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## Urticaria After Ingestion of Alcoholic Beverages

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Adverse reactions to alcoholic beverages are frequent and could be related to differences in metabolism between different ethnic groups. Asian people, for instance, have impaired alcohol metabolism and experience flushing (*oriental flushing syndrome*) after ingesting alcoholic beverages [1]. Linneberg et al [2] showed that Caucasians from Denmark with genetically determined fast metabolism of ethanol had an increased risk of alcohol-induced hypersensitivity reactions—much in the same way as Asian people—albeit because of different genes. Adverse reactions to the alcoholic beverage may also be due to foods [3] and food additives, such as preservatives [4]. Several authors have reported adverse reactions to alcohol and its metabolites (acetaldehyde [5,6] and acetic acid [7,8]).

We present the case of a 25-year-old woman with a personal history of atopy (allergic rhinitis) who complained of generalized urticaria and nausea immediately after ingestion of different alcoholic beverages (Port wine, white wine, vermouth, and beer), even in small amounts. The patient had been having these reactions for about 18 months. She had not experienced reactions to soft drinks (eg, nonalcoholic beer), vinegar, or foods, including foods cooked with alcoholic beverages. The episodes only occurred after ingestion of alcohol. She was referred to our immunoallergology outpatient clinic for an extensive diagnostic workup comprising a complete blood count, biochemistry, determination of serum immunoglobulins, skin prick tests with aeroallergens, and prick-prick tests with the suspect alcoholic beverages (Port wine, white wine, vermouth, and beer). The results of the blood tests were all normal, and those of the prick tests with aeroallergens were positive to grass pollen (4 mm) and *Dermatophagoides pteronyssinus* (4 mm) (Merck-Serono). Prick-prick tests with alcoholic beverages were negative. We then performed a single-blind oral challenge test with ethanol absolute (96°) diluted in orange juice (Compal Fresh), starting with a dose of 200 mL of orange juice alone (placebo), which was latter combined with 5 mL of ethanol. Twenty minutes after this dose, the patient reported palmar pruritus with no other symptoms. Therefore, we administered another dose of orange juice and 5 mL of ethanol. About 15 minutes later she complained of palmar and plantar pruritus, which was accompanied by erythema and

urticaria on the anterior surface of the left arm. Oral cetirizine was administered, and her condition resolved completely after 1 hour. We subsequently performed prick-prick tests with ethanol absolute (at concentrations of 10% and 96%), acetic acid (at 0.6%, 1.2%, and 9.6%), and acetaldehyde (at 0.1%, 1%, and 10%) [9]. The results were positive for acetic acid at 1.2% and 9.6%, with mean wheal diameters of 3 mm and 5 mm, respectively. We also performed prick-prick tests with acetic acid at 3 concentrations in a control group of atopic and nonatopic patients (3 each). The results were negative. Finally, the patient underwent a placebo-controlled, single-blind oral challenge test with increasing doses of sodium metabisulfite (Bial-Aristegui, 10 mg up to a cumulative dose of 100 mg). The results were negative.

We report the case of a patient who experienced urticaria immediately after ingestion of various alcoholic beverages (even in small amounts). The clinical history suggests that alcohol is the culprit agent, since the patient tolerated all other foods and had never experienced a reaction to food not ingested simultaneously with alcoholic beverages. Furthermore, the patient tolerated meals cooked with alcoholic beverages; consequently, it seems that alcohol was responsible for the reaction, since alcohol evaporates when cooked. The patient also tolerated processed foods that are traditionally high in additives such as sulfites. Therefore, we started the workup by performing skin prick tests with the drinks involved (Port wine, white wine, vermouth, and beer), and the results were negative. We then performed an oral challenge test with alcohol, which seemed to be the causative agent. We used a previously described protocol [9], with orange juice both as placebo and as a vehicle for the intake of alcohol, which was administered at increasing doses (5, 10, and 15 mL; 30 minutes between each dose). We chose to repeat the first dose of alcohol instead of increasing it, because the patient experienced palmar pruritus after intake of 5 mL. Unlike Ehlers et al [1], who did not record positive results until a cumulative dose of 30 mL was reached, we observed a reaction after a cumulative dose of only 10 mL. Furthermore, the reaction was similar to that initially reported by the patient (Figure). Alcohol is metabolized within minutes after ingestion in acetaldehyde and acetic acid [10]. Therefore, after establishing alcohol as the culprit agent, we continued to study whether these metabolites were implicated by performing skin prick tests to acetic acid at nonirritant concentrations [9]. The results were positive for the patient but negative in the controls. Finally, the oral challenge test with sulfites was negative, thus ruling out involvement of the most commonly implicated additives in adverse reactions to alcoholic beverages. Keller and Schwanitz [5] suggested that a positive reaction with a small amount of alcohol, together with a positive skin prick test result to acetic acid, supports the hypothesis that the metabolite is responsible for symptoms. However, the authors did not consider this mechanism to be a type I hypersensitivity reaction and preferred the term

anaphylactoid reaction. On the other hand, Boehncke and Gall [9] showed that in patients for whom alcohol itself was the culprit agent, reactions were observed at a higher cumulative dose of alcohol (>30 mL) in the oral challenge test, whereas all skin test results were negative.



Figure. Patient's reaction to ethanol oral challenge test. A, Urticarial lesions on the arm; B, Palmar erythema.

We report the case of a patient with immediate-type reaction to alcohol. Given the patient's history and the results of the diagnostic workup, we think that the causal agent is acetic acid. The reaction appears to be IgE-mediated.

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#### Conflicts of Interest

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#### Previous Presentation

Data from this study were presented in poster form at the 32<sup>nd</sup> meeting of the Portuguese Society of Allergology and Clinical Immunology (SPAIC).

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## Generalized Urticaria Due to Yellow Pitahaya (*Selenicereus megalanthus*)

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**Key words:** Food allergy. *Selenicereus megalanthus*. Yellow pitahaya. Cactaceae family.

**Palabras clave:** Alergia a alimentos. *Selenicereus megalanthus*. Pitahaya amarilla. Familia Cactaceae.

Pitahaya, also known as dragon fruit, belongs to the Cactaceae family. There are 2 varieties: red pitahaya, which is from Central America, and yellow pitahaya (*Selenicereus megalanthus*), which is from Asia. Yellow pitahaya has a grayish-white flesh, with numerous edible black seeds and yellow skin. It is generally consumed fresh and is used to prepare soft drinks, juices, jelly, ice cream, and yoghurt. We report the case of a patient who was referred to our department because of an allergic reaction after eating fresh yellow pitahaya on 2 occasions.

The patient was a 7-year-old girl who complained of intense pruritus on her neck and back after eating yellow pitahaya. The pruritus resolved several hours after administration of oral dexchlorpheniramine at home. One week later, 5 minutes after eating yellow pitahaya, she presented generalized pruritus, facial erythema, and urticaria, which resolved after administration of antihistamines and corticosteroids in the emergency department. The patient tolerated other fruits, nuts, and vegetables and had no reactions to latex. The only remarkable feature of her clinical history was mild new-onset rhinitis in spring for which she had not received treatment.

Skin prick tests were performed with profilin, latex (ALK-Abelló), fruit, nuts (Leti), commercial extracts of the most common pollens in our catchment area, and commercial peach extract containing lipid transfer protein (LTP) (30 µg/mL, ALK-Abelló). The only positive result was for Gramineae. A prick-to-prick test with yellow pitahaya was negative for both skin and flesh. Total IgE was 16 kU/L. Ten minutes after an oral challenge with yellow pitahaya (half a fruit), the patient developed pruritic wheals on her back, abdomen, and arms. The symptoms resolved with intramuscular methylprednisolone and dexchlorpheniramine.

In order to study the yellow pitahaya allergens recognized in our patient, we first obtained pitahaya extract, which was lyophilized and triturated before being extracted (10%) in 0.9% saline solution with magnetic stirring for 90 minutes at 4°C. The solution was centrifuged and the supernatant filtered (0.4 µm) before storage in aliquots at -20°C until use.

Both the pitahaya extract and the molecular weight markers were analyzed using SDS-PAGE (16% acrylamide gel) under nonreducing conditions using the method described

by Laemmli [1]. The polyacrylamide gel proteins were transferred electrophoretically onto nitrocellulose strips [2]. Once the transfer was complete, the strips were saturated with 1% casein in phosphate-buffered saline (PBS) for 1 hour at room temperature before being incubated for 18 hours with the patient's serum (diluted 1:5). As a negative control, 1 strip containing the same extract was incubated with 1% casein in PBS. After washing with 0.1% Tween-20 in PBS, the strips were incubated for 2 hours at room temperature with anti-human IgE monoclonal antibody HE-2 ascitic fluid diluted 1:3000 [3]. After further washing, the strips were incubated again at room temperature for 1 hour with rabbit anti-mouse immunoglobulin conjugated to horseradish peroxidase (RAM-HRP, DAKO) and diluted 1:5000. Finally, the strips were washed and the IgE-binding proteins were detected using enhanced chemoluminescence (Amersham Biosciences) following the manufacturer's instructions.

The Figure shows the immunoblot results. The patient's serum IgE recognized proteins of diverse molecular weights in the yellow pitahaya extract. The most intense bands were high-molecular-weight (HMW) bands ranging from 75 kDa to 100 kDa.

Allergy to pitahaya is uncommon and this is the first case reported of allergy to yellow pitahaya. Our search of the literature revealed only 2 cases of pitahaya allergy, and in both cases the allergy was to the red variety. Furthermore, the immunology workup showed that the serum of both patients recognized a band of approximately 1 kDa, which could correspond to the LTP of pitahaya [4,5]. In our patient, only HMW bands were recognized. The most intense bands ranged from 75 kDa to 100 kDa, a finding that coincides with reports by García-Menaya et al [6] in the case of allergy to prickly pear, which also belongs to the Cactaceae family.

In summary, we have presented the first case of allergy to yellow pitahaya, in which an IgE-mediated hypersensitivity mechanism was demonstrated by means of an oral challenge test and an immunology workup. An HMW protein (75-100 kDa) is likely to have triggered the reaction. More complex methods for identifying proteins are necessary to accurately determine the group of food allergens to which this protein belongs.

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### Conflicts of Interest

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**Online Medical Consultations Applied to Allergy**

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**Palabras clave:** Interconsulta no presencial. Alergia. Tecnologías online. Reducción del gasto sanitario. Niños.

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The demand for specialist consultations is growing in the public health service in Navarra, Spain, resulting in longer waiting lists, increased health costs, and undesirable delays in the evaluation of certain patients. Most consultations received at the allergy department in our hospital come from primary care. Improving communication between general practitioners (GPs) and specialists could resolve numerous queries and avoid unnecessary referrals, thereby reducing costs and improving quality of care. However, making decisions based simply on “corridor talk” has negative and even legal implications [1]. The lack of relevant patient information and the absence of a written document recording the exchange of information are the most important obstacles.

The growth of online technologies is a fact in Navarra’s public health system, where all physicians now have access to electronic medical records (EMRs). In 2005, the Primary Care-Allergy Coordination Committee at our hospital designed an online medical consultation model (OMC) to facilitate the rapid exchange of information between GPs and allergists and provide access to additional EMR data to guide clinical decisions. It had the added advantage of leaving a written record of each communication. The slogan used to promote the use of the protocol was “Not sure whether to refer? Make an OMC”. We present the results of our experience with the OMC for the period spanning 2005 to 2011.

The system was designed drawing on the experience of countries with geographically very disperse populations that have created online patient-professional platforms that have produced encouraging results in pilot studies [1,2]. We developed an e-consultation form with the following fields: identification of patient and GP, personal medical history, and reason for consultation. The GP filled in and sent this form to an allergist who within 48 hours issued a report that

was recorded in the EMR and automatically sent to the GP. The report included advice on how to manage the patient and specified whether or not the patient should be referred to the allergy department. A third option was to recommend that the patient be referred at a later stage, i.e. if the allergist's advice did not produce the desired outcome. The committee promoted the protocol through internal communication channels and explanatory visits to primary care centres.

We analyzed the source of (adults vs children) and reasons for OMCs (respiratory symptoms, cutaneous symptoms, adverse drug reactions [ADRs], adverse food reactions [AFRs], doubts about immunotherapy, miscellaneous, and administrative issues). We also recorded the allergists' recommendation (refer, do not refer, act and then refer if necessary).

We received 667 OMCs: 481 (72.1%) for adults and 186 (27.9%) for children. The reasons for the OMCs for the total sample and for adults/children separately were ADRs (185 [27%], 163/22), respiratory symptoms (145 [22%], 97/48), cutaneous symptoms (97 [14%], 76/21), AFRs (92 [14%], 36/56), immunotherapy doubts (52 [7.8%], 48/4), miscellaneous (49 [7%], 29/20), and administration issues (47 [7%], 32/15). In 60% of cases (64% in adults, 50.5% in children), the OMCs were resolved online, and in an additional 13% (14%, 13%), referral was recommended only if the allergist's advice was ineffective. AFRs and

respiratory symptoms were the most common reasons for referral (Figure).

Demand for specialist consultations is increasing exponentially in the Spanish public health system, leading to long wait lists. While specialist consultation (and early intervention) will clearly benefit some patients, for others, it will have little value. We designed our OMC system in the hope that it would reduce unnecessary referrals by facilitating and leaving a legally documented account of communication between GPs and allergists. Because the system needed to be dynamic, we established a deadline of 48 hours.

Almost 75% of the OMCs were resolved online, avoiding unnecessary face-to-face encounters that would have been of little additional value for the patients and resulting in considerable health cost savings. The proportion of cases resolved was higher in adults than in children. The system proved very useful for resolving problems related to immunotherapy, cutaneous symptoms, and diseases of doubtful allergic etiology. Most (88%) of the consultations in these areas were resolved online. ADRs were the main reason for consultation for adults and nearly 70% (17% of all OMCs) were resolved online. In children, referral was recommended for 2 of every 3 ADRs, possibly indicating a different pattern among children (fewer adverse effects, more recent reactions...). A similar proportion of OMCs related to respiratory symptoms were

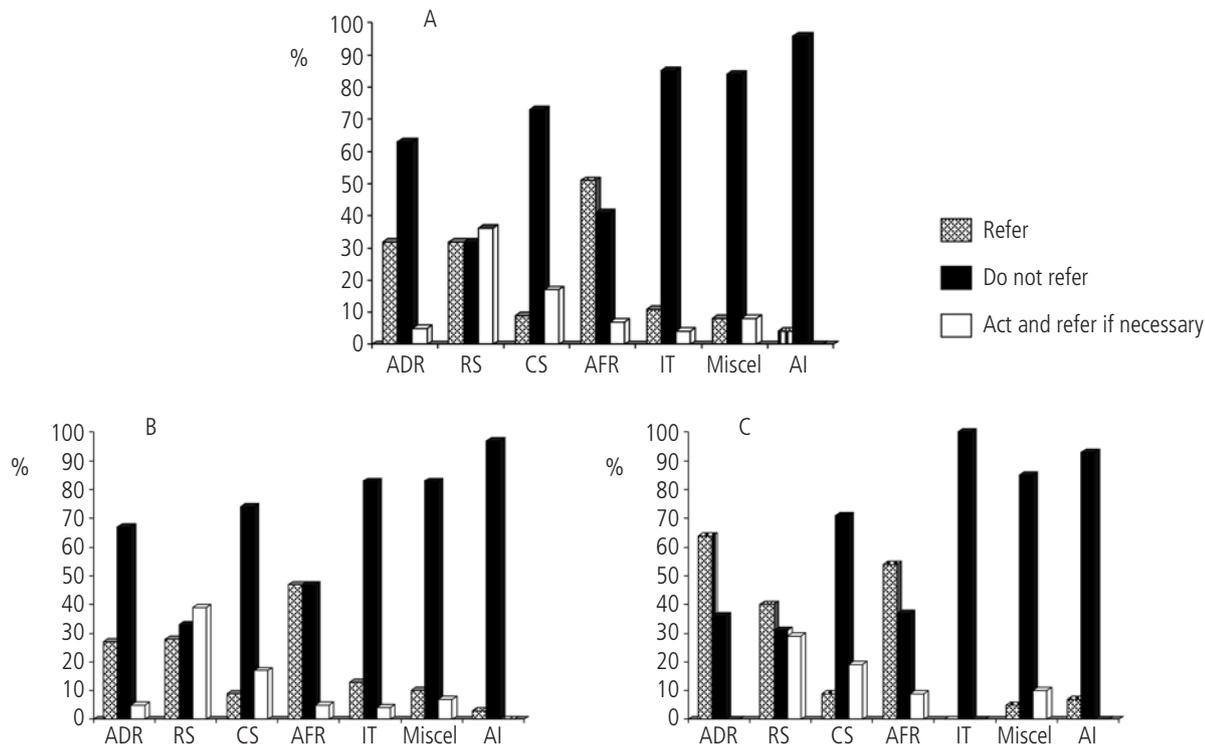


Figure. Advice on referral for whole sample (A), adults (B), and children (C) according to the reason for consultation. ADR indicates adverse drug reaction; RS, respiratory symptoms; CS, cutaneous symptoms; AFR, adverse food reaction; IT, doubts regarding immunotherapy; Miscel, miscellaneous; AI, administrative issues.

resolved in the 2 groups. Referral was recommended for a third of patients, a third of cases were resolved online, and in the remaining third advice was given about additional tests or treatment.

Direct referral was recommended for over half of the queries about AFRs. These were the most common reason for OMCs in children but only the fourth most common in adults, possibly explaining the higher proportion of direct referrals among children (36% vs 22% in adults).

Although the number of OMCs received was modest (667), the project was welcomed by GPs since it allowed them to quickly resolve doubts regarding given cases. Moreover, it served as a deterrent for poorly supported requests for specialist visits.

The literature describes online platforms designed to replace face-to-face primary care consultations [1,2]. These projects have been criticized because of confidentiality concerns and the fact that physicians frequently have to work with incomplete and unstructured information. These shortcomings have led to recommendations to regulate such platforms [3]. The goal of the OMC system at our hospital was not to reduce the number of face-to-face specialist visits but rather to improve the quality of care by avoiding unnecessary visits that could be solved with better communication between GPs and specialists. We designed a system that guaranteed confidentiality and allowed physicians to work with accurate information.

The preliminary results of our OMC project applied to allergy consultations are promising. We think that this project, to our knowledge the first of its kind, is applicable to the Spanish public health system since it helps to reduce workload and improves the efficiency and dynamics of specialist consultations. It also allows a prioritization of cases that will benefit from early intervention and a reduction in costs derived from unnecessary visits.

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#### *Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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## Celiac-Like Sprue in Nijmegen Breakage Syndrome: Successful Treatment With Budesonide

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**Key words:** Nijmegen breakage syndrome. Celiac-like sprue. Malabsorptive enteropathy. Budesonide. Immunodeficiency.

**Palabras clave:** Síndrome de Nijmegen. Enteropatía malabsortiva. Budesonida. Inmunodeficiencia.

Nijmegen breakage syndrome (NBS) is a rare DNA repair disorder characterized by microcephaly, normal intelligence, primary immunodeficiency, and predisposition to cancer [1,2]. It has been reported in different populations but the vast majority of patients are of Slavic origin (Central-East Europe) and are homozygous for a founder mutation of the *NBS1* gene: the 5-base-pair deletion 657del.A.

Lung infections are a common presentation of primary immunodeficiency. Gastrointestinal disorders such as diarrhea, malabsorptive enteropathy, and inflammatory bowel disease may also be the first manifestation of underlying immunodeficiency [3,4]. Patients with NBS usually present with lung infections or lymphoid malignancy. Gastrointestinal manifestations other than infections are not readily recognized in NBS [1,2].

We present a 20-year-old man with NBS who developed malabsorptive enteropathy. Four years earlier, he had been investigated for recurrent lung infections. Hypogammaglobulinemia was detected and substitution therapy with intravenous immunoglobulin (IVIG) was initiated. The diagnosis of NBS was confirmed by mutation analysis of the *NBS1* gene, which revealed the typical deletion.

Laboratory investigations at the time of diagnosis yielded the following results: hemoglobin, 133 g/L; red blood cell count,  $4.5 \times 10^{12}/L$ ; white blood cell count,  $14.7 \times 10^9/L$  with 90% neutrophils and 10% lymphocytes (absolute lymphocyte count,  $910/mm^3$ ); serum proteins, 55 g/L; and albumins, 31 g/L. Immunoglobulin (Ig) levels were decreased: IgA, 0.12 g/L, IgM, 0.18 g/L, and IgG, 0.8 g/L. Phenotypic analysis of peripheral blood lymphocytes revealed a low  $CD4^+$  lymphocyte count, at  $136 \text{ cells}/mm^3$ . The result of qualitative HIV DNA by PCR test was negative.

At the age of 19 years, the patient had started to complain of abdominal discomfort associated with loose, frequent or fatty stools.

Microcephaly and characteristic facial features such as large ears, a prominent midface, and a receding mandible (Figure A) were observed, together with several café-au-lait spots and clinodactyly. The patient's height (175 cm) was normal. His body weight (44 kg) and body mass index ( $14.35 \text{ kg}/m^2$ ) were below the fifth percentile for his age and his head circumference (49 cm) was below the third percentile.

During follow-up, several courses of oral metronidazole were given for presumed giardiasis, without improvement. Repeated stool cultures for pathogenic microbes and smears for *Giardia* species were negative. Microscopic examination of duodenal aspirate and specimens of duodenal biopsy were negative for trophozoites. Histological examination of the duodenal biopsy specimen showed subtotal villous atrophy (Figure B). Serum endomysial and reticulin antibodies, as well as IgA and IgG antibodies against tissue transglutaminase, were negative. Serologic HLA typing showed an absence of celiac disease-associated HLA alleles (HLA-A1, B8, cw7, DQ2, DQ8). The colonoscopic examination was normal.

A gluten-free diet with supplementation with liposoluble vitamins was attempted but the patient's enteropathy worsened. Also, in spite of regular IVIG substitution, the serum IgG trough level decreased from 5 g/L to less than 1.5 g/L. The patient developed symptoms of osteomalacia with excruciating bone pain, restricting his physical activity. The gluten-free diet was stopped 4 months later.

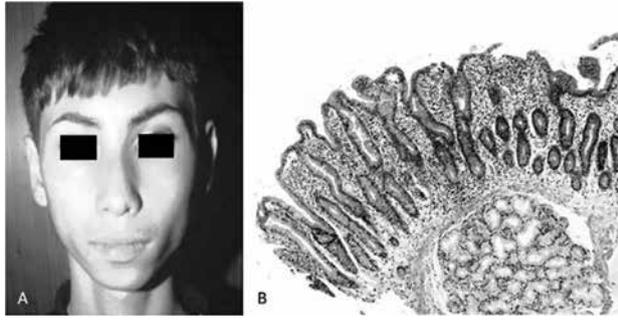
Laboratory investigations performed at that time revealed total serum  $Ca^{++}$ , 1.38 mmol/L (ionized  $Ca$  0.98<sup>++</sup> mmol/L); low phosphorus levels, 0.34 mmol/L; and low serum albumins, 21 g/L. Thyroid function tests were normal and alkaline phosphatase levels were increased (1995 IU/L; normal 300 IU/L). The serum parathormone level was elevated (300 pg/mL; normal range, 18-65 pg/mL).

Oral budesonide at a dose of 6 mg/d together with a high dose of synthetic vitamin D analog and calcium supplementation was started. Over the next 6 months the symptoms of chronic diarrhea subsided and the daily dose of budesonide was reduced to 3 mg and discontinued after 1 year of treatment. He gained weight (up to 50 kg) and was able to sit and walk again. His mineral bone density and serum biochemical analyses normalized. At the same time, stable trough IgG levels above 5 g/L were achieved through standard, monthly IVIG therapy. Duodenal biopsy was repeated and histological examination revealed normal morphology of the small intestine. At the time of writing, 18 months after completion of treatment with budesonide, our patient is in good general health and is free of celiac-like sprue symptoms.

In certain forms of primary immunodeficiency, gastrointestinal disorders such as acute or chronic diarrhea, sprue-like enteropathy, inflammatory bowel disease, or neoplasms may be a cause of significant morbidity.

The true incidence of gastrointestinal disease in NBS is unknown. In the first report of the International Nijmegen Breakage Syndrome Study Group, gastrointestinal infections and chronic diarrhea were reported in only 3 of 55 patients [1]. However, in a preliminary report from the NBS Registry, the frequency of GI infections was 15% [2]. By contrast, 20% to 60% of patients with common invariable immunodeficiency (CVID) develop chronic diarrhea, which is frequently associated with giardiasis [5]. At first, we treated our patient for presumed giardiasis but the symptoms of his enteropathy worsened.

In our patient the diagnosis of celiac-like sprue was confirmed by the histologic finding of flat villous lesions. It



**Figure.** A, Facial characteristics in our patient: microcephaly, prominent midface and receding mandible. B, Photomicrograph of duodenal biopsy specimen revealing diffuse enteritis and subtotal villous atrophy, increase in intraepithelial lymphocytes, enterocytes with stratified nuclei, and hyperplastic, elongated crypts (Marsh stage 3). (hematoxylin & eosin, original magnification x200).

has been proposed that villous flattening observed in CVID is an immune-mediated, inflammatory phenomenon resembling celiac disease but without the presence of gut autoantibodies and without response to a gluten-free diet. Investigations in our patient showed a lack of antibodies to gliadin, endomysium, and tissue transglutaminase, as well as an absence of celiac-associated HLA genes. These findings are similar to those reported for celiac-like sprue in CVID [4]. Altogether, these findings indicate that chronic, noninfectious enteropathy is due to a dysregulated T-cell system. Luzi et al [6] reported that the presence of villous atrophy in CVID was significantly associated with decreased CD4<sup>+</sup> lymphocyte counts (<400/mm<sup>3</sup>), similarly to in our patient.

Systemic steroids have been found to be useful for the treatment of inflammatory bowel disease-like disease or celiac-like sprue in CVID [4,5,7]. In patients with CVID, a gluten-free diet led to additional weight loss in celiac-like sprue, and remission was achieved only with the use of steroids [7]. Steroids are necessary to reduce small bowel inflammation and restore normal mucosal architecture.

Oral budesonide, a synthetic steroid with potent topical glucocorticoid activity but low systemic bioavailability, has been successfully used to treat celiac-like sprue in CVID patients who do not respond to systemic steroids [8,9]. We have reported on the successful use of oral budesonide for celiac-like sprue in NBS.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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### Eleven Cases of Omeprazole Hypersensitivity: Diagnosis and Study of Cross-Reactivity

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**Key words:** Hypersensitivity. Omeprazole. Proton pump inhibitors. Skin tests.

**Palabras clave:** Hipersensibilidad. Omeprazol. Inhibidores de la bomba de protones. Test cutáneos.

Proton pump inhibitors (PPIs) are widely used for the treatment of acid-related gastrointestinal diseases [1]. Omeprazole was the first PPI to be developed, followed by lansoprazole, pantoprazole, rabeprazole, and esomeprazole [2]. Hypersensitivity reactions to omeprazole are rare, although several case series have been published [1,3-5].

We report on 11 cases of allergic reactions to omeprazole that were diagnosed in our department between 2003 and 2013. We used skin tests and/or oral challenges to confirm the diagnosis. Eleven patients (8 women and 3 men) aged 31 to 64

years (mean age, 43.09 years) were referred to our department with adverse reactions to omeprazole. Onset of symptoms was immediate in 5 patients and occurred after 1 hour in the other 6 patients. The symptoms reported were anaphylaxis (4 patients), urticaria (6 patients), and urticaria accompanied by angioedema (1 patient). In 7 patients, other drugs were implicated when the patients described the reaction with omeprazole. These were ibuprofen in 3 patients; amoxicillin-clavulanic acid and ibuprofen in 1 patient; amoxicillin and ibuprofen in 1 patient; amoxicillin-clavulanic acid in 1 patient; and amoxicillin and clarithromycin in 1 patient. We performed a single-blind oral challenge with ibuprofen and skin tests and a single-blind oral challenge with amoxicillin, amoxicillin-clavulanic acid, and clarithromycin. All the results were negative and we therefore ruled out these drugs as casual agents. All the patients had previously tolerated omeprazole. The patients gave their written consent before the skin and oral challenge tests.

Skin prick tests were performed with the undiluted commercial preparation for omeprazole (Normon SA) and esomeprazole (Astra Zeneca SA) at 40 mg/mL, pantoprazole (Combino Pharma SL) at 20 mg/mL, lansoprazole (Normon SA) at 15 mg/mL, and rabeprazole (Janssen-Cilag SA) at 20 mg/mL. Intradermal tests were performed with omeprazole (0.4 mg/mL and 4 mg/mL), esomeprazole (0.4 mg/mL and 4 mg/mL), pantoprazole (0.2 mg/mL and 2 mg/mL), lansoprazole (0.15 mg/mL and 1.5 mg/mL), and rabeprazole (0.2 mg/mL and 2 mg/mL). Histamine and buffered saline were used as positive and negative controls, respectively. The

Table. Results of the Allergy Study

Case	Omeprazole	Rabeprazole	Lansoprazole	Pantoprazole	Esomeprazole	OCT
1	ND	ND	ND	ND	ND	OMEPR +
2	ND	ND	ND	ND	ND	OMEPR +
3	ND	ND	ND	ND	ND	OMEPR +
4	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	OMEPR +
5	SPT + IDT ND	SPT - IDT +	SPT - IDT +	SPT - IDT +	SPT - IDT +	ND
6	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	OMEPR + PANTOP -
7	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	SPT - IDT -	OMEPR ND LANSOP - PANTOP - RABEP -
8	SPT - IDT+	SPT - IDT+	SPT - IDT-	SPT - IDT+	SPT - IDT-	ND
9	SPT + IDT+	SPT - IDT+	SPT - IDT+	SPT + IDT+	SPT + IDT+	ND
10	SPT + IDT+	SPT + IDT+	SPT + IDT+	SPT + IDT ND	SPT + IDT ND	ND
11	SPT - IDT+	SPT - IDT+	SPT - IDT+	SPT + IDT+	SPT + IDT+	ND

Abbreviations: IDT, intradermal test; Lansop, lansoprazole; ND, not done; OCT, oral challenge test; Omepr, omeprazole; Pantop, pantoprazole; Rabep, rabeprazole; SPT, skin prick test.

results of skin tests carried out in 10 control patients, (5 atopic and 5 nonatopic) were negative.

In the case of patients who did not undergo skin tests or who had negative results in these tests, we carried out a single-blind oral challenge with omeprazole and other PPIs to investigate cross-reactivity. Dose were increased at 1-hour intervals, as follows: omeprazole (5, 10, and 20 mg), lansoprazole (3.75, 7.5, and 15 mg), rabeprazole (5, 10, and 20 mg), pantoprazole (10, 20, and 40 mg) and esomeprazole (5, 10, and 20 mg). In nonimmediate reactions, the therapeutic dose was subsequently taken at home every 24 hours for 7 days. The results of the allergy study are shown in the Table.

Skin tests were carried out in 8 of the 11 patients. Patients 1, 2, and 3 did not undergo skin tests, because we only started to perform skin tests with PPIs in 2009 and these patients had already been studied. The result of the oral challenge with omeprazole in these patients (1, 2, and 3) was positive. Patients 1 and 3 experienced generalized urticaria several hours after the challenge (cumulative dose, 35 mg) and patient 2 experienced anaphylaxis (intense itching with hives on the chest and back, dyspnea, and wheezing) 50 minutes after the second dose (cumulative dose, 15 mg). The symptoms of all 3 patients resolved with systemic antihistamines and corticosteroids. Since data on sensitization to omeprazole and cross-reactivity between PPIs were lacking, we advised the patients to avoid this group of drugs.

The skin tests with PPIs were positive for omeprazole in 5 patients (5, 8, 9, 10, and 11). In addition, 3 patients (5, 9, and 10) had a positive skin prick test to omeprazole. All patients with positive skin test results for omeprazole also had positive skin tests results for the other PPIs tested. Patients 5, 9, 10, and 11 tested positively to the PPIs studied, and patient 8 had a positive skin test to rabeprazole and pantoprazole. However, because of cross-reactivity between PPIs, we recommended that the patients avoided this group of drugs.

Patients 4, 6, and 7 had negative skin test results for all the PPIs tested. The diagnosis was based on a positive oral challenge with omeprazole in patients 4 and 6, with a delayed reaction in both. After the oral challenge test, the therapeutic dose was subsequently taken at home every 24 hours for 7 days. Six days after the oral challenge (cumulative dose, 155 mg), patient 4 experienced generalized urticaria. Patient 6 experienced urticaria on her legs 4 days after the oral challenge test (cumulative dose, 105 mg). Patient 7 refused to undergo the oral challenge test with omeprazole. Owing to the negative skin test results and in order to investigate possible cross-reactivity between PPIs, we performed a single-blind oral challenge with the other PPIs. Patient 6 tolerated pantoprazole, and no other PPIs were tested. Patient 7 tolerated lansoprazole, pantoprazole, and rabeprazole. As patient 4 refused an oral challenge with the other PPIs, we recommended avoidance of all the drugs in this group.

PPIs have revolutionized the treatment of acid-related disorders [3]. Omeprazole is widely used, and the incidence of allergic reactions to this agent has increased in recent years [4]. Diagnosis of hypersensitivity to PPIs is difficult, since PPIs are often used in combination with other drugs [1]. Seven of our 11 patients were taking drugs other than omeprazole. Although skin tests have been used to investigate reactions

to PPIs, this is not standard practice. Bonadonna et al [1] analyzed 53 patients with immediate reactions to PPIs and compared the diagnostic performance of skin tests with that of oral challenge tests. Abdul Razzak et al [4] described a series of 9 patients sensitized to omeprazole, of whom 5 had a positive intradermal test result with omeprazole. In a report of 9 patients with IgE-mediated allergy to omeprazole, Lobera et al [3] reported that 8 of the patients had positive skin test results. In our series, we obtained positive skin test results in 5 out of 8 patients.

Bonadonna et al [1] suggested the usefulness of skin tests in patients with immediate hypersensitivity reactions to PPIs, but our findings do not necessarily support this. For example, patients 4 and 6 had negative omeprazole skin tests, yet reacted when challenged with omeprazole. This indicates that the negative predictive value of skin testing is poor. Furthermore, patients 8 to 11 had positive skin tests, but they were not challenged with any PPIs. Therefore, the positive predictive value of skin testing is uncertain. In our series, skin tests were negative in patients with a delayed reaction.

Numerous studies have investigated cross-reactivity between PPIs [1]. Omeprazole and pantoprazole have a methoxy and a difluoromethoxy chain in their benzimidazole ring respectively, whereas lansoprazole and rabeprazole do not. Pérez Pimiento et al [2] described a case of anaphylaxis due to lansoprazole with cross-reactivity to rabeprazole. The authors considered that the analogous chemical structure could have been responsible for the cross-reactivity. Bonadonna et al [1] observed that patients with hypersensitivity to pantoprazole had positive skin test results to omeprazole and, more rarely, esomeprazole. Patients monosensitized to lansoprazole and rabeprazole had negative test results for omeprazole, pantoprazole, and esomeprazole. In our series, we did not observe comparable results.

We have reported on a series of 11 patients sensitized to omeprazole. Diagnosis was based on skin tests and oral challenges. More studies with a larger number of patients are needed to investigate the usefulness of skin tests in patients with immediate hypersensitivity reactions to PPIs.

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***Lolium perenne* Pollen From a Polluted City Shows High Allergenic Potency and Increased Associated Enterobacteriaceae Counts**

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**Key words:** Grass pollen. Pollution. Enterobacteriaceae. Allergenic potency. Asthma.

**Palabras clave:** Polen de gramíneas. Contaminación. Enterobacteriaceae. Potencia alérgica. Asma.

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Numerous studies have shown that air pollution worsens asthma and increases emergency room visits due to asthma exacerbations [1]. However, pollution is also deposited on the ground and can directly affect seed, root, and plant development and bacteria associated with the plant. In addition, the environmental stress generated by pollutants can make pollens more allergenic [2-4].

In recent years, endotoxins from Gram-negative bacteria have been associated with airway inflammation and exacerbations in asthmatic patients; nevertheless, in early childhood, endotoxins may drive immune development towards the nonallergic type 1 helper T cell (T<sub>H</sub>1) profile [5,6]. Gram-negative bacteria and endotoxins have been detected on the surface of allergenic pollen, although the role of these entities in pollinosis remains unclear [7,8].

Against this background, we conducted a study in 2 Spanish cities sharing the same type of pollen and situated about 40 km apart. One was Puertollano, which has intense industrial activity and high levels of pollution, and the other was Ciudad Real, which has a service-based economy and low levels of pollution. The main objective of our study was to determine whether air pollution increases the allergenicity of *Lolium perenne* (ryegrass) pollen collected in Puertollano compared with that collected in Ciudad Real and a commercial sample (Allergon). We selected ryegrass because it is the most frequent cause of seasonal respiratory allergy worldwide. Our secondary objective was to analyze the presence of gram-negative bacteria (Enterobacteriaceae) in pollen samples from the 2 cities.

During the peak pollination period (May), *L. perenne* plants were collected from areas of Puertollano and Ciudad Real 200 to 300 m away from road traffic to reduce the impact of diesel exhaust particles. Mature pollen was obtained by suction.

The grass pollen species from Puertollano and Ciudad Real and the commercial pollen (Allergon) were extracted in 50% wt/vol phosphate-buffered saline (PBS) at 4-8°C. The extracts were stirred for 2 hours (1000 rpm) and the solution

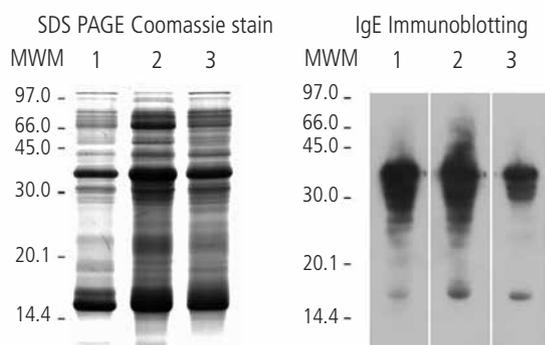
was centrifuged at 10 000g for 30 minutes. The resulting supernatant was passed through glass filters and dialyzed (cutoff 3.5 kDa) against distilled water for 12 hours at 4°C. The extract was then vacuum-filtered through 0.22- $\mu$ m filters (Millipore) and frozen at -20°C for lyophilization. The protein concentration of the final extract was determined by the Bradford assay as previously described.

Proteins from the extract were analyzed using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), according to Laemmli. The binding of IgE antibody to allergens was analyzed using Western blot with a pool of sera from grass-sensitized patients and antihuman IgE peroxidase conjugate (SouthernBiotech). Chemiluminescence detection reagents (Western Lightning Chemiluminescence Reagent Plus Perkin Elmer Inc.) were added according to the manufacturer's instructions.

Enzyme-linked immunosorbent assay (ELISA)-inhibition test of the different grass extracts was performed by preincubating the pool of sera with extracts of the samples (Allergon, Puertollano, and Ciudad Real) at concentrations ranging from 0.040  $\mu$ g/mL to 30  $\mu$ g/mL. After washing with PBS 0.05% Tween 20, plates were neutralized with 1% bovine serum albumin (1 hour at room temperature), washed, and incubated with free-phase samples (2 hours at room temperature). IgE binding was detected using a biotinylated human anti-IgE monoclonal antibody (1:1000; 50  $\mu$ L/well; Operon) followed by incubation with a mouse anti-IgE antibody marked with streptavidin peroxidase. After a final wash, a substrate solution was added and the color was allowed to develop. The enzyme reaction was stopped and the absorbance values were measured at 450 nm.

We also performed a study of Enterobacteriaceae according to the method described by Spiewak et al [7]. Briefly, 10-fold serial dilutions of the pollen sample extracts were prepared, and 0.1 mL of each dilution was spread on duplicate sets of eosin methylene blue agar plates (Difco). The plates were incubated for 24 hours at 37°C. The colonies were counted, and the results were reported as colony forming units (cfu) per gram of pollen.

Immunoblotting showed that *L perenne* pollen from Puertollano had greater recognition than the pollen from Allergon and Ciudad Real (Figure).



**Figure.** SDS PAGE and immunoblotting: lane 1, Allergon; lane 2, pollen from Puertollano; lane 3, pollen from Ciudad Real. SDS PAGE indicates sodium dodecyl sulfate polyacrylamide gel electrophoresis.

Likewise, the ELISA-inhibition test showed a greater inhibition capacity in *L perenne* from Puertollano.

Analysis of Enterobacteriaceae revealed bacterial counts of up to 97 600 cfu/g in the sample from Puertollano compared to 25 600 cfu/g in the sample from Ciudad Real.

We found that *L perenne* pollen from the polluted city showed higher allergenic potency. These results are consistent with those obtained by other authors. Cortegano et al [2] found that *Cupressus arizonica* pollen from polluted areas expressed a large amount of Cup a 3, an allergen belonging to the pathogenesis-related protein family. Aina et al [3] reported that *Poa annua* pollen exposed to cadmium-contaminated soils produced high levels of allergenic proteins. The authors also detected stress-related allergenic proteins such as a PR3 class 1 chitinase-like protein. Eckl-Dorna et al [4] detected an increase in the protein and allergen content of *Secale cereale* pollen exposed to high levels of ozone.

We found significantly higher Enterobacteriaceae counts in the pollen from Puertollano, suggesting that this pollen had an increased capacity for endotoxin release. Endotoxins amplify the immune response and induce airway inflammation, worsening the clinical course of asthma and increasing bronchial hyperresponsiveness [6-8].

Our study of the clinical course of pollen-allergic patients with asthma in Puertollano and Ciudad Real showed that asthmatics from Puertollano had increased symptoms and medication use associated with the concentration of pollutants, in particular with ozone exceedances [9,10]. Our current findings could help to explain the poorer clinical course of asthmatic patients from Puertollano, although the proinflammatory effect of pollution itself on the airways must not be ignored.

In conclusion, patients living in areas with high levels of pollution are at risk of the direct effect of pollution on the airways. Moreover, *L perenne* pollen from polluted areas can induce a more intense response in grass-allergic patients than pollen from nonpolluted areas.

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#### Conflicts of Interest

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#### Previous Presentations

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**Tolerance to Cephalosporins in Nonimmediate Hypersensitivity to Penicillins in Pediatric Patients**

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**Key words:** Drug allergy. Delayed drug hypersensitivity. Penicillin hypersensitivity. Cephalosporins.

**Palabras clave:** Alergia a medicamentos. Hipersensibilidad retardada a medicamentos. Hipersensibilidad a penicilinas. Cefalosporinas.

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$\beta$ -Lactam antibiotics are widely used as first-line treatment of infectious diseases and as prophylactic treatment before surgery. All antibiotics belonging to this family are characterized by a common ring, known as the  $\beta$ -lactam ring. Penicillins have a thiazole ring, and cephalosporins a dihydrothiazine ring [1].  $\beta$ -Lactams also possess at least 1 side chain, which is responsible for the differences within each group. Cephalosporins have 2 side chains. Some cephalosporins share identical side chains with penicillin, as is the case with amoxicillin, which shares a side chain with cefadroxil, ampicillin, and cephalexin [1,2].

Given their widespread use in the population,  $\beta$ -lactams are the most frequently involved drug in hypersensitivity reactions to antibiotics. Not all aspects of the cross-reactivity pattern between penicillins and cephalosporins have been clarified. Cephalosporins and penicillins share the  $\beta$ -lactam ring, which is considered the main antigenic determinant. A study conducted in 41 adults diagnosed with immediate hypersensitivity reaction to penicillin found no adverse effects after administration of cephalosporins [2].

A study conducted in a group of 1170 children with suspected immediate allergic reactions to cephalosporins, penicillins, or both showed that 58.3% of cases had positive skin or challenge test results, with cross-reactivity between cephalosporins and penicillin ranging between 0.3% and 23.9% [3]. The overall incidence of adverse reactions from cephalosporins has been shown to range from 1% to 10% [4].

All first-generation cephalosporins have the potential for cross-reactivity, probably because their structural features are similar to those of penicillin, whereas most second- and third-generation cephalosporins are highly unlikely to be associated with cross-reactivity because of differences in their chemical structure [5].

Much of the information available on cross-reactivity between cephalosporins and penicillins comes from studies of immediate hypersensitivity reactions and adult studies. Few studies have evaluated cross-reactivity between these 2 groups

Table. Clinical Data of Patients

Case	Gender	Age, y	Drug	Cephalosporin Administered	Case	Gender	Age, y	Drug	Cephalosporin Administered
1	Male	12	Ax	Cefixime	16	Female	1.6	Ax-Clav	Cefuroxime
2	Male	3.9	Ax-Clav	Cefuroxime	17	Male	4.1	Ax	Cefuroxime
3	Female	6.3	Ax	Cefuroxime	18	Male	3.1	Ax-Clav	Cefuroxime
4	Male	5.6	Ax	Cefaclor	19	Female	1.4	Ax	Cefuroxime
5	Male	5.6	Ax-Clav	Cefuroxime/Cefixime	20	Female	4	Ax	Cefuroxime
6	Female	4.9	Ax	Cefuroxime	21	Male	2.25	Ax-Clav	Cefuroxime
7	Male	3.41	Ax-Clav	Cefuroxime	22	Male	1.8	Ax-Clav	Cefuroxime
8	Male	7	Ax	Cefuroxime	23	Female	3.5	Ax-Clav	Cefuroxime
9	Male	8.9	Ax	Cefuroxime	24	Female	1.25	Ax	Cefuroxime
10	Male	7	Ax-Clav	Cefuroxime	25	Male	1	Ax	Cefixime
11	Male	2.6	Ax	Cefuroxime	26	Male	2.5	Ax	Cefuroxime
12	Male	8.3	Ax	Cefuroxime	27	Male	1	Ax	Cefuroxime
13	Female	4.1	Ax	Cefuroxime/Cefaclor	28	Female	7.6	Ax	Cefuroxime
14	Male	3.7	Ax	Cefuroxime/Cefaclor	29	Male	4	Ax-Clav	Cefuroxime/Cefaclor
15	Male	2.7	Ax-Clav	Cefuroxime	30	Male	5.5	Ax-Clav	Cefuroxime

Abbreviations: Ax, amoxicillin; Ax-Clav, amoxicillin-clavulanate.

in delayed reactions, and, to our knowledge, no studies have been published on this problem in children.

The aim of our study was to evaluate tolerance to cephalosporins in pediatric patients diagnosed with nonimmediate allergy to penicillins.

We studied 30 patients diagnosed with delayed hypersensitivity to penicillins in the Pediatric Allergy Department of the Gregorio Marañón Maternity and Pediatric Hospital.

All patients underwent skin prick and intradermal tests with known concentrations of the culprit drug [6]. The reagents used included amoxicillin (GSK) 20 mg/mL, benzylpenicillin (Normon), penicilloyl-polylysine ( $5 \times 10^{-5}$  mmol/L, Diater) and minor determinant mixture ( $2 \times 10^{-2}$  mmol/L, Diater). We also performed prick tests with 1 or 2 cephalosporins as alternative drugs (cefuroxime 2 mg/mL, cefaclor 2 mg/mL, and cefixime 2 mg/mL) [7]. Histamine 10 mg/mL and sodium chloride (0.9%) were used as positive and negative controls, respectively. Immediate readings were taken after 15 minutes and late readings at 24 hours. A prick or intradermal test result was considered positive if the largest diameter of the wheal was  $\geq 3$  mm or  $\geq 5$  mm, respectively, as recommended by the guidelines of the European Academy of Allergy and Clinical Immunology [8]. The same experienced nurses performed the tests. In patients with negative skin tests against penicillin, allergy was demonstrated by oral challenge test.

Once nonimmediate allergy to penicillins was confirmed, we performed a controlled challenge test with oral cephalosporin (cefuroxime, cefaclor, and cefixime) according to the clinical situation of the individual patient. All patients received one-quarter of the total dose followed by the remainder of the dose and were kept under observation for 1 hour after the last dose. They followed 1 week of home treatment with therapeutic doses of the drug adjusted to body weight.

Out of 30 patients, 21 were men and 9 women. The median age at the time of the reaction was 3.9 years (1-12) years. Amoxicillin was involved in 18 patients (60%) and amoxicillin-clavulanate in 12 patients (40%). Our findings agree with those reported in the literature, where amoxicillin alone or in combination with clavulanic acid is the drug most frequently involved in drug-induced reactions in children [9]. Maculopapular rash was recorded in 29 patients (96%), and osteoarticular involvement with skin involvement was recorded in 6 patients (20%).

We performed 34 challenges in 30 patients with cephalosporins (Table). All patients tolerated the drugs.

Our study confirms good tolerance to cephalosporins in patients diagnosed with nonimmediate hypersensitivity reaction to penicillins. If the results of a graded challenge test are negative, the patients do not need to avoid the tested cephalosporin.

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### Rabbit Meat Anaphylaxis

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Key words: Anafilaxia. Albúmina sérica. Panalérgeno.

Palabras clave: Anafilaxia. Serum albumin. Panalérgen.

We present the case of a 17-year-old woman monitored at our Allergology Service for allergic rhinitis and moderate persistent bronchial asthma. She was sensitized to house dust mite, grass pollen, and cat and rabbit epithelia. She kept a rabbit at home and had sporadic contact with cats. She had received specific immunotherapy against house dust mites for 5 years and had taken oral ebastine and inhaled salmeterol/fluticasone, which led to partial control of her bronchial symptoms. She currently lives without pets.

In January 2011, she experienced generalized maculopapular rash, itching, shortness of breath, coughing, wheezing, and pharyngeal tightness 30 minutes after ingestion of rabbit paella (rice, red and green pepper, onion, garlic, paprika, and rabbit meat) and went to the hospital emergency department where she was diagnosed with generalized urticaria and severe bronchospasm. She denied contact with animals and reported that she tolerated all the suspect foods except paprika and rabbit, which she has not eaten since. She also tolerates all kinds of mammal and bird meats, processed meats, eggs, and dairy products. She has never been exposed to hare and has never eaten hare meat. The patient did not report associated cofactors (eg, physical exercise, nonsteroidal anti-inflammatory drugs, and alcohol). Prick testing was performed with the following groups of allergens: aeroallergens, namely, dust mites, pollens, musts, epithelia (horse, goat, pig, rabbit, guinea pig, cat, hamster, sheep, dog, and cow), and latex; standard foods (eggs, milk, and grains), mix of meats (pork, rabbit, chicken, and lamb), nuts, vegetables, fish, seafood, fruits, *Anisakis simplex*, mustard, legumes, and soy; individual meats (horse, pork, rabbit, chicken, and veal). Spices were also tested (prick), as were paprika and red and green pepper (prick-prick). Prick-prick testing was performed with raw and cooked meat (rabbit, pork, beef, and chicken). The histamine control was positive (5 x 4 mm). Forced basal spirometry and exhaled nitric oxide were determined. IgE was determined using ImmunoCAP Specific IgE (Pharmacia) CAP system and IgE-immunoblotting (ALK-Abelló) with extracts of rabbit epithelium, rabbit meat, dog epithelium, and pork.

In the case of aeroallergens, the results were positive for grass pollen, grains, *Phleum pratense*, *Phragmites communis*, *Olea europaea*, *Dermatophagoides pteronyssinus*,

*Dermatophagoides farinae*, *Lepidoglyphus destructor*, cat epithelia (4 × 4 mm), and rabbit epithelia (6 × 5 mm). All results for standard foods, spices and peppers, and raw and cooked meats were negative. The only positive result in the prick test with individual meats was for rabbit meat (10 × 7 mm). Prick-prick testing with rabbit meat was positive (raw, 9 × 7 mm; cooked, 4 × 4 mm). Forced basal spirometry was normal, and exhaled nitric oxide was 54 ppb.

The results of testing with the ImmunoCAP revealed total IgE of 676.9 kU<sub>A</sub>/L. The results for specific IgE (IU/mL) were as follows: *D pterynossinus*, >100; *D farinae*, >100; *Phleum pratense*, 1.1; cat epithelia, 1.1; dog epithelium, 0.5; rabbit epithelium, 4.19; rabbit meat, 0.51; rabbit serum proteins, 0.90; rabbit urine proteins, 0.83. The results of testing for hamster epithelium, horse dander and epithelium, bovine serum albumin (BSA), pork, beef, chicken, paprika, and mustard were negative. Immunoblotting with the patient's serum sample revealed recognition of rabbit epithelium proteins (60, 35, and 75 kDa), whereas only a single band (60 kDa) was observed with the rabbit meat sample.

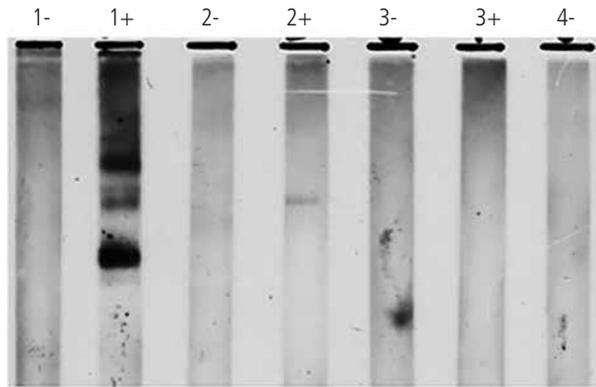


Figure. IgE immunodetection. Lane 1, rabbit epithelium; lane 2, rabbit meat; lane 3, dog epithelium; lane 4, pork; -, negative controls incubated with buffers instead of patient serum; +, incubation with patient serum.

The patient was sensitized to house dust mites and grass and olive pollen.

The only positive results in prick testing, prick-prick testing, and CAP were detected with rabbit meat.

The prevalence of allergy to meat is fairly low, and reports on this allergy are scarce. In adults, prevalence has been reported to be 8.2% [1].

Several allergens are found in the flesh of mammals, including serum albumins, bovine serum  $\gamma$ -globulin, actin, and tropomyosin, although few seem to be clinically relevant. Various clinical allergic reactions have been described after ingestion, inhalation, or contact with meat products, and symptoms vary in severity (oral allergy syndrome, urticaria, dermatitis, asthma, and anaphylaxis), thus indicating an IgE-mediated mechanism [2]. The literature contains descriptions of patients allergic to cow's milk and sensitized to BSA who experience symptoms if the meat is undercooked [3-4]. There have also been reports of cross-reactivity between cat epithelium and pork and/or lamb and of allergy to hamster epithelium with symptoms after ingesting horse meat [5],

suggesting that albumins may be responsible for both respiratory and environmental allergies. BSA has been reported to be the main allergen in children, whereas  $\gamma$ -globulins and myoglobins may be equally or more relevant in adults [6].

The rabbit belongs to the Leporidae family (rabbits/hares). The literature contains cases of severe reactions after exposure to rabbit epithelium but few cases of allergy due to ingestion of rabbit meat. In 2006, Fernández Rivas and Benito Sastre [7] reported the cases of 2 patients with rhinoconjunctivitis and asthma caused by exposure to inhaled rabbit epithelium who subsequently developed anaphylaxis after ingestion of rabbit meat. In the first case, the reaction was associated with physical exercise, and in the second, the patient presented oropharyngeal pruritus, rhinoconjunctivitis, and asthma. Albumin was the culprit allergen (>60 kDa). In 2007, Osorio Galindo [8] reported the case of a patient with occupational asthma due to exposure to rabbit meat vapors who experienced respiratory symptoms after ingestion, suggesting that the patient experienced primary sensitization by inhalation to cat epithelium, subsequent sensitization by inhalation to rabbit derivatives, and evolution to sensitization to rabbit meat by ingestion. In contrast with cases published to date, the patient in the present case experienced an immediate reaction after eating rabbit meat (symptoms of generalized cutaneous and acute respiratory anaphylaxis), with no associated cofactors or history or symptoms of oral allergy syndrome due to rabbit meat (this type of meat was common in the patient's diet). In our case, the 60-kDa protein detected could correspond to albumin. The patient was only sensitized to rabbit, with IgE specific for BSA. The results for other meats were negative, and the patient only presented symptoms after ingestion of rabbit meat and good tolerance to other mammalian meats.

In conclusion, we present the case of a patient diagnosed with initial sensitization to inhaled rabbit products (epithelium, urine, and serum) at age 11 years. She became sensitized to rabbit meat, and, at age 16, reported symptoms of anaphylaxis secondary to ingestion (severe bronchospasm). The 60-kDa band identified could correspond to albumin, a panallergen responsible for cross-reactivity between rabbit epithelium and rabbit meat.

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**Tolerance of Triflusal in Patients With Immediate Cutaneous Hypersensitivity to Nonsteroidal Anti-inflammatory Drugs**

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**Key words:** Urticaria. Angioedema. NSAIDs. Triflusal.

**Palabras clave:** Urticaria. Angioedema. AINEs. Triflusal.

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When used as an antiplatelet agent, acetylsalicylic acid (ASA) plays an important role in reducing ischemic complications arising from coronary artery disease [1,2,3]. ASA is a nonselective inhibitor of cyclo-oxygenase that prevents synthesis of thromboxane A<sub>2</sub>, an inducer of platelet aggregation [1,4]. Dual antiplatelet therapy can prevent cardiovascular thromboembolic events in risk populations, in which the most commonly used agents are clopidogrel and ASA [1,5].

Patients with hypersensitivity reactions to ASA who require antiplatelet therapy can use clopidogrel as an alternative [5]. However, if dual antiplatelet therapy is necessary, tolerance to ASA should be induced [6]. In some cases, complete desensitization is not possible or the underlying disease makes the procedure risky.

Triflusal is structurally related to the salicylates [5]. Its efficacy in preventing cardiovascular events after acute myocardial infarction is similar to that of ASA, although it has a more favorable safety profile and better digestive tolerance [1,5]. In addition, triflusal is well tolerated by patients with asthma induced by nonsteroidal anti-inflammatory drugs (NSAIDs). Based on the classification of Kowalski et al [8], we present prospective data on patients with cutaneous hypersensitivity reactions to ASA to confirm tolerance to triflusal.

This prospective study was conducted between 2009 and 2012 in 18 patients (9 men) aged 23 to 80 years (mean, 45 years) with immediate cutaneous reactions (7 urticaria, 6 angioedema, and 5 urticaria and angioedema) after intake of NSAIDs confirmed by oral challenge test with ASA. None of the patients had a history of chronic urticaria or respiratory disease. The most frequently involved drugs were ibuprofen and aspirin (11 and 9 patients, respectively).

The results of skin tests (prick and intradermal) with several NSAIDs (ASA, ibuprofen, dypirone, diclofenac, indomethacin, and ketorolac) performed to rule out selective IgE-mediated reactions were negative in all the patients.

In order to confirm hypersensitivity to ASA, all 18 patients underwent a controlled, single-blind, oral challenge test with aspirin. Increasing doses of ASA were administered orally at intervals of 60 minutes (50, 125, and 250 mg on day 1; and 500 mg on day 2). In some patients, dosing started at 25 mg.

All the patients experienced urticaria, angioedema, or both, that is, the same manifestations as in the initial case (8 patients) after the highest dose. Seventeen patients were classified as having cross-intolerance because of reactions with more than 1 NSAID. In the remaining patient, who reported reactions only with ASA, cross-intolerance was not ruled out. The clinical characteristics of the patients and the results of the challenge tests are shown in the Table.

Table. Clinical Data of Patients

Age	Gender	Symptoms	Drug Not Tolerated	Triggering Dose of ASA
63	Male	A	ASA, ibuprofen, dypironel, diclofenac	25 mg
32	Female	A	ASA, indomethacin	125 mg
65	Male	U	ASA, ibuprofen, dypirone	250 mg
27	Female	A	Dypirone, ASA	500 mg
22	Female	A	Ibuprofen, paracetamol	125 mg
37	Female	U/A	Dypirone, ibuprofen	500 mg
39	Male	U	Ibuprofen	500 mg
46	Male	U	Ibuprofen, ASA	500 mg
72	Male	U/A	ASA	100 mg
46	Male	U/A	ASA, ibuprofen	250 mg
45	Female	U/A	ASA, dexketoprofen	125 mg
54	Female	U	Ibuprofen, ketorolac, dypirone	500 mg
28	Female	A	Ibuprofen	125 mg
36	Male	A	ASA, Ibuprofen	500 mg
38	Male	U	Ibuprofen	125 mg
33	Female	U	Ibuprofen	500 mg
52	Male	U/A	Ibuprofen	500 mg
80	Female	A	Ibuprofen, ASA	250 mg

Abbreviations: A, angioedema; ASA, acetylsalicylic acid; U, urticaria; U/A, urticaria-angioedema.

All of the patients underwent a controlled, oral, single-blind challenge test with triflusal at increasing doses (75 mg, 150 mg, and 300 mg administered at 60-minute intervals) until a cumulative dose of 525 mg was reached. On day 2, the patients received 300 and 600 mg of triflusal.

All 18 patients tolerated a cumulative dose of triflusal of 525 mg, and 6 patients tolerated a cumulative dose of 900 mg. No adverse events were reported.

Patients with intolerance to ASA who need antiplatelet therapy can use clopidogrel as the first alternative drug. If dual antiplatelet therapy is necessary, tolerance should be induced with ASA [6]. Adverse reactions are common during induction. These are usually mild, although they can be dangerous, particularly in patients who have recently experienced a cardiovascular event. Treatment with triflusal has a similar efficacy to that of ASA in the prevention of cardiovascular

events (death, nonfatal myocardial infarction, and nonfatal cerebrovascular events) with a significantly lower incidence of nonfatal cerebrovascular events and cerebral hemorrhage [1,4]. The recommended dosage in adults is 600-900 mg/d (600 mg qd, or 300 mg bid or tid) [9]. Our study shows that triflusal is well tolerated by patients with immediate cutaneous hypersensitivity to ASA. Similar results were obtained in a previous study in patients with NSAID-induced asthma [7]. The fact that triflusal is a weaker cyclo-oxygenase inhibitor than ASA may explain this difference [7].

In our opinion, triflusal is a safe alternative drug in patients with immediate cutaneous hypersensitivity to NSAIDs if dual antiplatelet therapy is necessary.

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**Conjunctival Sensitization to Hydrolyzed Wheat Protein in Facial Soap**

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**Key words:** Allergic conjunctivitis. Wheat. Facial soap.

**Palabras clave:** Conjuntivitis alérgica. Trigo. Jabón facial.

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Hydrolyzed wheat protein (HWP) is used in many foods and in personal hygiene products, including skin cosmetics, shampoo, hair conditioner, and facial soap. Allergic contact dermatitis due to HWP has been reported by several authors [1-5]. Here, we describe an extremely rare case of bilateral allergic conjunctivitis caused by HWP in facial soap.

A 28-year-old woman with no previous history of atopy or allergic contact dermatitis developed severe bilateral allergic conjunctivitis 1 hour after washing her face with a new soap (Cha no Shizuku, Yuuka Co Ltd). She attended our hospital 2 days after the onset of allergic conjunctivitis and stated that soap bubbles had entered her eyes while she was washing her face. She had no history of skin disorders or allergic conjunctivitis. We checked the ingredients of her facial soap and confirmed that it contained HWP. On examination, the patient's vision was better than 20/20 in both eyes, and she had bilateral severe conjunctival hyperemia and edema (Figure). The cornea was clear. The facial skin, upper and lower eyelids, anterior chamber, iris, and lens were normal, as were funduscopy findings. The skin prick test was positive after 30 minutes for facial soap and wheat (1:20 wt/vol; Torii Pharmaceutical Co, Ltd); the result of the skin prick test with the saline control was negative. Total IgE in tear fluid was grade 2 (elevation of total IgE) according to the Allerwatch test (Hitachi Chemical Co., Ltd and Wakamoto Pharmaceutical Co, Ltd) [6], and wheat-specific IgE in tear fluid was grade 4 (the highest specific IgE level) according to the IMM-FAST Check J2 test (Mitsubishi Kagaku Iatron Inc) [7-8]. The results of skin prick tests for other major allergens, such as pollen, dust mite, and animal dander, were all negative, and tear levels of specific IgE were not elevated. The patient was diagnosed with allergic conjunctivitis induced by HWP in soap. She stopped using the facial soap and was treated with eye drops (0.1% betamethasone sodium phosphate [Shionogi] and 0.025% levocabastine hydrochloride [Santen Pharmaceutical]), which were administered 4 times daily to both eyes. Her symptoms subsided within a few days, and the allergic conjunctivitis resolved completely in 1 week.

In this patient, acute allergic conjunctivitis was presumably caused by direct contact with facial soap containing HWP. Acute allergic conjunctivitis induced by facial washes is



**Figure.** Ocular findings before treatment. Note the bilateral allergic conjunctivitis caused by facial soap containing hydrolyzed wheat protein.

extremely rare and has never been described in the literature to our knowledge.

The early symptoms of allergy to HWP-containing soap are facial dermatitis, contact dermatitis, and allergic rhinitis [1-5]. Long-term use of HWP-containing soap may also induce wheat-dependent exercise-induced anaphylaxis [9-10]. In the case we report, the patient developed bilateral allergic conjunctivitis after washing her face with HWP-containing soap because soap bubbles entered her eyes. However, she did not experience facial dermatitis or rhinitis because she rinsed her face thoroughly with water and dried it with a clean towel. This suggests that HWP-containing soap residue in the conjunctival sac can penetrate the conjunctiva, a thin mucous membrane with abundant blood vessels, more easily than facial skin. In addition, soap contains surfactants that can damage the conjunctival barrier, thus facilitating penetration of HWP into the conjunctival epithelium. If HWP-containing soap enters the eyes of a patient with HWP hypersensitivity, he/she should immediately rinse the eyes thoroughly.

We report a case of hypersensitivity reaction to HWP-containing soap. On May 20, 2011, the company voluntarily began to recall about 46 million cakes of HWP-containing soap. However, many other cosmetics and soaps still contain HWP. Thus, we believe that this case emphasizes the need for caution when HWP-containing cosmetics are used by persons with HWP allergy or wheat allergy. Treatment with topical antiallergic agents and corticosteroids can achieve rapid resolution of allergic conjunctivitis caused by HWP-containing soap.

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