65.71) than in the simplified protocol (€43.98) (Table, B). Similarly, the simplified protocol had the lowest expenses for consumables and amortization of equipment (€14.39) and general costs (€10.00), whereas the long protocol consumed more resources (€84.94 and €15.00, respectively). The estimated total costs were €85.80 for the 5-breath method, €165.70 for the long protocol, and €68.40 for the simplified protocol.

Based on the number of challenge tests necessary to obtain a positive result, the cost of a positive test was lower for the simplified protocol (€198.30) than for the 5-breath method and the long protocol (€260.00 and €530.10, respectively).

To our knowledge, the only previous estimation of the costs of methacholine challenge testing was performed by the Centers for Medicare and Medicaid Services, who assigned a reimbursement of €147.50 for each test [7]. Our data show that costs vary considerably depending on the method chosen. While the long protocol exceeds this amount (€165.65), the costs of the 5-breath method and the simplified protocol are substantially lower. In fact, using the simplified protocol enables more than half of the expected costs to be saved (€68.37).

The costs generated by methacholine challenge testing must be interpreted in the context of global asthma costs, particularly in patients with poorly controlled asthma, which generates the highest consumption of resources. In Spain, up to 70% of the overall asthma cost is attributed to poor control, and the annual cost of the use of medical resources in patients with poorly controlled asthma has been reported to amount to €1451.30 [8]. In this situation, the cost of the methacholine challenge test seems acceptable, especially if we take into consideration the importance of identifying and characterizing the disease, the association with quality of life, and the potential ability to monitor treatment [9,10].

In conclusion, our results show that performing the methacholine challenge test using the simplified protocol of the dosimetric method [3,5] is more cost-effective than the long protocol of the same method and the 5-breath method of Chai et al [4]. Therefore, it should be considered the preferred approach, both for diagnosis of patients with suspected asthma and to ensure better disease control.

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Rivaroxaban-Induced Drug Reaction With Eosinophilia and Systemic Symptoms

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, severe, acute, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities, lymphadenopathy, and internal organ involvement [1]. Given the variability of the clinical picture, the diagnosis of DRESS is based on the accountability score proposed by Kardaun et al [2]. Rivaroxaban (Xarelto) is a new oral anticoagulant (factor Xa inhibitor) indicated for prevention of venous thromboembolism in adults after elective hip or knee replacement surgery. We report a case of rivaroxaban-induced DRESS occurring 10 days after initiation of therapy.

A 65-year-old man who had been receiving long-term treatment with atorvastatin and *Serenoa repens* underwent hip prosthesis surgery and was treated with rivaroxaban (10 mg, 1 tablet per day) for prophylaxis of thrombophlebitis starting on the day of discharge from hospital, 1 week after surgery. Ten days later, he began to experience chills with fever that persisted and rose to 40.5°C followed by generalized skin erythema with pruritus on day 15. He was admitted to hospital on day 18 to undergo a series of investigations. The chest x-ray showed a discreet bilateral pulmonary infiltrate. The findings of venous ultrasound of the lower limbs and abdominal ultrasound examination were normal. Blood and urine cultures were negative. The patient received histamine H_1 antagonists and was discharged from hospital. Rivaroxaban was administered until day 20. Forty-four hours after discontinuation of rivaroxaban, the patient was admitted to the intensive care unit with hypotension and bradycardia. At admission, he had anemia, elevated white blood cell count with increased neutrophils and eosinophils, acute renal failure (filtration rate 45 mL/min) with no proteinuria, and mild cholestasis. Levels of alanine aminotransferase, gamma-glutyamyl transpeptidase, and direct bilirubin were increased, and prothrombin time was prolonged. Arterial blood gas analysis revealed hypoxia. The patient was treated with intravenous fluids and atropine. A computed tomography scan of the chest showed bilateral pulmonary infiltrates suggestive of alveolitis, marked thickening of the perilobular interstitium, marked peribronchovascular edema,

and multiple mediastinal lymphadenopathies (Figure, A). The abdominopelvic computed tomography scan showed lumbar lymphadenopathy and a bilateral perirenal infiltrate (Figure, B). Peripheral eosinophilia peaked at 1065/mm^3 the following day. The clinical course after circulatory stabilization was favorable, but the patient had persistent low-grade fever (38.2°C) and rash on the lower limbs for several days. A series of tests were performed to rule out other differential diagnoses, as follows: protein electrophoresis; measurement of ferritin; assessment of thyroid hormones; immunological tests; viral serology tests (hepatitis, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and human immunodeficiency virus); serology of Lyme disease, mycoplasma, and chlamydia; and the urinary antigen test for the diagnosis of pneumococcal pneumonia and Legionella urinary antigens. Blood and urine cultures were also negative.

Given the severity of the clinical presentation and the associated unexplained prolonged high fever, rash, eosinophilia, pulmonary infiltrates, acute renal failure, multiple lymphadenopathies, and abnormal liver function, a diagnosis of DRESS was proposed. The Kardaun score was 6, which indicates DRESS with a high degree of certainty. The patient was discharged from the intensive care unit after introduction of oral corticosteroids at 0.5 mg/day. He underwent subsequent corticosteroid tapering over 3 months, with no recurrence once the regimen was complete.

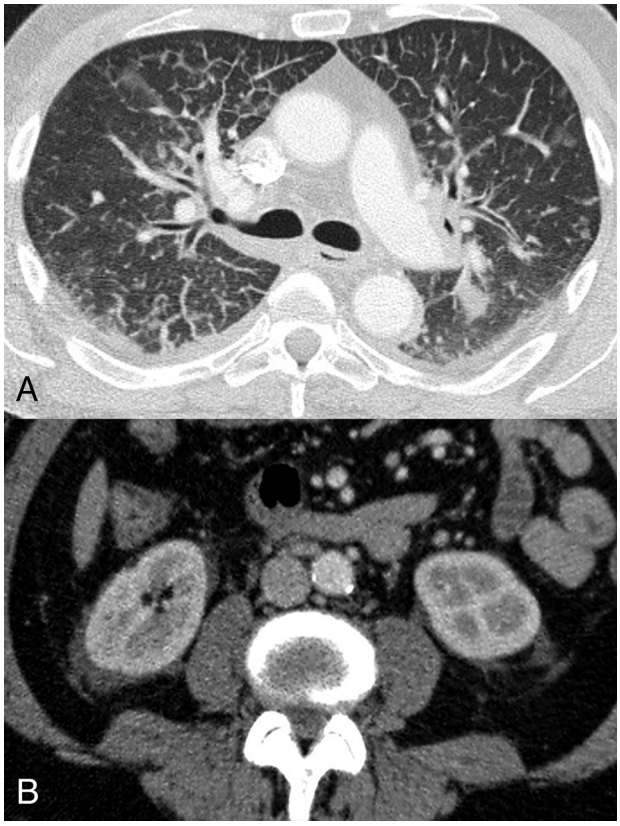

Figure. Chest (A) and abdominopelvic (B) computed tomography scan showing bilateral pulmonary infiltrates suggestive of alveolitis, marked thickening of the perilobular interstitium, marked peribronchovascular edema, multiple mediastinal and lumbar lymphadenopathies, and a bilateral perirenal infiltrate.

DRESS is a severe, idiosyncratic reaction that characteristically arises within 1-8 weeks after exposure to the culprit drug. In the case we report, the reaction began 10 days after initiation of rivaroxaban. The clinical features included cutaneous eruption, fever, multiple lymphadenopathies, hematological abnormalities (most often eosinophilia), and visceral involvement (ie, hepatitis, interstitial nephritis, and pneumonitis). The initial symptoms in the present case were fever and skin eruption 10 days after exposure to the drug. Hepatitis is common (60%-80%), although kidney and lung involvement are less common (10%-30% and 5%-25%, respectively) [3]. The laboratory abnormalities in the present case included elevated white blood cell count with increased eosinophils, acute renal failure, and mild cholestasis. All the alternative diagnoses were ruled out through negative results in viral, bacterial, and immunological examinations.

In order to help clinicians confirm the diagnosis of DRESS, the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) devised a scoring system based on clinical features, extent of skin involvement, organ involvement, and clinical course [4]. RegiSCAR proposes a series of criteria for DRESS, according to which hospitalized patients with drug rash must have at least 3 of 4 systemic features (fever, lymphadenopathy, internal organ involvement, hematological abnormalities). In the present report, our patient developed all 4 criteria of the DRESS syndrome, and the Kardaun score was 6 (certain) [3].

Identification and prompt withdrawal of the offending drug is the mainstay of treatment for patients with DRESS. Although optimum treatment remains controversial, patients are usually treated with corticosteroids [1].

DRESS is most commonly induced by antiepileptic agents (sulfonamides) [5] and rarely by anticoagulants [6,7]. Patch tests have proven useful for identification of the causative drug when patients are receiving several drugs simultaneously [7]. However, the diagnostic value of patch testing remains unclear, and the results of patch testing vary significantly depending on the specific drug. Patch tests appear to be most reliable for antiepileptic medications or proton pump inhibitors but remain negative in testing with allopurinol or sulfasalazine [8,9]. In the present case report, patch tests were not applied, as rivaroxaban was the only causative drug that could be identified. Indeed, the patient's regular treatment (atorvastatin and *Serenoa repens*) had been continued, and the patient had not taken other drugs that were discontinued for fewer than 14 days before onset.

We describe a clinical observation of rivaroxaban-induced DRESS. The clinical course was favorable, with progressive regression of symptoms after initiation of corticosteroids.

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Conflicts of Interest

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Measurement of Lung Function and Bronchial Inflammation in Children Is Underused by Spanish Allergists

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Palabras clave: Niños. Asma. Pruebas de función pulmonar. Inflamación. Hiperreactividad bronquial.

Asthma is the most common chronic respiratory disease in children [1]. Atopy is an important risk factor in the onset, persistence, and severity of asthma, and sensitization to aeroallergens has been demonstrated in more than 80% of asthmatic children [2]. Consequently, the role of allergists in the correct diagnosis, treatment, and follow-up of pediatric asthma is decisive.

Assessment of lung function and bronchial inflammation are key components in the diagnostic workup and follow-up of allergic respiratory diseases, including asthma [3]. Even young children can perform many of the tests used and benefit from them [4]. However, the availability of tests and expertise in using them among allergists are unknown.

We designed an electronic mail–based survey that was sent to the allergy departments of Spanish tertiary teaching hospitals. We questioned health professionals on their knowledge of the main physiologic and inflammatory tests (spirometry, bronchodilator test, plethysmography, impulse oscillometry, exercise test, challenge tests [mannitol, methacholine, adenosine], specific bronchial challenge, exhaled nitric oxide [eNO], and induced sputum) and the availability of these tests in their institutions. We also recorded the age of the patients attended (>18 years, >14 years, all ages).

In order to quantify experience with each test, we analyzed the frequency with which they were used for clinical or research purposes. Therefore, experience was classified as scarce, medium, and broad.

Experience with spirometry and/or eNO in children was considered scarce if <5 tests per day were performed; broad experience was defined as >10 tests per day. For the bronchodilator test, experience was considered scarce if <3 tests per day were performed; broad experience was defined as >5 tests per day. As for exercise, mannitol, and methacholine

Table. Experience of Spanish Allergy Departments in Performing Lung Function and Bronchial Inflammation Tests in Pediatric Patients

		Experience of Allergy Departments, No. (%)		
		Scarce	Medium	Broad
Lung function tests	Spirometry	11 (40.74%)	7 (25.92%)	9 (33.33%)
	Bronchodilator test	12 (44.44%)	7 (25.92%)	8 (29.62%)
	Plethysmography	0	2 (7.40%)	1 (3.70%)
	Oscillometry	0	0	2 (7.40%)
Bronchial hyperresponsiveness tests	Exercise	12 (44.44%)	9 (33.33%)	0
	Mannitol	11 (40.74%)	1 (3.70%)	0
	Methacholine	11 (40.74%)	7 (25.92%)	2 (7.40%)
	Adenosine	1 (3.70%)	0	0
	Specific bronchial challenge	12 (44.44%)	0	0
Inflammatory tests	Exhaled nitric oxide	14 (51.85%)	6 (22.22%)	5 (18.51%)
	Induced sputum	6 (22.22%)	0	1 (3.70%)

challenge tests, <3 tests per month was considered scarce experience, whereas >5 tests was considered broad experience. Experience with the least used and least indicated tests in children (ie, plethysmography, oscillometry, adenosine challenge, specific bronchial challenge, and/or induced sputum) was considered scarce if the tests were performed <5 times per year and broad if they were performed >10 times per year. Intermediate frequencies indicated medium experience.

Replies were received from 38 of the 42 centers surveyed. Eleven were rejected, as the patients attended were aged >18 years. Of the 27 valid surveys, 2 were from centers that attended patients >14 years, and the remaining 25 were from centers that attended patients of all ages.

The results for lung function, bronchial hyperresponsiveness, and inflammatory tests are shown in the Table.

With respect to lung function tests, surprisingly, experience in basic tests such as spirometry was broad in only one-third of tertiary hospitals. In contrast, almost half of them had scarce experience. Similar results were obtained with the bronchodilator test. Although plethysmography and oscillometry were infrequent, the few centers that did perform them reported broad experience.

Of the bronchial hyperresponsiveness tests available, exercise and specific bronchial challenge were used extensively, despite their limited indication in children. On the other hand, mannitol and/or methacholine challenge tests were rarely applied in routine practice. Only 2 centers claimed to have wide experience in these techniques, even though the methacholine challenge test is the most sensitive test for studying bronchial hyperresponsiveness and is clearly indicated in the diagnosis of pediatric asthma [5].

Bronchial inflammation is underanalyzed in children, as most of the centers surveyed admitted having scarce experience in eNO in daily clinical practice, even though this is a noninvasive and easy test for analysis of inflammation in asthma [6].

Many studies analyze education of asthmatic patients by surveying the patients themselves [7]. Despite the importance of specialist training, very few studies analyze knowledge of asthma among pediatricians [8], compare the knowledge of physicians and specialists [9], or even analyze differences in asthma management between respiratory specialists such as pulmonologists and allergists [10]. No self-critical reports have been made to date regarding the evaluation of asthma knowledge among specialists.

Experience with and availability of pediatric lung function testing and/or inflammatory tests must be promoted among allergists. The poor results obtained can be explained mainly by the inadequacy of equipment in allergy departments and the fact that tests are often performed in respiratory or pediatric departments. In addition, scant referral of children with respiratory disease from primary health physicians to allergists implies that the figure of the allergist is not recognized by the general population, pediatricians, or physicians as a specialist with competence in the care of asthmatic children. The present study reveals for the first time the urgent need to increase use of the lung function laboratory by clinical allergists.

To our knowledge, the data we provide are the first to be reported on evaluation of allergy and respiratory specialists based on expertise in asthma and lung function, which seems to be crucial for improving management of asthmatic children. Our results show that there is much room for improvement in the measurement of lung function and bronchial inflammation in children.

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Conflicts of Interest

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Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) Caused by Etoricoxib

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Palabras clave: COX-2. Etoricoxib. Pruebas epicutáneas. SDRIFE.

A 61-year-old woman was referred to our allergy department because she had developed erythema of both axillae, the inframammary folds, and the cubital and popliteal fossae (gluteal and inguinal areas), without systemic symptoms, 6 hours after taking, for the first time, etoricoxib 90 mg to treat osteoarticular pain. She had also taken an ibuprofen pill (600 mg) 5 hours before the episode.

The patient was attended in the emergency room and no systemic signs or symptoms were found on physical examination. A full blood test with blood count and biochemistry, including liver enzymes (aspartate aminotransferase and alanine aminotransferase), was performed and showed normal results. She was treated with methylprednisolone and achieved complete recovery in 5 days, without any residual lesions. Etoricoxib and ibuprofen were discontinued.

The patient had no previous history of drug hypersensitivity and while she had tolerated ibuprofen previously, she reported never having taken a selective cyclooxygenase 2 (COX-2) inhibitor. After this episode, she tolerated paracetamol 1 g. She was seen in our allergy department 3 months after the initial episode. As we suspected that ibuprofen was the most probable cause of the episode, with the patient's informed consent, we first administered a simple-blind oral challenge test (SBOCT) with the progressive administration of etoricoxib (90 mg). Six hours later, she developed erythema of the inframammary folds and inguinal and gluteal areas (Figure). She was treated with methylprednisolone, which led to complete recovery in 4 days.

Two weeks later, after assessing the risk-benefit profile, we performed a closed patch test (Nonwoven Patch Test Strips Curatest, Lohmann & Rauscher International) with ibuprofen (5%, petrolatum), etoricoxib (8%, DMSO), and celecoxib (10%, DMSO) to determinate cross-reactivity. Positive readings were obtained for etoricoxib and celecoxib on day 2 and day 4. A patch test with DMSO at the same concentration was negative. Patch tests with these drugs were also carried out on 10 healthy control individuals, all of whom had negative results. An SBOCT with the progressive administration of a total dose of 600 mg of ibuprofen was performed, and was negative.

Etoricoxib is a nonsteroidal anti-inflammatory drug that selectively inhibits COX-2. Adverse cutaneous effects with

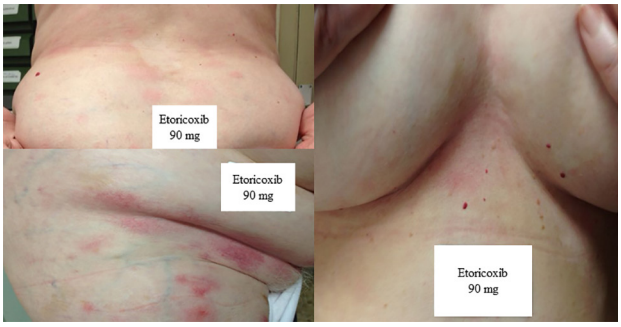

Figure. Positive simple-blind oral challenge test with etoricoxib.

this drug are rare and include leukocytoclastic vasculitis [1], fixed drug eruption [2], and Stevens-Johnson syndrome [3].

SDRIFE is a type IV hypersensitivity reaction, characterized by 5 criteria: exposure to a systemically administered drug either following the first or subsequent dose, sharply demarcated erythema of the gluteal/perianal and/or inguinal/perigenital area, involvement of at least 1 other intertriginous/flexural localization, symmetry of affected areas, and absence of systemic symptoms and signs [4].

There has only been 1 published case of SDRIFE due to COX-2 inhibitors. It involved a woman who developed symmetric pruritic erythematous patches on the abdominal, inguinal, and gluteal areas 4 days after the oral administration of celecoxib. The patient underwent an SBOCT with celecoxib, which yielded a positive result 6 hours after the intake of 100 mg. Patch tests with celecoxib as is, 50%, and 10% (all in petrolatum) were negative. Etoricoxib was not tested [5].

We have reported a case of SDRIFE due to etoricoxib confirmed by a positive SBOCT and a positive patch test. To our knowledge, this is the first published case of SDRIFE caused by etoricoxib. Cross-reactivity with celecoxib was demonstrated by a positive patch test. In such cases, avoidance of all COX-2 inhibitors should be considered.

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Conflicts of Interest

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Previous Presentation

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A Desensitization Method to Maintain Enzyme Replacement Therapy in Mucopolysaccharidosis Type VI

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Palabras clave: Mucopolisacaridosis VI. Terapia de reemplazo enzimático. Reacción anafiláctica. Desensibilización.

Mucopolysaccharidosis type VI (MPS-VI) is a progressive lysosomal storage disease characterized by dermatan and chondroitin sulfate accumulation in many tissues and organs due to N-acetylgalactosamine 4-sulfatase enzyme deficiency [1,2]. Disease-specific treatment with galsulfase exists. Adverse reactions reported during infusion are fever, pruritus, rash, urticaria, headache, hypotension/hypertension, abdominal pain, shortness of breath, chills, joint pain, hypersensitivity, and anaphylaxis [3]. The rate of serious reactions is 2%, and severe infusion-associated reactions have been described as infrequent. Clinical trials have not produced sufficient data for management considerations[4].

Here we report a case of a recurrent serious infusion-associated reaction in the fourth year of treatment that was successfully managed with a different method of desensitization to that described.

A 5-year-old boy with thickened facial features and an inability to walk was admitted to our department with urinary and fecal incontinence. This boy was born from the mother's seventh pregnancy and was her only surviving child. Three prior pregnancies had ended in stillbirths, and of the siblings born alive, all boys, 1 died of myelomeningocele at the age of 2 months, and the other 2 died at the ages of 5 and 7 years; they had had similar symptoms to those of our patient. On physical examination, the patient's height and weight were in the third percentile. Thickened facial features, dolichocephaly, corneal opacity, upper airway obstruction, pectus carinatum, kyphoscoliosis, claw hand, joint range-of-motion limitations, bilateral inguinal hernia surgery scars, and a large Mongolian spot were present.

Aortic and mitral valve prolapse, mitral and tricuspid valve regurgitation were detected on cardiac evaluation, and dysostosis multiplex was evident on radiological examination. Arylsulfatase B (ASB) activity was 0 in the enzyme analysis (activity of 7.14 in the control assay), and a homozygous c.962t>C (p.l321p) mutation was identified in the ASB gene. The same mutation was first described in homozygosis in a patient with an intermediate phenotype born from a consanguineous marriage [5]. Based on these findings, a diagnosis of MPS-VI was made. Following successful decompression surgery for spinal cord compression, the patient started walking and urinary-fecal incontinence improved following enzyme replacement therapy (ERT) for 1 year.

Galsulfase ERT at 1 mg/kg weekly was initiated. Pheniramine was administered intravenously at a dose of 1 mg/kg as premedication for the first 3 infusions. In the fourth year of treatment, the patient developed a generalized rash over the entire body and on the lips following enzyme infusion for 4 hours.

At the time the rash developed, the blood pressure measurement was 110/70 mm Hg, and no decrease was detected. Infusion was stopped, and 1 mg/kg methylprednisolone and 1 mg/kg pheniramine were given. After 2 hours, when the rash had completely disappeared, infusion was resumed at a lower rate. An urticarial rash was observed again after 10 minutes. The lips and eyes were also swollen, and cyanosis developed. Saturation was measured as 83%, and agitation was observed. Blood pressure was measured as 90/55 mm Hg.

At this point, the infusion was terminated, and oxygen and intramuscular adrenaline were administered, followed immediately by 2 mg/kg intravenous (IV) methylprednisolone and 1 mg/kg pheniramine. The patient improved and was discharged without completing enzyme treatment. Neutralizing antibody activity detection was 0 dilution factor (DF), and anti-rhASB (1 770 000 DF) antibodies were detected in an enzyme-linked immunosorbent assay–based antigen–antibody assay at 4 weeks after the reaction. A skin test was not performed because of the anaphylactic findings, and causality was definitive for this reaction.

The drug hypersensitivity reactions observed in the patient were considered to be IgE-mediated. Because a standard sample desensitization has not been previously reported in the literature, we prepared a patient-specific treatment program (Table). As premedication, we administered an infusion of 1 mg/kg IV methylprednisolone and 1 mg/kg IV pheniramine 12 hours and 2 hours before the enzyme infusion, respectively. Three vials were given consecutively after reconstitution because the duration of enzyme activity in the formulation is 24 hours.

The aim of this procedure was to use the full enzyme preparation. ERT was given over approximately 42 hours, as specified in the protocol, for 24 courses of treatment in total. Urticaria and anaphylaxis were not observed during this period. The skin prick test was applied by standard methods using a solution of 1 mg/mL galsulfase in month 6 [6,7]. Because the skin prick test was negative, a 1:1000 dilution intradermal skin test was performed, yielding an induration and hyperemia measuring 30×36 mm and 10×16 mm, respectively. The histamine reaction used as a positive control was measured as an edematous reaction of 5×5 mm and a hyperemia of 20×20 mm. Physiological saline was used as a negative control, and no reactions were observed.

The protocol was well tolerated. In the desensitization protocol, the enzyme infusion time was gradually reduced after 6 months without adverse effects. Our patient has received ERT in 4-hour infusions in the last 2 months. During and

Table. One-Year Enzyme Replacement Therapy (ERT) Desensitization Protocol

Time	Steroid Administration and Dosage	Total Steroid Dose	Antihistamine Administration and Dosage	Total Anti-Histamine Dose	Duration of Infusion	Allergic Reaction
6 mo (every wk)	1 mg/kg 12 h before ERT 1 mg/kg 2 h before ERT 1 mg/kg ERT 1 mg/kg 24 h after ERT	4 mg/kg	Before starting ERT 1 mg/kg 24 h after ERT	2 mg/kg	42 h (14 h per vial)	None
6 mo (every wk)	1 mg/kg 2 h before ERT 1 mg/kg before starting ERT	2 mg/kg	2 h before ERT 1 mg/kg at the beginning of the third vial of ERT	2 mg/kg	40 h Gradually reduced to 4 h (time of administration for vials reduced weekly by half an hour; total of 1.5 h per vial)	None
1 mo (every week)	1 mg/kg 2 h before ERT 0.5 mg/kg before starting ERT	1.5 mg/kg	1 mg/kg before starting ERT	1 mg/kg	4 h	None
End	0.5 mg/kg 2 h before ERT 0.5mg/kg before starting ERT	1 mg/kg	0.5 mg/kg before starting ERT	0.5 mg/kg	4 h	None

after this protocol, no adverse effects were seen in relation to corticosteroid use.

To continue ERT in MPS-VI patients receiving rhASB, corticosteroid use may be considered 12 hours and 1 hour before the infusion when an infusion reaction develops despite using antipyretics and antihistamines [3]. In the literature, there is no standard desensitization program, and only a small number of cases involving treatment of infusion-associated reactions have been reported [8,9]. Complications and/or adverse effects from the long-term use of corticosteroids administered for desensitization were not detected in our patient. Considering the potential benefits, the objective in this case was to continue ERT, and indeed, we identified multisystemic positive effects with this therapy in our patient. Our premedication and desensitization protocol has been beneficial in this case, but more reports of desensitization management in a larger number of cases are needed to develop a standardized protocol for infusion-associated reactions.

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Successful Desensitization to Cetuximab in a Patient With a Positive Skin Test to Cetuximab and Specific IgE to Alpha-gal

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Cetuximab (Erbitux, Merck KGaA) is an IgG1 chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). It is approved for the treatment of RAS wild-type metastatic colorectal cancer as well as head and neck cancer. Severe reactions tend to occur during the first administration [1]. In 2008, severe anaphylactic reactions after the first infusion of cetuximab were reported for the first time, and the authors demonstrated that pre-existing specific IgE (sIgE) antibodies to galactose-alpha-1,3-galactose (alpha-gal) were responsible for the reactions [2]. Alpha-gal is present on the Fab portion of the cetuximab heavy chain. Very few cases of desensitization to cetuximab have been described since these first reports of severe reactions [3-5]. Moreover, in recent years, severe hypersensitivity reactions to red meat with a delay of several hours have been reported in patients with IgE to alpha-gal [6].

Here, we present the case of a 50-year-old man without a previous history of atopy or drug allergy who was diagnosed with pyriform sinus squamous cell cancer in 2014. The cancer was treated by surgery followed by chemotherapy and radiation therapy. The disease progressed, however, and a year later the patient was diagnosed with lung metastases.

In April 2015, the patient experienced dizziness, severe hypotension, visual disturbances, and chills 15 minutes after starting to receive the first dose of intravenous cetuximab. The infusion rate was 5 mg of cetuximab per minute, as recommended by the manufacturer. No urticarial reactions were noted. Prior to administration, the patient had been prophylactically treated with intravenous ondansetron, dexamethasone, ranitidine and dexchlorpheniramine. The infusion of cetuximab was stopped, and the patient showed gradual improvement with the administration of corticosteroids and fluid therapy. Epinephrine was not administered at the discretion of the oncology infusion service. Serum tryptase was not measured during the reaction. The patient did not receive the previously programmed first dose of paclitaxel

Table. 10-Step Cetuximab Desensitization Protocol Modified From Madrigal-Burgaleta et al [7][a]

Total Dose	440 mg		Solution Concentration		Total Dose in Each Solution, mg	
Solution A	250 mL		0.03520 mg/mL		8.8000	
Solution B	250 mL		0.35200 mg/mL		88.000	
Solution C	250 mL		1.48896 mg/mL		372.24	
Step	Solution	Rate, mL/h	Administered Volume, mL	Time, min	Administered Dose, mg	Cumulative Dose Infused, mg
1	A	88	22	15	0.0	0.0
2	A	100	25	15	0.88000	0.88000
3	A	200	50	15	1.76000	2.64000
4	A	400	100	15	3.52000	6.16000
5	B	88	22	15	0.0	6.16000
6	B	100	25	15	8.80000	14.96000
7	B	200	50	15	17.6000	32.56000
8	B	400	100	15	35.2000	67.76000
9	C	88	22	15	0.0	67.76000
10	C	125	250	120	372.24000	440.00000

[a]The solutions were prepared by the pharmacy department's cytotoxic unit. Hong et al [5] argued that they did not dilute their solutions because cetuximab is distributed at a fixed concentration in a proprietary buffer solution. However, the pharmacy department at our hospital did not find any warning from the manufacturers or any other data indicating that diluted or very diluted cetuximab in a saline solution could affect its stability or properties.

as associated therapy for his cancer, although a week later he started to receive a weekly therapeutic dose of paclitaxel, which he tolerated well. The patient was referred to our drug allergy unit for evaluation following this reaction.

Skin prick and intradermal tests were performed with cetuximab. The skin prick test with undiluted cetuximab (5 mg/mL) was negative, but the intradermal test (1:1000 dilution) was clearly positive. The skin tests were performed in accordance with previously published recommendations [7]. Although skin tests with cetuximab have not been yet validated, there are several reports of the absence of nonirritant reactions with even higher concentrations than the one we used [5-8]. We measured baseline serum tryptase and total IgE and specific IgE levels to alpha-gal using the ImmunoCAP system. The serum tryptase level was normal (4.2 µg/L). Total IgE was elevated (112 IU/mLl) and specific IgE against alpha-gal was positive (1.14 kU/L). Thus, the patient was diagnosed with IgE-mediated hypersensitivity to cetuximab demonstrated by in vivo and in vitro tests. We suggested to his oncologist that cetuximab administration could be achieved via a desensitization protocol, as demonstrated for other antineoplasic agents. The oncologist approved this option.

Cetuximab desensitization was pursued after specific informed consent was obtained from the patient. We used a 10-step rapid desensitization protocol as previously described by Madrigal-Burgaleta et al [7] (Table). This protocol is a modified, shorter version of the standardized Brigham and Women´s Hospital protocol [9] and lasts approximately 255 minutes. It also complies with the safety measures defined for hazardous drug handling by nursing staff. We use this protocol to achieve desensitization to different drugs at our drug allergy unit. All desensitizations are performed at this unit, which has a dedicated area containing 10 beds for patients with drug allergy problems. The area is located very near to the hospital's intensive care unit. The patient was provided with one-to-one nurse to patient care, with surveillance by trained expert personnel, as recommended [1,5,7,9]. We administered a total cumulative therapeutic dose of 440 mg of cetuximab (250 mg/m^2). Three different solutions of cetuximab (A, B, and C) diluted in 250 mL of sodium chloride were used. Premedication with oral acetylsalicylic acid (300 mg) and montelukast (10 mg) daily was administered on the 2 days prior to desensitization as well as on the day of the procedure. Just before starting the desensitization procedure, we administered intravenous dexchlorpheniramine (5 mg) and dexamethasone (12 mg) following the manufacturer's instructions, in addition to intravenous ondansetron (8 mg) and ranitidine (50 mg). Throughout the desensitization, the patient's vital signs remained stable, and no symptoms were observed.

We repeated this protocol weekly for 9 consecutive weeks with the same cumulative dose of cetuximab, recommended by the oncologist. On all occasions, the patient's vital signs remained stable, and no symptoms were noted. After these 9 weeks we retested specific IgE against alpha-gal, and the result was negative (0.15 kU/L).

In 2009, Jerath et al [3] described the use of a successful cetuximab desensitization regimen in a patient with an IgE-mediated hypersensitivity reaction who required continuation of treatment, similarly to our patient. They used 5 different solutions of cetuximab and 20 steps, and described pre-existing detectable anti-cetuximab IgE antibodies (1.06 kU/L). However, they did not perform skin tests with cetuximab. In the same year, Saif et al [4] attempted empirical desensitization in 2 patients who had had acute reactions to panitumumab, a humanized monoclonal antibody against EGFR. These patients were successfully switched to cetuximab therapy using this empirical desensitization protocol. However, it is unclear whether either of the patients described had hypersensitivity

to cetuximab, because neither of them had received cetuximab previously or been evaluated for the presence of preformed anti-cetuximab IgE.

In a later study, Hong et al [5] reported a successfully managed hypersensitivity reaction using a 1-solution, 5-step desensitization protocol. Skin tests to cetuximab were positive on intradermal testing using a 1:10 dilution. The protocol was carried out 7 times and the patient showed no reactions on any of the occasions. The authors did not measure specific IgE to cetuximab. A strong correlation between the occurrence of hypersensitivity reactions to cetuximab and the presence of anti-cetuximab IgE in the sera of patients before an initial injection of cetuximab has been demonstrated, and fatal reactions have even been reported [10].

In conclusion, we have described a successful, safe weekly cetuximab desensitization protocol in a patient with an IgE-mediated hypersensitivity systemic reaction to cetuximab, demonstrated by both a positive skin test to cetuximab and specific IgE to alpha-gal. Early signs of anaphylaxis, such as cutaneous symptoms, may not have been present on the day of the reaction because the patient was premedicated before receiving cetuximab. Desensitization protocols such as the one described here permit patients to continue safely with first-choice therapies, leading to improved prognosis. The protocols should be implemented with the involvement of a multidisciplinary team and drug desensitization experts in appropriate facilities. To our knowledge, there have been no previous reports of successful desensitization to cetuximab in patients with both a positive skin test and specific IgE. Of particular note in our case is the negative result for specific IgE against alpha-gal after desensitization. Others patients with demonstrated hypersensitivity reactions to cetuximab could benefit from using such a protocol.

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A Case of Erythritol Allergy Studied by Basophil Histamine Release and CD203c Expression In Vitro in Addition to a Challenge Test In Vivo

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Erythritol is a natural sugar alcohol produced by glucose fermentation. It is contained in fruit, mushrooms, and fermented foods such as wine, soy sauce, and bean paste [1]. More than 90% of ingested erythritol is not metabolized and is excreted unchanged in the urine. Thus, erythritol is considered to have very few calories (0.24 kcal/g). In Japan, erythritol has been widely used as a sweetener and consumed in low-calorie foods and toothpastes since 1990. Here, we report a case of immediate-type allergy to erythritol, as examined in vitro by the basophil histamine release test (HRT) and the expression of CD203c on basophils, along with an in vivo challenge test with erythritol.

An 18-year-old woman with a history of atopic dermatitis in childhood experienced anaphylaxis after eating desserts on 3 occasions. During the first episode, she experienced systemic urticaria after eating a piece of chocolate cake. During the second episode, after eating jelly containing 11 g of erythritol, she developed systemic urticaria with abdominal pain, and then lost consciousness. During the third episode, this time after eating ice cream, she developed systemic urticaria and had respiratory difficulties. A skin prick test with erythritol dissolved in distilled water showed no reactions, even at a concentration of 200 mg/mL. We then performed an oral challenge test at our hospital. No symptoms were observed with 0.11 g and then 0.37 g of erythritol powder, equivalent to 1% and 3.3% of the erythritol contained in the jelly ingested in the second episode. However, 13 minutes after taking 1.1 g of erythritol (10% of the amount ingested in the second episode), wheals, eyelid edema, oral discomfort, and cough were observed. These symptoms disappeared shortly after treatment with an antihistamine and a corticosteroid. Neither wheezing nor hypotension was induced in this challenge test.

As in vitro tests, we performed an HRT and a basophil activation test (BAT). The HRT with basophils from the patient and 2 healthy adult volunteers did not show any release of histamine by erythritol at concentrations from 0.1 mg/mL to 10 mg/mL (data not shown). By contrast, the BAT, performed with the Allergenicity Kit (Immunotech, a Beckman Coulter Company) showed small, but apparent, surface expression of CD203c on basophils of the patient induced by erythritol in a concentration-dependent manner (Figure). Sucrose, another sugar alcohol, did not induce any changes in CD203c expression on the patient's basophils, and basophils obtained from the 2 volunteers showed no reactions to either erythritol or sucrose. Based on these observations, we diagnosed the

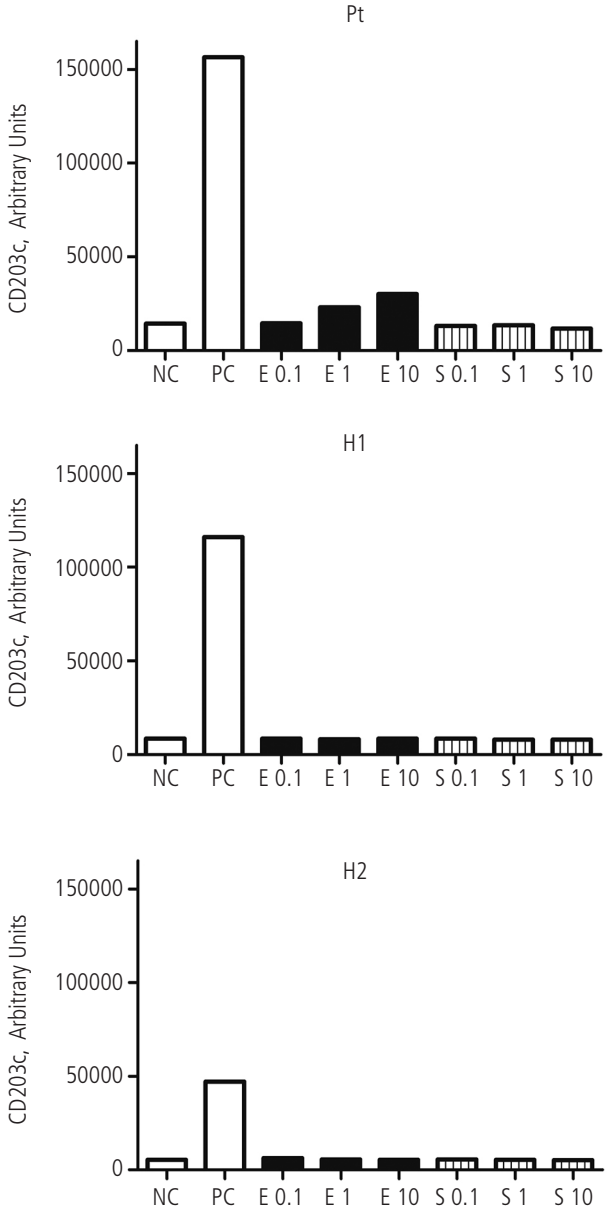

Figure. Basophil activation test (BAT) with erythritol and sucrose. Whole blood of patient (Pt) and 2 healthy adult volunteers (H1, H2) was stimulated with erythritol (E0.1, 0.1 mg/mL; E1, 1 mg/mL; E10, 10 mg/mL), sucrose (S0.1, 0.28 mg/mL; S1, 2.8 mg/mL; S10, 28 mg/mL), negative control (NC), or positive control (PC, anti-IgE antibody supplied in the Allergenicity Kit); the expression of CD203c on basophils was then analyzed by flow cytometry.

patient's reaction as an erythritol-induced immediate-type allergy. We instructed her not to eat food containing erythritol, and to date, she has not experienced any anaphylactic episodes.

As far as our extensive review of the literature revealed, only 7 cases of erythritol allergy, including our case, have been reported [1-5]. The mean (SD) age of the 7 patients is 20.6 (15.4) years old, and 4 of them were female. Five patients undertook oral challenge tests, and they all had positive reactions. Intradermal skin tests with erythritol were performed in 3 cases and they were all positive. However, only 4 (57%) of the 7 patients showed a positive result against erythritol in the skin prick tests, suggesting that a negative skin prick test result by itself is insufficient to rule out erythritol-induced allergy.

The HRT was negative in all 3 patients described in the literature, whereas the BAT was positive in all 4 cases in which it was used. Our case is the first report of the use of both the BAT and HRT against erythritol using basophils from the same patient. In the HRT, peripheral blood basophils are isolated from whole blood and incubated with the substances to be tested; the amount of histamine released from the basophils is measured as an index of activation. The BAT, by contrast, analyzes, via flow cytometry, cell markers (eg, CD203c) expressed on the surface of activated basophils, using whole blood and stimuli. Thus, the performance of the BAT is somewhat more physiological than that of the HRT in that basophils are stimulated in whole blood, rather than by themselves. Generally, small molecules of less than 1000 Da have no antigenicity by themselves in buffer solution. Thus, they must bind to carrier macromolecules such as hapten [6] to evoke an immediate-type allergic reaction. Since the molecular weight of erythritol is small (approximately 122 Da), erythritol alone should not have antigenicity. Previous reports have suggested that erythritol molecules might gain antigenicity by binding to plasma proteins [1,3]. However, pretreatment of erythritol with serum of the patient did not significantly increase histamine release in the HRT (data not shown), implying that mechanisms other than those underlying the "hapten theory" for erythritol might have been involved in our patient. Alternatively, the enhanced expression of CD203c by erythritol may not be related to the degranulation of basophils [7].

In conclusion, we have reported a case of erythritol-induced immediate-type allergy with a negative HRT result and a positive BAT result. To diagnose an allergic reaction with small molecules like erythritol, BAT is worth trying regardless of the result of the HRT.

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Conflicts of Interest

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Previous Presentation

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Anthropometric and Spirometric Correlates of FeNO in Healthy Schoolchildren

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Palabras clave: Óxido nítrico exhalado. Espirometría. Niños. Epidemiología. Fisiología pulmón.

Clinical experience with the measurement of fractional exhaled nitric oxide (FeNO) suggests that this technique has a promising role in the identification of eosinophilic airway inflammation in population-based settings, including epidemiological studies and asthma screening. This noninvasive marker could serve as a potentially useful tool for the detection of early stages of asthma in children on the assumption that a cutoff point of 35 ppb would indicate airway inflammation, while levels of below 20 ppb would make such a diagnosis unlikely [1]. However, more evidence is needed regarding physiological values and determinants of FeNO in healthy children [2,3].

Numerous factors have been found to affect FeNO levels in healthy children, including age, sex, height, weight, diet, atopy, genetics and smoking; of these age is the most important factor [1]. The evidence for other determinants of FeNO in healthy children is less conclusive [4]. In the area of anthropometric variables, chest size could be taken into account as a potential correlate of FeNO levels. Moreover, it cannot be excluded that FeNO levels relate to lung function in healthy children.

The aim of the study was to assess the association between FeNO levels and chest size and lung function in healthy children aged 6 to 9 years, which is an age group frequently chosen for respiratory health surveys. In order to achieve this aim, we analyzed the correlation between FeNO levels and chest circumferences and spirometric variables.

The study was performed in Silesian Voivodeship, Poland. The targeted participants were 525 children from 7 primary schools randomly selected in the towns of Bytom and Chorzów; the parents of 385 of these children agreed to their participation in the project. Based on the answers to the ISAAC questionnaire, 129 children without a diagnosis of asthma, spastic bronchitis, hay fever, atopic eczema or other allergic diseases, chest wheezing out of the cold, and recent dyspnea attacks (in previous 12 months) were included in the study. The measurements included height (cm), body mass (kg), and chest circumferences (cm) during inhalation and exhalation. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio, and indices of forced expiratory flow (FEF) at different percentages of vital capacity (FEF_{25}, FEF_{50}, FEF_{75}) were obtained according to the recommendations of the American Thoracic Society and the European Respiratory Society using an EasyOne spirometer (NDD Medical Technologies); the results were expressed in absolute values and percentage of predicted values [5]. FeNO was measured with the children in a sitting position using the NIOX MINO device (Aerocrine). The test was composed of a maximum of 5 attempts until 1 acceptable measurement was obtained.

The statistical significance of differences in quantitative variables was evaluated using the nonparametric Wilcoxon test. Associations between FeNO levels and spirometric variables, chest size measurements, and demographic variables were examined using Spearman correlation analysis and verified by multivariate linear regression analysis with FeNO as the dependent variable. Separate models were analyzed for each candidate explanatory variable (FVC, FEV_1, FEV_1/FVC, and chest circumferences), controlled for sex, age, and height. Statistical significance was set at a *P* level of less than .05. The study protocol was approved by the ethics committee at the Medical University of Silesia (decision number, KNW/0022/KB1/37/I/14).

The study group was composed of 84 children (girls, 38.1%) aged 6 to 9 years who provided acceptable measurements. FeNO levels were above 20 ppb in almost all the children (90.5%), between 20 and 35 ppb in 8.3%, and above 35 ppb in 1.2% (1 child). Mean (SD) FVC was 104.1% (13.3%) of predicted, mean FEV_1 was 96.8% (10.2%) of predicted, mean FEV_1/FVC was 86.8% (5.9%) of predicted, and mean chest circumference was 61.1 (5.4) cm on exhalation and 65.9 (5.3) cm on inhalation (mean relative difference, 7% [1%]). Mean FeNO was 12.3 (7.9) ppb and individual values did

Table. Association Between Fractional Exhaled Nitric Oxide (FeNO) and Chest Circumferences: Results of Multivariate Regression Analysis

Model FeNO = sex+age+height+:	*P* values for regression coefficients (type III sum of squares)					
	Sex	Age	Height	Chest circumference (exhalation)	Chest circumference (inhalation)	Relative difference of chest circumferences
+ chest circumference (exhalation)	.3	.7	.02	.02	-	-
+ chest circumference (inhalation)	.2	.8	.03	-	.07	-
+ relative difference between chest circumferences	.6	.5	0.1	-	-	.02

not correlate with sex, age, weight, or spirometric variables expressed as percentage of predicted; they were, however, related to height (r=0.25, *P*=.02) and difference between chest circumferences on inhalation and exhalation (r=0.24, *P*=.02). In a set of separate multivariate regression models, FeNO appeared to be associated with chest circumferences and height (Table). On controlling for sex, age, and height, FeNO was not significantly associated with spirometric variables. Children with a FeNO above 20 ppb had similar lung function (% of predicted) compared with the remaining individuals (FVC, 104.1% vs 105.1%; FEV1, 96.8% vs 96.9%; FEF_{25}, 90.9% vs 94.4%; FEF_{50}, 103.4% and 103.7%; and FEF_{75}, 91.1% vs 105.0%). This last difference was statistically significant (*P*=.03).

Our findings showed the role of height and chest size measurements among correlates of FeNO in healthy children. We did not observe the effect of age reported for children younger than 12 years of age [1]. The absence of this effect in our study could be explained by the narrow age span of the children examined.

In asthmatic children the correlation between FeNO levels and spirometric outcomes is weak but interestingly FeNO levels are associated with bronchial responsiveness in children with and without respiratory symptoms [6]. Our study of children without known respiratory disorders showed that FeNO did not correlate with spirometric variables in this group of children, although FEF_{75} levels were lower in children with FeNO above 20 ppb than in children with FeNO below 20 ppb. This finding may suggest potential involvement of a "small airway" component and requires further exploration. Similarly, in a group of 60 healthy Spanish children, no correlations were observed between FeNO and FVC, FEV_1, FEV_1/FVC ratio, or FEF_{50} [7].

In our study, chest size was expressed by 2 measurements: circumference on inhalation and circumference on exhalation. Each of these measurements, as well as the relative difference between them, appeared to correlate with FeNO after adjustment for sex, age, and height. Such a relationship is in line with the concept that FeNO levels are associated with airway size. However, the finding is not supported by the effect of vital capacity on FeNO.

Our study has some limitations. First of all, it involved a small group of individuals. Secondly, the protocol included indirect markers of airway size, namely chest circumferences and lung capacities and volumes. Nevertheless, based on our findings we suggest that the effect of airway size on FeNO cannot be ignored. Studies addressing that issue should contribute to the discussion on physiological values of FeNO with a potential benefit in the field of respiratory epidemiology.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Eosinophilic Esophagitis: A New Possible Comorbidity in Difficult-to-Control Asthma?

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Palabras clave: Asma de difícil control. Esofagitis eosinofílica. Infecciones respiratorias. Esofagoscopia. Enfermedad por reflujo gastroesofágico.

Difficult-to-control asthma is defined as asthma in which associated comorbidities and/or triggers are not controlled or in which other entities that could cause asthma have not been eliminated. These factors hinder the daily control of asthma and complicate the prevention of exacerbations [1].

Gastroesophageal reflux disease (GERD) can occur in association with uncontrolled severe asthma [2], but we now know that many patients diagnosed with refractory GERD in the late 20th century actually had eosinophilic esophagitis (EoE) [3,4].

A 29-year-old woman with a previous history of pollen-induced allergic rhinoconjunctivitis and asthma that clearly improved after pollen immunotherapy administered over 3 years had been asymptomatic for the previous year except for exercise-induced asthma in the springtime. She came to our clinic complaining of nocturnal breathlessness, dry cough, and dyspnea on minimal exertion for the past 6 months, despite treatment with salmeterol and fluticasone (50/500 mcg) and montelukast. Wheezing was observed on physical examination. Spirometry and chest radiography were normal. Skin prick tests were positive to pollens and negative to mites, fungi, and epithelia. Total IgE was 800 kU/L and specific IgE (kU/L) showed high titers to lolium (>100 kU/L), olive (>100 kU/L), and cypress (6 kU/L) pollens. The eosinophil cationic protein showed a figure of 18 mcg/L.

The dose of inhaled corticosteroids was increased, but 2 weeks later the patient required urgent treatment due to an asthma exacerbation. She was discharged from the emergency room within 24 hours, and continued with the same treatment plus a cycle of descending doses of oral corticosteroids.

During the following 4 months she experienced 5 asthma exacerbations, with persistent coughing and an episode of choking, despite treatment with deflazacort. Moreover, she complained of vomiting and epigastric pain over the previous week and had only been able to tolerate liquids in the last 2 to 3 days. On physical examination she showed tachypnea when speaking and scattered wheezing was detected on auscultation. The spirometry showed bronchial obstruction (spirometry 1, Table) with a positive bronchodilator test (14% increase in forced expiratory volume in the first second). A chest x-ray and a computed tomography thorax scan showed a rounded image in the upper lobe of the left lung. The patient was admitted and diagnosed with a lung abscess.

An upper digestive endoscopy was requested but it could not be performed until 3 weeks later due to the intense esophageal edema. When the endoscopy was finally performed, a "ringed esophagus" was found; 5 biopsies of the esophagus were obtained and over 50 eosinophils per high power field (eos/hpf) were detected in all the samples. Biopsies of the stomach and duodenum showed no eos/hpf. The patient was diagnosed with EoE. After 2 months of therapy with omeprazole (80 mg/d), a new upper endoscopy showed over 25 eos/hpf in all the esophageal biopsy samples [3].

The patient improved after treatment with amoxicillin-clavulanic acid, bronchodilators, and oral corticosteroids. At discharge, she continued with her asthma treatment. The patient chose to follow symptomatic treatment for EoE (oral fluticasone 440 ugs/12 h) [5] rather than an elimination diet [6,7].

Six months later, the patient had only mild dysphagia and no symptoms of asthma (spirometry 2, Table) despite a progressive reduction in asthma treatment, which was

Table. Spirometry Results for Patient Over the Course of Evaluation and Treatment[a]

Spirometry	FEV_1, L	FVC, L	FEV_1/FVC	FEF_{25-75}, L/s	PEF, L/s
1	2.05 (68%)	3.21 (93%)	63%	1.31 (34%)	3.30 (48%)
2	3.07 (103%)	3.22 (94%)	95%	3.22 (94%)	4.88 (71%)
3	2.40 (82%)	3.23 (95%)	74%	1.94 (50%)	4.16 (61%)
4	3.08 (105%)	3.28 (96%)	93%	4.68 (122%)	6.67 (99%)
5	2.96 (102%)	3.29 (98%)	90%	4.70 (124%)	7.8 (117%)

Abbreviations: FEV_1, forced expiratory volume in the first second; FEV_{25-75}, forced expiratory flow at 25% to 75% of vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow.
[a]Results shown as absolute values and percentage of predicted.

eventually stopped; she only received oral fluticasone 440 µg/12 h for EoE.

One year later she had no symptoms of esophageal dysfunction. A new esophagoscopy with biopsy was performed; the EoE had subsided (2 eos/hpf) and oral fluticasone was removed. After 25 days, the patient experienced a further exacerbation and came to the emergency room complaining of dysphagia and dyspnea of 1 week's duration. The spirometry data at that time is shown in the Table (spirometry 3). Asthma therapy (salmeterol and fluticasone 50/250 µg) was restarted. A new esophagoscopy confirmed reactivation of the EoE (>30 eos/hpf in the 3 sections of the esophagus). The patient decided to start treatment with an elimination diet. An allergy study including skin tests and specific IgE to milk, cereal, eggs, legumes, fish/seafood, and nuts was negative.

One month after starting the six food elimination diet, the patient was asymptomatic and the spirometry was normal (spirometry 4, Table). No eos/hpf were found in any segment of the esophagus, although the "ringed oesophagus" persisted. The patient experienced asthma exacerbations, with dry cough, dyspnea, and wheezing, a month after introducing milk and again when she started eating legumes; spirometry, however, was normal. A new esophagoscopy confirmed reactivation of the EoE (>50 eos/hpf). There were no histological or clinical signs of reactivation upon introducing the other foods into her diet. The patient is currently following a milk- and legume-free diet and has no digestive symptoms. Further endoscopies have shown no eosinophils and she has only needed rescue salbutamol for isolated asthma attacks in the spring of the last 2 years (spirometry 5, Table) and for mild symptoms triggered by respiratory infections.

We have described a case of a patient with uncontrolled asthma in which respiratory and esophageal symptoms followed a parallel course. A lung abscess, probably a consequence of microaspirations due to the intense esophageal edema [1], led to the admission of our patient; following this, her asthma got worse whenever her digestive symptoms appeared. On 3 occasions, (upon removing oral topical corticosteroids and after introducing legumes and cow's milk into her diet), she also experienced exacerbation of her asthma. The patient's EoE has been in remission for the last 2 years, during which time she has been following an elimination diet; she has had only occasional symptoms of asthma. These observations suggest that the EoE in this patient acted as a comorbidity interfering with asthma control.

The approach to severe uncontrolled asthma requires the detection and control of comorbid conditions to control the disease, although it is sometimes difficult to know to what extent the comorbidity influences the development and maintenance of difficult-to-control asthma [8-10]. We suggest investigating symptoms of esophageal dysfunction in such cases, particularly in atopic patients, in order to rule out not only GERD but also EoE.

The clinical course observed in our patient and the results of the studies performed suggest that this patient's difficult-to-control asthma was triggered by a new comorbid disease not described so far: eosinophilic esophagitis due to cow's milk and legumes. More studies, however, are needed to evaluate this association.

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Component-Based Allergen-Microarray: Der p 2 and Der f 2 Dust Mite Sensitization Is More Common in Patients With Severe Asthma

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Key words: Asthma severity. Allergy. Dust mite. Microarray. Component-resolved diagnosis.

Palabras clave: Gravedad de asma. Alergia. Ácaros del polvo. Micromatriz. Diagnóstico por componentes.

IgE-mediated sensitization to aeroallergens, and to dust mite allergens in particular, is an important risk factor for asthma [1]. Some studies have suggested that exposure to dust mite allergens could contribute to the severe form of this disease, showing a positive correlation between dust mite sensitivity and asthma severity [2-3]. Patients with severe asthma are particularly difficult to treat [4]. Thus, accurate identification of specific sensitization is very important for the successful control of severe asthma through appropriate treatments in atopic patients [3]. Skin tests and specific IgE quantification with traditional assays are typically used by clinicians to identify the cause of allergies, but these tests do not provide an absolute predictive value [5]. Molecular diagnosis has recently been introduced into the field of allergology. The ImmunoCAP ISAC test uses more than 100 purified natural and recombinant allergen components spotted onto a microarray plate, allowing the quantification of specific IgE against a large number of allergens with only 30 µL of serum sample. Moreover, this test has been shown to discriminate between genuine allergy and sensitization, and to identify cross-reactivity to proteins with similar protein structures [5-6]. It has been demonstrated both with challenge and epidemiological studies that mite sensitization is a marker of allergic asthma [7-9]. The main dust mite allergens are proteins from *Dermatophagoides pteronyssinus* (Der p) (Der p 1, Der p 2 and Der p 10) and *Dermatophagoides farina* (Der f) (Der f 1 and Der f 2), and high cross-reactivity between different dermatophagoides allergens from groups 1 and 2 has been demonstrated [6].The ImmunoCAP ISAC technique could therefore be of interest in this context. To confirm that dust mite sensitization is a marker of asthma severity and to determine whether the ImmunoCAP ISAC test allows discrimination between patients with intermittent,

Table. Demographic and Clinical Characteristics of the Patients and Results of the Study[a]

Characteristics	Groups According to Asthma Severity			Total Population (n=126)	*P* Value[b]
	Intermittent (n=39)	Mild to Moderate (n=42)	Severe (n=45)		
Mean age, y	34.7	37.5	47.9	40.4	<.0001
Range	18-66	18-68	21-74	18-74	
SD	12.8	12.6	15.7	14.9	
Sex, No. (%)					
Men	18 (46.2)	14 (33.3)	20 (44.4)	52 (41.3)	.436
Women	21 (53.8)	28 (66.7)	25 (56.6)	74 (58.7)	
FEV_1, % (range)	98.8 (75-128)	82.85 (57-111)	70.69 (28-124)		
Missing values, No.	27	22	19		
Rhinitis, No. (%)	35 (89.7)	36 (85.7)	26 (57.8)	97 (77.0)	.0006
Conjunctivitis, No. (%)	33 (84.6)	24 (57.1)	8 (17.8)	65 (51.6)	<.0001
Treatment, No. (%)					
Inhaled corticosteroid	10 (25.6)	42 (100.0)	45 (100.0)	97 (77.0)	
β_2-agonist (long-acting)	18 (46.2)	30 (71.4)	42 (93.3)	90 (71.4)	
Results					
Skin prick test sensitization, No. (%)					
Dust mite allergen	19 (48.7)	23 (54.8)	29 (65.9)	71 (56.8)	.273
Birch pollen	21 (53.9)	17 (40.5)	7 (15.9)	45 (36.0)	.001
ImmunoCAP ISAC, No. (%)					
Dust mite allergen	17 (43.6)	17 (40.5)	29 (64.4)	63 (50.0)	.052
Birch pollen	25 (64.1)	17 (40.5)	13 (28.9)	55 (43.7)	.005
Sensitization to Der p 2, No. (%) (ImmunoCAP ISAC)	14 (35.9)	14 (33.3)	26 (57.8)	54 (42.9)	.040
Sensitization to Der f 2, No. (%) (ImmunoCAP ISAC)	14 (35.9)	14 (33.3)	28 (62.2)	54 (44.4)	.011

Abbreviation: FEV_1, forced expiratory volume in the first second.
[a]Percentages of positive skin prick test and specific IgE results by ISAC microarray were calculated for birch pollen (Bet v 1 and Bet v 4) and dust mite (Der p 1, Der p 2, Der f 1, Der f 2, Der p 10, and acarieneur2).
[b]*P* values, calculated using the χ^2 test, show differences of proportions between the 3 groups (intermittent asthma, mild to moderate asthma, and severe asthma).

mild to moderate persistent, and severe persistent asthma according to sensitization profiles, we compared aeroallergen sensitization profiles of patients with atopic asthma by using the skin prick test and the ISAC technique. This study was performed in 2011 drawing from the data of 126 patients aged 18 to 74 years diagnosed with atopic asthma in the pneumology department of the University Hospital of Strasbourg in France. The following clinical data were collected from the patients' medical records: forced expiratory volume in the first second (FEV_1), rhinitis and conjunctivitis diagnosis, treatments, and skin prick tests results. Patients treated with omalizumab and patients with nonatopic asthma were excluded. The patients included in this study were divided into 3 groups based on their asthma severity (intermittent, mild to moderate persistent, and severe persistent) according to the former Global Initiative for Asthma classification [10]. Serum samples kept at -20°C were defrosted in order to perform the ImmunoCAP ISAC test. Skin prick tests were performed using commercial extracts of a panel of aeroallergens including dust mite, cat, and pollens (ash, grass, and birch pollen) (Stallergenes). Skin reactions were assessed after 20 minutes. Results were considered positive when the mean wheal diameter was at least 3 mm greater than the negative control. Serum specific IgE was quantified for all patients using the commercial allergen microarray ImmunoCAP ISAC version CRD103 following the manufacturer's instructions (Thermo Fisher Scientific, Phadia SAS). Values superior to 0.3 ISAC Standardized Units (ISU) were considered positive according to the manufacturer's recommendation. Percentages from the 3 asthma severity groups were compared using the χ^2 test, while means were compared using 1-way analysis of variance. All analyses were performed using SAS version 9.3 (SAS Institute). Differences were considered statistically significant when the *P* value was less than .05. Of the 126 individuals enrolled in our study 39 had intermittent asthma and 87 had persistent asthma (mild to moderate in 42 cases and severe in 45). The characteristics of the patients and results are presented in the Table. The patients' mean age was significantly higher in the severe asthma group, and rhinitis and conjunctivitis were significantly less frequent in these patients. Skin prick test results showed no significant differences between the 3 groups of asthmatics for sensitization to dust mite, cat, grass, and ash allergens. However, birch

pollen sensitization was significantly less common in patients with severe persistent asthma (15.9%) than in those with intermittent asthma (53.9%) or mild to moderate persistent asthma (40.5%). The ImmunoCAP ISAC test showed similar results with a significant difference between the 3 groups for birch pollen sensitization only. However, in contrast to the skin prick tests results, the difference across the 3 groups was close to statistical significance for dust mite allergens (*P*=.052). Furthermore, when the intermittent and mild to moderate persistent asthma groups were considered together, the proportion of dust mite sensitivity in this merged group was significantly lower than in the severe asthma group (42.0% vs 64.4%, *P*=.01). This result shows that patients with severe persistent asthma were more sensitized to dust mite than other patients. When dust mite allergens (Der p 1, Der p 2, Der f 1, Der f 2, Der p 10) were analyzed separately, the ISAC results demonstrated significant differences between the 3 groups for Der p 2 (*P*=.040) and Der f 2 (*P*=.011), with more frequent sensitization to both allergens observed in patients with severe asthma. Some studies have suggested a positive correlation between dust mite sensitization and asthma severity [2-3]. However, our skin prick test results did not demonstrate a significant difference in dust mite sensitization across the 3 groups of patients with asthma. Interestingly, the results obtained with the ImmunoCAP ISAC method showed that compared with patients with milder stages of asthma, those with severe persistent asthma were more frequently sensitized to dust mite allergens, especially to Der p 2 and Der f 2. Thus the ImmunoCAP ISAC test allows significant discrimination between patients with severe asthma and others according to dust mite sensitization. Both the skin prick test and the ImmunoCAP ISAC test showed similar results for the other aeroallergens tested. Thus, specific IgE quantification with the ImmunoCAP ISAC test is of interest for asthma severity diagnosis only according to dust mite sensitization.

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Conflicts of Interest

The study authors have received grants from Anergis, Astra-Zeneca, ALK, Amgen, Boehringer, Chiesi, GSK, Novartis, Mundipharma, Roche, Stallergènes and personal fees from Anergis, Astra-Zeneca, ALK, GSK, Novartis, Mundipharma, and Stallergènes.

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