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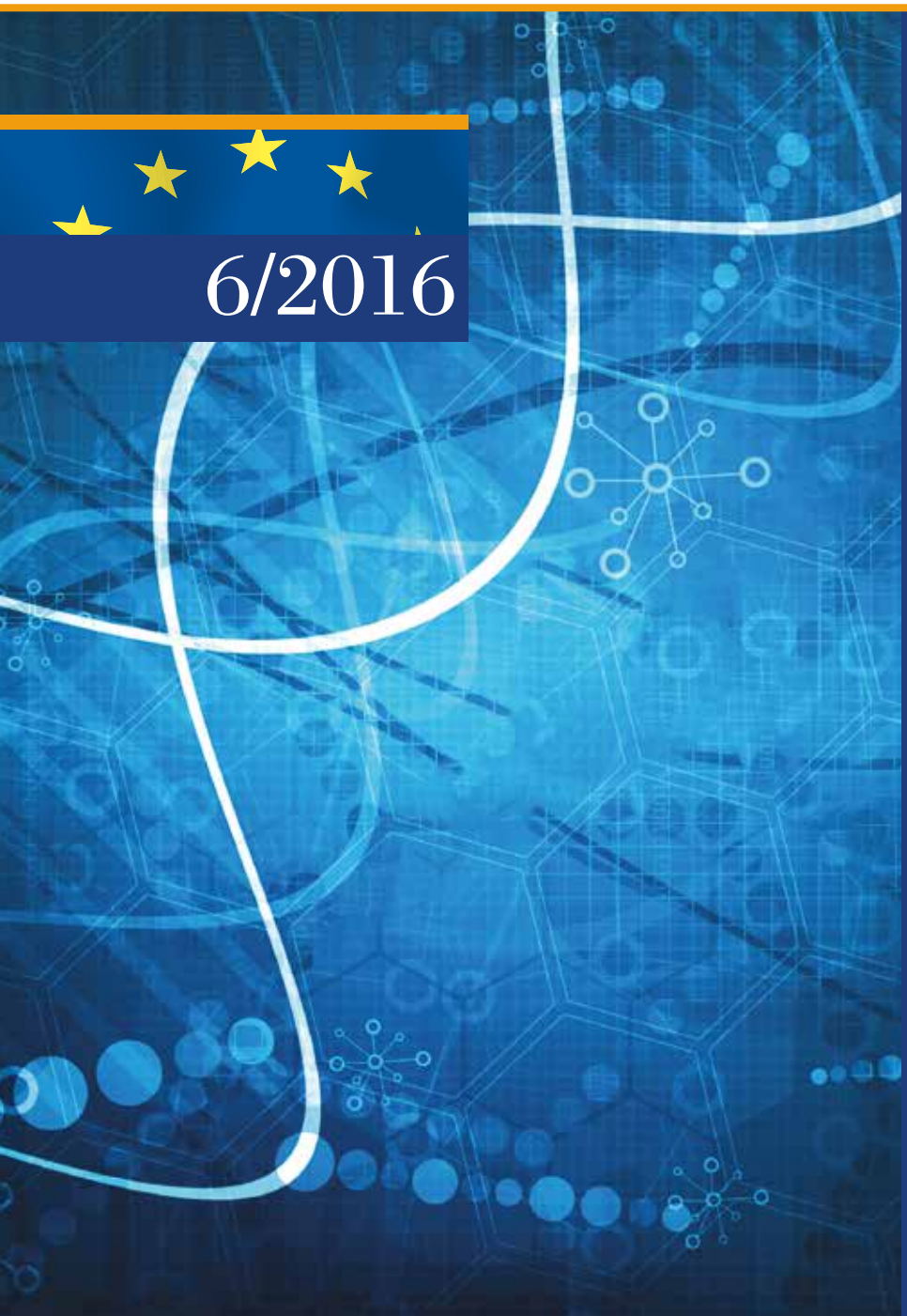

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Original Articles

Case Reports

I. Mota, Â. Gaspar, M. Chambel, S. Piedade, M. Morais-Almeida

Hypersensitivity to beta-lactam antibiotics: a three-year study

Immunoallergy Department, CUF Descobertas Hospital, Lisbon, Portugal

Key words
adults; beta-lactams; drug allergy; children; skin tests

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Summary
Background. *Beta-lactams antibiotics (BL) are the most frequent elicitors of allergic drug reactions. The aim of our study was to characterize the patients referred with suspected hypersensitivity (HS) to BL.* ***Methods.*** *Over a three-year period (2011-2013), a total of 234 adult and paediatric patients (pts) with suspected HS to BL were investigated according to the European Network for Drug Allergy guidelines.* ***Results.*** *HS to BL was confirmed in 43 pts (18%), without differences between adult and paediatric pts; anaphylaxis was reported by 20 pts. Diagnosis was ascertained by: serum-specific IgE antibodies in 5 pts (12%), skin prick tests in 5 (12%), intradermal tests in 25 (58%), 3 with delayed reading, and the remaining 8 (18%) by drug provocation tests. Penicillins / derivatives were the culprit drugs in 39 pts, mainly amoxicillin, and cephalosporins in 4.* ***Conclusions.*** *In most of these patients with suspected HS to BL, allergological work-up was negative and HS was excluded. One fourth of confirmed cases had a plausible non-IgE mediated mechanism.*

Introduction

Hypersensitivity to beta-lactams antibiotics (BL) continues to be the most commonly reported cause of adverse drug reactions mediated by specific immunological mechanisms, being the reactions classified as immediate or non-immediate. Immediate reactions usually appear within the first hour after BL administration, and are mediated by specific IgE-antibodies; the remaining reactions, not immediate, usually occur within 24 hours after drug intake (1). The symptoms can range from urticaria to anaphylaxis (2) (most in immediate reactions), to maculopapular exanthema and delayed urticaria (non-immediate reactions). T cells are implicated in all types of hypersensitivity reactions to BL, indirectly by regulating IgE production or directly as effector cells. A Th1 pattern is observed in both CD4(+) and CD8(+) peripheral T cells in non-immediate reactions, whereas a Th2 pattern is expressed in CD4(+) T cells in immediate reactions (3).

IgE responses to benzylpenicillin (BP), the first antibiotic producing the benzyl penicilloyl structure, are characterized by an acute release of inflammatory mediators, resulting in urticaria, angioedema and eventually anaphylactic shock. BP has been progressively replaced by other compounds, as amoxicillin (AX) and, to a lesser extent, cephalosporins, carbapenems, monobactams or the related betalactamase-inhibitor clavulanic acid, which are responsible for IgE selective responses and cross-reactivity reactions (4).

BL (penicillins, cephalosporins, carbapenems, monobactams and beta-lactamase inhibitors) are the most widely used antibiotic drugs worldwide and constitute the most commonly reported cause of drug allergy, with a prevalence rate of 0.7 to 10% in adults and children (5-8). In large-scale studies, 80 to 90% of patients with a history of penicillin allergy were considered not to be allergic, but recent data suggest that this number may even be as high as 95% (9,10). Potential reasons that can explain the dissociation between patients labelled as allergic and those with confirmed allergy include

misdiagnosed reaction, reaction due to underlying disease, levels of specific IgE that wane over time and outgrown allergy to BL (10). Patients labelled as penicillin-allergic are more prone to receive broader spectrum antibiotics, with more adverse effects, if not less effective alternative drugs, with consequent increase of bacterial resistance. Furthermore, alternative drugs are usually more expensive with the consequent increase in medical costs (11).
According to the ENDA / EAACI (*European Network of Drug Allergy / European Academy of Allergy and Clinical Immunology*), the evaluation of BL hypersensitivity includes a detailed clinical history, *in vitro* quantification of specific IgE-antibodies, skin tests, and drug provocation test (DPT) (12,13).
The aim of this study was to describe the work-up activity developed at our Immunoallergy outpatients' hospital of a large group of patients with suspected hypersensitivity to BL.

Materials and methods

Patients

The authors included in this evaluation a group of consecutive patients, adults and children, who were referred to our drug allergy center of CUF Descobertas Hospital (Lisbon, Portugal) with suspected hypersensitivity to BL, over a three-year period (from January 2011 to December 2013). Clinical data with detailed description of symptoms and circumstances of the reaction was collected in clinical files and a proper questionnaire adapted from ENDA (14) was filled in. All patients were fully informed about the procedures (risks and possible adverse reactions) and all of them signed an informed consent according to the Helsinki Declaration. The diagnostic procedures followed the ENDA/EAACI recommendations (12,13).

In vitro tests

Serum-specific IgE antibodies (*ImmunoCAP®, Thermo Fisher Scientific, Uppsala, Sweden*) for penicillin G/V, AX and ampicillin were used. Assays were performed at least 4 weeks interval after the clinical reaction and a *cut-off* value ≥ 0.35 kU/L was considered for positivity.

In vivo tests

Skin prick tests (SPT) were the first step of the *in vivo* investigation, and only if negative, intradermal tests (IDT) were carried out. Skin tests were accomplished using solutions, daily prepared, of benzylpenicilloyl octa-L-lysine (PPL) (5×10^{-5} mM) and sodium benzylpenilloate - minor determinant (MD) (2×10^{-5} mM) (*DAP® Penicillin, Diater, Madrid, Spain*), penicillin G (25.000 IU/mL), AX (25 mg/mL) and clavulanic acid (CLV) (2.5 mg/mL), and cefuroxime (2.5 mg/mL) (12). Histamine (10 mg/mL) was used as a positive control for SPT and 0.9% saline solution as a negative control.
To all patients that reported symptoms compatible with severe reactions, IDT were carried out beginning with more diluted solutions (PPL diluted 1/100, MD diluted 1/1000, Penicillin G 2.500 IU/mL, AX 2.5 mg/mL and cefuroxime 0.25 mg/mL), which were gradually increased until the appearance of a positive skin response or until reaching the maximum concentration described above.
First readings were taken after 15 and 20 minutes for SPT and IDT, respectively. Both tests were performed on the volar forearm. In SPT a mean wheal larger than 3 mm, accompanied by erythema, with a negative response to negative control was considered positive. IDT were done by the injection of 0.02-0.05 mL of the hapten solution, raising a small wheal that was marked initially. In IDT an increase in mean diameter greater than 3 mm of the wheal area marked initially was considered positive. All patients, particularly in case of high suspicion of non-immediate reactions, were advised of the possibility of having a late reaction within an interval of 24-48 hours, and a delayed reading has been taken. Other drugs (penicillin derivatives / cephalosporins) were tested according to the suspicion.

Drug provocation tests (DPT)

After skin tests, the patients underwent oral challenges with the culprit drug, whether previous investigation (SPT and IDT) was unequivocally negative. By contrast, in the patients where SPT or IDT have been positive a DPT with alternative BL drug has been conducted. DPT was always fulfilled in posterior appointment to allow delayed readings of the skin tests. The therapeutic dose of selected drug was administered stepwise, increasing each 20 to 30 minutes, or as a single dose, according to clinical history documented. The patients were retained in the hospital for at least 2 hours after the last dose and were informed about the possibility of delayed reactions after hospital discharge. Depending on the likelihood of the reaction during the time of the procedure, some patients were given further doses to fulfilled 24 to 72 hours of oral challenge. If necessary, the oral challenge was prolonged until 5 to 7 days. The telephone number of medical staff, and appropriate medication in case of late allergic reaction including antihistamine and corticosteroid drugs, were provided on hospital discharge, and were available during the follow-up period.
All tests were performed under strict medical surveillance, by professionals with experience in recognition and management of acute reactions. Epinephrine and other appropriate medication and resuscitation equipment have been always available during carrying out of the tests.

Results

A total of 234 patients with clinical suspicion of hypersensitivity reactions to BL were evaluated over the three years (**table 1**

and **figure 1**). The mean age was 36 [standard deviation (SD) ± 16.2] years old (2-75 years), and 68% where female. Thirty seven (16%) had less than 18 years old, with a mean age of 7.8 (SD ± 3.7), and 54% were boys. In 161 patients (69%) penicillins / derivatives were the culprit drug, AX alone in 49 patients (21%), and in association with CLV in 75 patients (32%). Cephalosporins were involved in 26 patients (11%). Reactions with more than one BL were reported by 11 patients. Atopy, personal history of allergic disease and family history of BL allergy is presented in **table 1**.

***Table 1** - Clinical characteristics of study population comparing with confirmed cases.*

	HS to BL	Total population
n (%)	43 (18)	234
Age (yrs, mean, SD)	37 (16.6)	36 (16.2)
Under 18 yrs (n, %)	7 (16)	37 (16)
Sex (female, %)	24 (56)	160 (68)
Atopy (n, %)	8 (19)	74 (32)
Personal history of allergic disease	23 (53)	154 (66)
Personal history of asthma	7 (16)	53 (23)
Family history of BL allergy	2 (5)	15 (6)
Clinical manifestations (n, %)		
Mucocutaneous	43 (100)	190 (81)
Respiratory	10 (23)	20 (9)
Gastrointestinal	7 (16)	16 (7)
Cardiovascular	3 (7)	10 (4)
Loss of consciousness	6 (14)	12 (5)
Swollen glottis	6 (14)	8 (3)
Anaphylaxis	20 (47)	30 (13)
Not specified	1 (2)	8 (3)
Drug involved (n, %)		
Benzylpenicillin	3 (7)	29 (12)
Ampicillin	1 (2)	3 (1)
Flucloxacillin	1 (2)	5 (2)
Amoxicillin	13 (30)	49 (21)
Amoxicillin-clavulanic acid	21 (49)	75 (32)
Cephalosporins	4 (9)	26 (11)
Unrecalled	2 (5)	54 (23)

BL, beta-lactam antibiotics; HS, hypersensitivity.

Hypersensitivity to BL was confirmed in 43 patients (18.4%), being 7 younger than 18 years old (18.9%) and 36 adults (18.3%). Only 19% of these patients were atopic (sensitized to at least one common aeroallergen). The majority (53%) had personal history of allergic disease, and 16% had asthma as co-morbidity. Only 5% had family history of BL allergy. Considering the confirmed cases, all patients had mucocutaneous symptoms, which were the only manifestation in 53% of them. Severe reactions (anaphylaxis) occurred in 20 patients (47%) with swollen glottis and loss of consciousness in 6 patients. Regarding medical approach of allergic reactions, we found that 50% of the patients who developed anaphylaxis were properly treated with epinephrine.

***Table 2** - Results of positive skin tests.*

BL drug	SPT	IDT		Total
		Immediate	Delayed	
PPL	3	6	-	9
Penicillin	1	5	1	7
AX	3	14	2	19
Cefazoline	-	3	-	3

AX, amoxicillin; BL, beta-lactam antibiotics; IDT, intradermal tests; PPL, benzylpenicilloyl octa-L-lysine; SPT, skin prick tests.

The hypersensitivity was ascertained by means of serum-specific IgE antibodies in 5 patients (12%), by SPT in 5 (12%), by IDT in 25 (58%) and the remaining 8 (18%) by DPT. The results of skin tests are described in **table 2**. Ten children with negative specific IgE antibodies and nonimmediate reactions were excused from skin tests and performed DPT with the culprit drug, which were negative.

Regarding the serum-specific IgE antibodies, the negative predictive value (NPV) was 82.4% and the sensitivity was 18.6%. Whereas, for the skin tests the NPV was 97.4% and the sensitivity was 85.7%.

Analyzing the five patients diagnosed by *in vitro* tests, positive results were obtained to AX in 4 patients [three with generalized urticaria (AX-IgE 1.87, 1.92 and 3.01 kU/L) and one with anaphylaxis with loss of consciousness (AX-IgE > 100kU/L)]. The other patient was positive to ampicillin (26,9 kU/L).

It is important to notice that although with negative skin tests by immediate reading, three patients presented delayed reading of IDT (**table 3**), one to penicillin and two to amoxicillin. Two of these have been referred with suspected allergy to BL presenting with generalized urticaria and the other with severe anaphylaxis with loss of consciousness.

Four patients experienced systemic reaction during skin testing (**table 3**), one child had anaphylaxis during IDT with amoxicil-

Table 3 *- Clinical characteristics of patients with delayed readings and systemic reactions with skin tests.*

Age of reaction	Culprit drug	Reaction	Timing	sIgE	SPT (+)	IDT (+)	Systemic reactions during ST
23	AX-CLV	Angioedema (face and lips)	IR	(-)	AX	NP	Pruritus and erythema of the upper limb after SPT
23	AX	Urticaria and angioedema (hands and legs)	IR	(-)	PPL, Penicil-lin, AX	NP	Pruritus and erythema of the upper limb after SPT
3	AX-CLV	Anaphylaxis (generalized urticaria, angioedema lips and tongue and dyspnea)	IR	(-)	(-)	AX 2,5 mg/mL (imme-diate reading)	Anaphylaxis 15 min after IDT (urticaria, prostration, rhinoconjunctivitis, cough, bronchospasm)
38	AX-CLV	Anaphylaxis (angioedema of face, swollen glottis, loss of consciousness)	NIR	(-)	(-)	AX 25 mg/mL (delayed reading, 10 h)	Pruritus and facial rash 1h after IDT
36	AX-CLV	Generalized urticaria	NIR	(-)	(-)	AX 25 mg/mL (delayed reading, 6 h)	no
46	Fluclox-acillin	Generalized erythema	NIR	(-)	(-)	Penicillin 25.000 IU/mL (delayed reading, 24 h)	no

AX, amoxicillin; AX-CLV, amoxicillin-clavulanic acid; IDT, intradermal tests; IR, immediate reaction; NIR, non-immediate reaction; NP, not performed; sIgE, specific IgE antibodies; SPT, skin prick tests; ST, skin testing; (+), positive; (-), negative.

Figure 1 *- Investigation allergological work-up performed.*

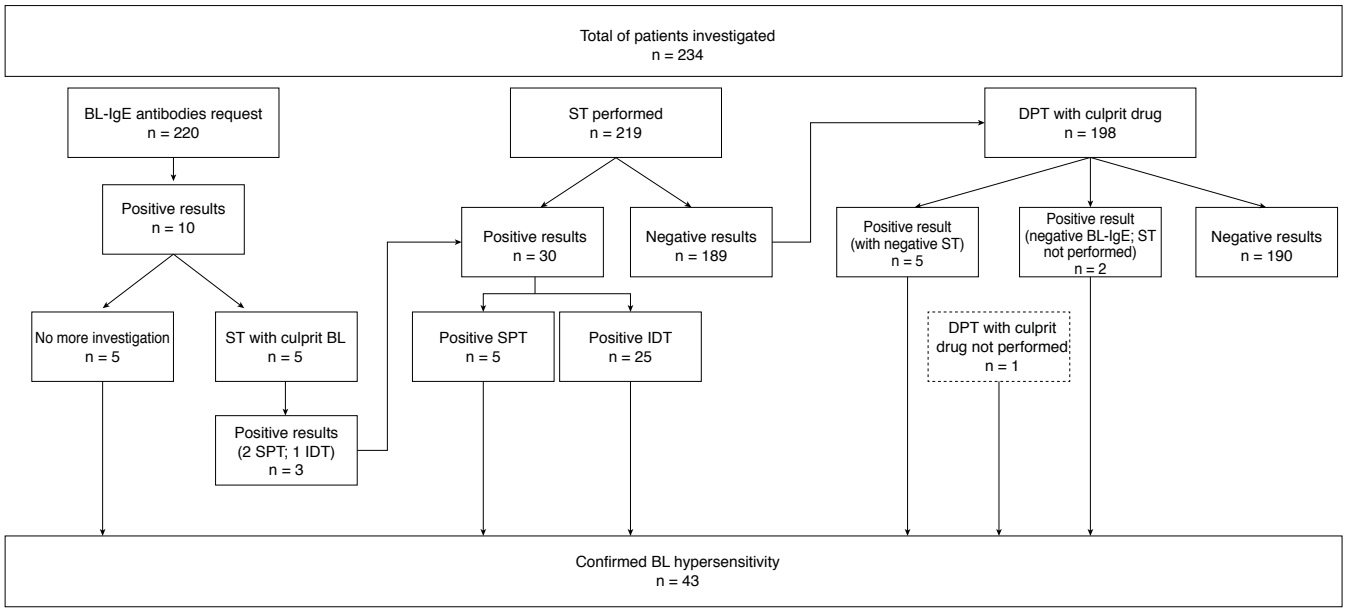

***Table 4** - Clinical characteristics of patients diagnosed by drug provocation test.*

Age (interval reaction-study) (yrs)	Type of reaction (time); day of intake	Reaction	Culprit drug	sIgE	ST	DPT(+)	Reaction during DPT	Time	DPT(-)	Conclusion
27 (10)	IR; 1	Anaphylaxis (urticaria, angioedema, loss of consciousness)	AX-CLV	-	-	AX	Anaphylaxis (pruritus, cough, bronchospasm, urticaria, angioedema, conjunctivitis, throat tightness) (250 mg)	30 min	0	HS non-IgE-mediated AX
						CFX	Facial and palmar pruritus, auricular angioedema	20 min		HS non-IgE mediated CFX
6 (5)	NIR; 4	Anaphylaxis (exanthema, vomiting)	AX	-	NP	AX	Vomiting	3h	CFX	HS non-IgE-mediated AX
44 (3)	NIR; 1	Exanthema (pelvic)	AX-CLV	-	-	AX	Exanthema (pelvic)	12h	CFX	HS non-IgE-mediated AX
2 (1)	NIR; 8	Exanthema (generalized)	AX-CLV	NP	NP	AX	Urticaria, angioedema	15 min	CFX	HS non-IgE-mediated AX
31 (1)	IR; 3	Anaphylaxis (urticaria, dyspnea)	AX-CLV	-	-	AX	Anaphylaxis (urticaria, cervical edema, throat tightness, cough (100 mg)	20 min	CFX	HS non-IgE-mediated AX
36 (3)	NIR; 2	Fixed drug eruption	AX-CLV	-	-	AX	Fixed drug eruption	day 5	CFX	HS non-IgE-mediated AX
33 (1)	IR; 1	Anaphylaxis (pruritus, urticaria, angioedema, laryngeal stridor)	AX-CLV	-	-				AX	Suspicion of HS to CLV (DPT with CLV not performed)
10 (9)	NIR; 8	Urticaria, angioedema	AX-CLV	-	-	AX-CLV	Nausea, abdominal pain, diarrhea	2h	AX	HS to CLV

AX, amoxicillin; AX-CLV, amoxicillin-clavulanic acid; CFX, cefuroxime; DPT, drug provocation test; HS, hypersensitivity; IR, immediate reaction; NIR, non-immediate reaction; NP, not performed; sIgE, specific IgE; ST, skin testing; +, positive; -, negative.

Table 5 *- Clinical characteristics of confirmed cases which involved cephalosporins.*

Age of reaction	Culprit drug	Reaction	Route	Timing	IDT +	DPT (-)
11	Cefatrizine; AX-CLV	Urticaria and angioedema (face and neck)	oral	IR	AX 25 mg/ml	CFX
40	Cefazoline	Anaphylaxis (urticaria, generalized angioedema, swollen glottis, hypotension)	i.v.	IR	Cefazoline 0,25 mg/ml	CFX
42	Cefazoline	Anaphylaxis (generalized urticaria, hypotension)	i.v.	IR	Cefazoline 2,5 mg/ml	AX
36	Cefazoline	Anaphylaxis (tachycardia, hypotension, bronchospasm, swollen glottis, angioedema lips)	i.v.	IR	Cefazoline 2,5 mg/ml	AX; CFX

AX-CLV, amoxicillin-clavulanic acid; CFX, cefuroxime; DPT, drug provocation test; IDT, intradermal tests; IR, immediate reaction.

lin (2.5 mg/mL), that resolved with intramuscular epinephrine; three adults had urticaria (face and upper limb), with resolution without need of epinephrine: one during IDT with amoxicillin (25 mg/mL), one during SPT with amoxicillin and the other during SPT with PPL, penicillin and amoxicillin.

Regarding DPT, 8 patients (6 with negative results in skin testing) revealed to be allergic when challenged with the culprit drug (**table 4**): 7 to AX and 1 to CLV (who had a negative oral challenge with AX).

Considering the 4 patients who was found to be allergic to cephalosporins (**table 5**), 1 reacted with cefatrizine and with AX-CLV, and had positive IDT with amoxicillin (injectable formulation of cefatrizine is not available in Portugal); and 3 patients reported intra-operative anaphylaxis with cefazoline and had positive IDT only with cefazoline.

The remaining 31 patients with confirmed hypersensitivity to other BL had negative DPT to the alternative BL antibiotic (cefuroxime, second generation cephalosporin).

Discussion

In this study, we evaluated a large group of patients including children and adults with suspected hypersensitivity to BL over a 3-year period time, and realized that only 18% of them were truly BL allergic. The diagnosis was based up on a positive serum-specific IgE determination (12%), skin tests (70%) or DPT (18%).

Overall, our results confirm that clinical history by itself is insufficient to label the patient as "penicillin allergic", since it will lead to over-diagnosis when solely used. Moreover, the occurrence of reactions in a distant past made it difficult for the patient to recall the symptoms, and some patients can outgrow penicillin allergy over time. Time interval until evaluation is critical. Patients with clear anaphylactic reactions did not always have positive skin tests or specific IgE, and that results could be in part caused by the time interval between drug exposure and the time of evaluation (15). In our study, 30 patients had reported anaphylactic reactions and only 20 of those were diagnosed as being BL allergic. In these patients, an extensive allergologic work-up was carried out to study other causes than could explain the anaphylactic reaction, either others drugs namely non-BL, general anesthetics or non-steroids anti-inflammatory drugs, either food allergy.

The work-up for the diagnosis of BL hypersensitivity included performing skin tests with major and minor determinants of BP, penicillin and other related-compounds and cephalosporins. AX was the most relevant, showing positive results in 19 patients. In spite of being considered time-consuming, skin testing followed by DPT continue to be the most accurate strategy to investigate these patients. These allergological tests should always be performed in hospital setting, by experienced medical staff. Even though the immediate reactions are considerably more common, delayed reactions should be kept in mind, and the patients must be advised that it can occur and must be registered. Furthermore, as reported in our study, skin testing can be responsible for systemic reactions, which should be promptly recognized and treated. We had 9.3% (4 patients) with systemic reactions in the positive tested patients (one with anaphylaxis during IDT), which represented 1.7% of systemic reactions in all tested patients. Comparable results were published by Co Minh *et al.* in a study performed over 8 years, where 14.7% (147 patients) had positive skin tests results and 8.8% of those (13 patients) showed a systemic reaction during skin tests, which represented 1.3% of all tested patients; among

those with systemic reactions, 5 reacted with SPT and 10 had clinical history of anaphylaxis (16).

In our study, considering the four patients who had systemic reactions during skin tests, in all the culprit drug was AX, in three associated with CLV. Two developed cutaneous symptoms during SPT, being the clinical history urticaria and angioedema, and the other two had reported anaphylactic reactions with drug intake and reacted with IDT (table 3). One was a 3-year-old child who developed an immediate anaphylactic reaction after IDT with 10-fold diluted solution of AX; the other was a woman who developed facial rash after 1 hour, along with positive delayed reading of IDT with AX.

There were two patients with negative allergological investigation tests, who had tolerated DPT with AX alone but had reacted with AX-CLV. Considering the period of time of the present study, CLV extract (*DAP® Clavulanic, Diater, Madrid, Spain*) was not still available in our country. However, DPT remains the gold standard for confirming or ruling out the hypersensitivity diagnosis. In some cases of nonimmediate reactors, the DPT must be prolonged, and a 5-day or even a 7-day challenge with the culprit BL may yield more positive reactions than the accepted 1-day or 2-day challenge (17,18). Therefore, the interpretation of skin testing should always be made with caution.

We found that in 18% of patients DPT has been paramount for the diagnosis validation, since this couldn't have been achieved without it. Similar results were found by Bousquet *et al.* (19), that included 1218 patients in whom BL allergy was confirmed in 21.1% by skin tests (178; 69.3%) or by DPT (79; 30.7%). In this study, 17.4% of the patients with negative skin tests to major and minor penicillin determinants were positive for a BL antibiotic. According to these authors, if all skin tests are negative, skin tests with other determinants and provocation tests under strict surveillance are mandatory.

Studies performed in a large series of patients with cutaneous symptoms showed that 19% were diagnosed as being allergic to BL (6,10). We found similar results, over a 3-year period time, since 18% of our patients were allergic to BL. In a previous Portuguese study, also performed in a drug allergy center, Silva R *et al.* (20) studied 67 patients with suspected BL hypersensitivity reactions and found a higher percentage (27%) of confirmed cases. Campina S *et al.* (21) studied 110 patients with suspected BL hypersensitivity, also referred to an allergy specialized center, and found an even higher percentage (44%) of confirmed cases. This study includes an adult population, and this may justify the higher percentage of confirmed diagnosis. In a large paediatric French study, over 20-year (22), 1431 children were studied with suspected BL hypersensitivity, but after work-up only 15.9% were diagnosed allergic to BL. In another large paediatric study, performed in Spain (8), 783 children were studied with suspected BL hypersensitivity, and after work-up an even lesser percentage (7.9%) were diagnosed allergic to BL.

The sensitivity of skin tests, previously around 95%, has been decreasing in publications from last decade (12,23). According to a study performed by Torres *et al.* (23), which included 290 patients, skin tests were positive in only 70.3% of them. The lower sensitivity of skin test explains why some cases of BL allergy, will fail to be diagnosed if DPT is not performed. In our study, five patients with negative skin test results reacted with culprit drug, resulting in 85.7% of sensitivity for the skin tests. We stress out that two women with negative skin tests had anaphylaxis during DPT with AX (immediately after 100 mg and 250 mg, respectively).

In skin test-negative patients, five of 189 reacted to the culprit drug, which represents a NPV of 97.4%. Comparing with the study performed by Goldberg and Confino-Cohen (24) they found that four out of 94 skin test-negative patients reacted to penicillin V or amoxicillin challenge, achieving a NPV of 95.7%. In skin test-positive patients, as defending by other authors (1,12,15,25), the diagnosis was confirmed, and DPT was not performed. The authors feel that on the basis of the current literature and standard of care, to demonstrate the positive predictive value of these skin tests is unnecessary and potentially dangerous.

Regarding *in vitro* tests, commonly used as the first approach in these patients, the specificity of BL-specific IgE antibodies ranges from 83.3 to 100% and the sensitivity from 12.5 to 45%, depending on the clinical manifestations (15). In our study, we found a sensitivity of 18.6% and a NPV of 82.4%.

As a result of our allergological investigation, we demonstrated that the majority of patients who were labelled as "allergic" can safely be treated with BL, and those whose BL hypersensitivity has been confirmed, a second generation cephalosporin can be used. Accurate diagnosis has an enormous economic and biological impact. These patients have no longer need to be prescribed with more expensive or less effective antibiotics. Studies have been published showing clear cost-implications associated with BL allergy, namely prolonged intravenous antibiotics instead of oral formulations, increased length of stay and total cost of hospital admission and a worrying growing of bacterial resistance resulting from the use of non-penicillin-based alternatives. Moreover, their potential toxicities and reduced efficacy must be considered (26). Owing to the possibility of cross-reactivity, patients with confirmed BL hypersensitivity were advised to avoid first generation cephalosporins (15,27,28).

Conclusions

Hypersensitivity to BL can be responsible for distinct reactions, ranging from mild symptoms to systemic and severe reactions. Clinical history might frequently lead to misdiagnosis, being the investigation negative and suspicion of hypersensitivity ruled out in most of the cases. The confirmed cases are mainly due to IgE-mediated reactions. However, one fourth of confirmed cases seem to have non-IgE mediated reaction.

We evaluated a large number of patients, under the same protocol. All patients were properly investigated with standardized *in vitro* and *in vivo* tests. Despite time-consuming, skin testing seems to be the more accurate approach to confirm BL hypersensitivity. Our results show that we should be aware for the possibility of systemic reactions either during skin tests or DPT. Most patients have positive results to several BL, within the same group, but others can have selective reactions. In our country, the oral formulation of penicillin is not available. For that reason, we did not perform DPT with this drug. Considering this, it is difficult to convince patients to undergo DPT which requires parenteral administration. This can be seen as a limitation, because due to this circumstance we might have missed selective hypersensitivity reactions.

Considering all the implications of a proper diagnostic approach, including systemic reactions during skin tests and DPT, all these patients should be evaluated in specialized centers. Accurate diagnosis of hypersensitivity to BL is crucial not only to improve patient safety, when they need to be treated with antibiotics, but also to avoid increased rates of bacterial resistance and to reduce medical costs. For these reasons, the study of all suspected cases of BL hypersensitivity is highly important and cost-effective.

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Comano thermal water inhalations in the treatment of allergic rhinitis: preliminary results

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Key words
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Summary
Background. *Comano thermal water, well known for its activity in the treatment of dermatological diseases, has been successfully employed in the treatment of upper airways disorders.* ***Objective.*** *The present preliminary study aimed to evaluate whether Comano thermal water may be able to improve nasal symptoms severity in patients with allergic rhinitis (AR).* ***Methods.*** *30 AR patients were enrolled (mean age 40.9 years; 13 males) and treated with inhalation of Comano thermal water for 15 days. Total symptom score (TSS) and visual analogue scale (VAS) for patient's perception of nasal patency were assessed at baseline, after treatment, and after a 2-week follow-up.* ***Results.*** *TSS significantly decreased after treatment as well as VAS significantly increased. The effects were partially long-lasting.* ***Conclusion.*** *Comano thermal water inhalation as monotherapy for AR was able to relieve nasal symptoms and patient's perception of nasal patency.*

Introduction

The term crenotherapy derives from old Greek (κρήνς = spring and θεραπεία = therapy). Crenotherapy, such as the use of thermal water, is popularly recognized as effective and safe, even though there is still a lack of a clear evidence about effectiveness and mechanism of action. Many ENT disorders are widely treated by crenotherapy, including respiratory infections (1). Crenotherapy may be internal or external. Internal crenotherapy includes: hydropinotherapy (such as administration of thermal water as beverage), irrigation, inhalation, and insufflation. External crenotherapy consists of balneotherapy, halotherapy, and pelohydrotherapy (such as mud bath). The fascination for thermal baths began at the time of Romans who spent many time at *Thermae*, that were a community wellness centre attended by all social classes. So, thermal establishments were very popular, insomuch as the term *SPA* derives from the Latin acronym: *salus per aquam* (health by water). On the other hand, crenotherapy, which is the oldest therapy for upper airways disorders in medical history, has not a unanimous acknowledgement (2). Thermal waters may be classified on the basis of their chemical-physical characteristics as: sulphurous, salso-bromo-iodic, bicarbonate, and bicarbonate-sulphate. Many clinical and empiric studies provided their efficacy in chronic and relapsing inflammatory disorders of upper airways (3).

Comano Terme is a municipality in the province of Trento (Northern Italy) placed at 400 m/a.s.l. and 46°01′00″N 10°52′00″E; in its territory the Terme di Comano is placed. Comano water is bicarbonate-calcium-magnesium. The thermal water of Comano is recommended since long time for cutaneous disorders (4,5) and upper airways diseases (i.e. allergic and vasomotor rhinitis and chronic and recurrent upper airways inflammatory disorders, such as rhinosinusitis, pharyngitis, laryngitis, in both adults and children). Its mechanisms of action

are: mucosal tissue optimisation, immune response stimulation, pro-inflammatory agents clearance, and increased muco-ciliary cleaning. As the sulphurous and salso-bromo-iodic thermal waters are particularly active, they can induce unpleasant side effects in the patients with hyperergic disorders (6). Comano water is mild, so it may be better tolerated. In this regard, there are four studies that investigated the efficacy and tolerability of Comano thermal water in patients with upper airways disorders. The first study showed that it was effective and safe in 40 patients with sub-acute and/or chronic inflammation of upper airways caused by mucosal hyperreactivity (7). The second study (randomized, placebo-controlled, and double-blinded) conducted on 30 patients suffering from vasomotor rhinitis demonstrated that Comano thermal water significantly affected nasal symptoms, improved nasal blood supply, and strengthened local nasal immune response (8). The third study (randomized, placebo-controlled, double blind) was carried out in 30 patients with chronic pharyngitis and showed that pharyngeal blood flow and pharyngeal secretory IgA significantly increased only in Comano group (9). The last open study was confirmatory and reported significant reduction of mucociliary clearance, increase of blood and air flow as well as of secretory IgA (10).
However, there were only anecdotic data about effectiveness in patients with allergic rhinitis (AR). Therefore, the present preliminary study aimed to evaluate whether Comano thermal water may be able to improve nasal symptoms severity in patients with allergic rhinitis.

Materials and Methods

Globally, 30 consecutive patients were enrolled (mean age 40.9 years; 13 males); the inclusion criteria were: i) age range between 18-65 years, ii) AR diagnosis based upon the concordance between typical history of allergic symptoms and documented sensitization, iii) presence of nasal symptoms (with moderate-severe obstruction and/or rhinorrhoea), iv) written informed consent. Exclusion criteria were: i) chronic illness, ii) immune deficiency, iii) continuous use of medications (e.g. antihistamines, corticosteroids) in past 4 weeks, and iv) concomitant use of immune-stimulants.
Patients were treated by Comano thermal water administered by inhalation. Daily, patients were treated with inhalation of 1 L of solution, supplied by Asema inhaler, for 10 minutes. The subjects had to normally breath; the inhaled drops had an 8-12 micron diameter at 37-38 °C temperature. Interfering drugs were prohibited. The thermal course lasted 15 days. Cetirizine syrup (1 drop / 3Kg bw) was permitted as rescue medication along the treatment period.
Nasal symptoms (itching, sneezing, rhinorrhoea, and obstruction) were scored using a four-point scale (0 = no symptom; 1 = mild symptom; 2 = moderate; 3 = severe) assessed by a doctor. The sum of these symptoms was calculated and expressed as Total Symptom Score (TSS). In addition, a visual analogue scale (VAS) was used for assessing the patient's perception of nasal patency. The VAS is a segment of 10 cm where the patients indicated the actual perception of nasal patency by marking a point. In this study, 0 implied the worst perception (such as complete nasal obstruction), while 10 corresponded to an optimal one (such as nose completely open).
The Patients were visited at baseline (T1), after treatment (T2), and after a 2-week follow-up (T3); all above-mentioned parameters were evaluated during each visit. Symptomatic use of cetirizine was recorded as days. Adverse events were as usually registered.
Statistical analysis was performed by ANOVA Friedman and by post hoc assessment by Wilcoxon test. Data are expressed as median and percentiles (25^{th} and 75^{th}, IQR). A p-value ≤ 0.05 was considered statistically significant. All data were analyzed using the Stata statistical package, Release 13.1 Statistical Software (StataCorp, College Station, TX, USA).

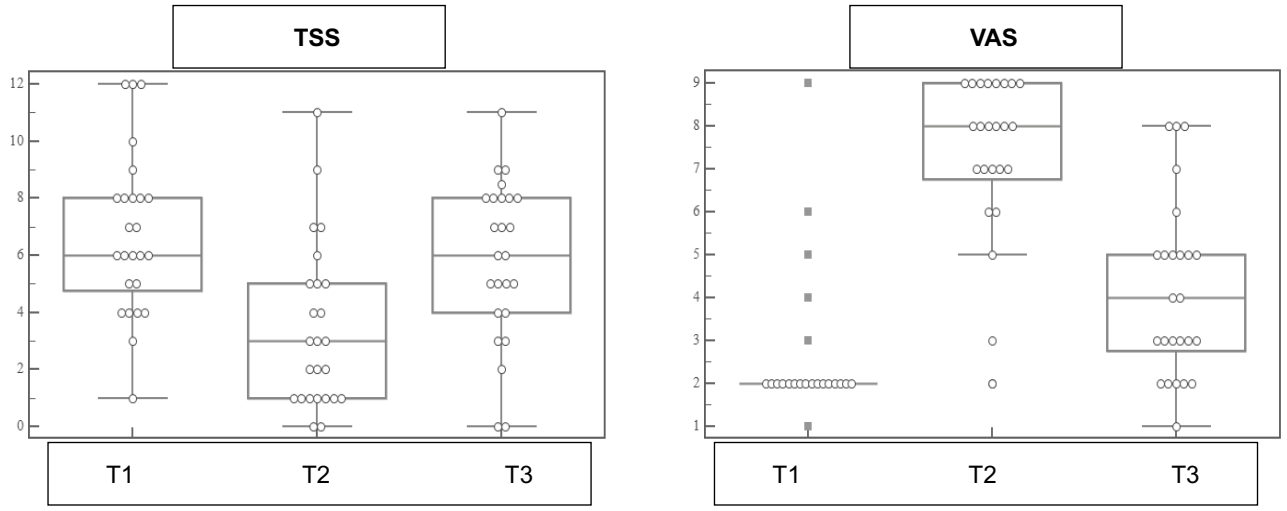
Results

All subjects completed the study, and the treatment was well tolerated without significant adverse event. **Figure 1** reports the findings.
TSS significantly changed during the study ($p < 0.001$): the basal values (M 6, IQR 4.5-8) significantly diminished ($p < 0.0001$) after treatment (M 3, IQR 1-5), but significantly increased ($p < 0.0001$) at follow-up (M 6, IQR 4-8), however a significant difference ($p < 0.04$) remained between T1 and T3.
VAS significantly changed during the study ($p < 0.001$): the basal values (M 2, IQR 2-2) significantly increased ($p < 0.0001$) after treatment (M 8, IQR 6.8-9), but significantly decreased ($p < 0.001$) at follow-up (M 4, IQR 2.8-5), however a significant difference ($p = 0.03$) remained between T1 and T3.
The mean number of days with antihistaminic use was 3.5 during the treatment period, and 4.4 during the follow-up.

Discussion

The present study demonstrates that intranasal administration of Comano thermal water was able to significantly reduce nasal symptoms in patients with allergic rhinitis. In addition, this treatment was also able to significantly affect the patient's perception of nasal patency. These findings support the concept that nasal inhalation of Comano thermal water may control allergic symptoms. It is to underline that the current treatment was administered as monotherapy: this aspect reinforces the effectiveness of nasal lavage in AR. The present study is also consistent with previous studies performed using Comano thermal water in patients with upper airways disorders (7-10).

Figure 1 *- Left quadrant: Total Symptoms Score (TSS) assessed before (T1) and after treatment (T2) and follow-up (T3). Right quadrant: VAS of nasal patency assessed before (T1) and after treatment (T2) and follow-up (T3).*



Comano thermal water has peculiar chemical-physical characteristics that depend on its composition: bicarbonate calcium-magnesium. This thermal water has a mild activity, even though sufficient for adequately treating many upper airways disorders, as evidenced by all these studies, and is well tolerated. So its use is safe and effective. The mechanism of action is based on ion composition and consists of: i) improving local mucosal blood supply, ii) restoring the mucosal integrity, iii) normalizing the epithelial clearance, and iv) stimulating local immune response, including recent evidence on the modulation of expression and secretion of some mediators, such as vascular endothelial growth factor (11), interleukin-6 (12), tumor necrosis factor-a (13). These last mechanisms may be involved in the cascade of events involved in skin regeneration process (14). All these effects may significantly improve clinical symptoms and objective signs. Therefore, Comano crenotherapy could be indicated in the treatment of AR.

The main shortcoming of this study is the lack of a control group. However, it has to be considered that nasal lavage is *per se* able of significantly improve nasal symptoms as clearly evidenced in previous studies. So, this study has been designed including a follow-up period able to evaluate the time without treatment as a control of the active period. Anyway, further controlled studies should be performed to confirm this preliminary experience. In this regard, preliminary studies investigated the microbiota characteristics of Comano water as well as of the skin of patients with cutaneous disorders (15,16). Thus, promising outcomes could derive from this issue.

In conclusion, the present study provided the preliminary evidence that Comano thermal water inhalation as monotherapy for AR was able of relieving nasal symptoms and patient's perception of nasal patency. Thus, this outcome could suggest that one course of this thermal water could be effective, so reducing the use of pharmacological therapy.

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Comparing the compliance to a short schedule of subcutaneous immunotherapy and to sublingual immunotherapy during three years of treatment

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Key words

subcutaneous immunotherapy; sublingual immunotherapy; patient's preference; compliance

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Summary

Background. *Allergen immunotherapy (AIT) in its two forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) is an effective treatment of respiratory allergy, but is particularly concerned by the issue of compliance.* ***Objective.*** *We aimed a real-life study at evaluating the compliance to SLIT and to SCIT administered by a short-course of four injections during a 3-year period of observation.* ***Methods.*** *A group of 145 patients (79 males, 66 females, age ranging from 14 to 69 years), suffering from pollen-induced rhino-conjunctivitis with or without asthma, were included in the study. Following adequate education on AIT and according to patient's preference, 72 patients chose to be treated with short-course SCIT and 73 chose to be treated with SLIT. The latter was performed by allergen extracts from different manufacturers according to the suggested schedules.* ***Results.*** *The rate of withdrawal was as follows: after one year, 15.6% for SCIT and 33.4 for SLIT; after two years, 25.6% for SCIT and 44.8% for SLIT; after three years, 26.7 for SCIT and 46% for SLIT. There was no significant difference in the rate of withdrawal between males and females. Regarding the safety, no systemic reaction requiring medical treatment was observed either in SCIT or SLIT group.* ***Conclusion.*** *The findings of this study confirm that involving the patient in the choice of the route of administration is associated to a satisfactory compliance to AIT. In particular, more than 70% of patients treated with a short schedule of SCIT completed the three-years course of treatment that is recommended for AIT, while this goal was reached by 54% of SLIT treated patients.*

Introduction

Allergen immunotherapy (AIT) is an effective treatment of respiratory allergy, but is affected, as any other medical treatment, by the issue of compliance. The early studies were performed when only subcutaneous immunotherapy (SCIT) was available, detecting a low compliance, that ranged from 45% to 60%. The demanding schedules used, with very frequent injections, accounted for this outcome, as shown by patients' recognition of inconvenience as the major cause of noncompliance (1). Sublingual immunotherapy (SLIT), that is administered at home by patients themselves, is free from such problem and should have compliance characteristics similar to drug treatment. In fact, first studies on SLIT reported very good compliance, ranging from 79% to 97% (1). A study compared the compliance with SCIT and SLIT administered in hospital or in private office settings in a large group of children (2). With SCIT, applied on 1886 subjects, 207 (10.9%) were noncompliant, with no significant difference between the two settings. The major reasons for withdrawing were the cost (35%), family problems (21%), inconvenience (20%), lack of efficacy (16%), and adverse reactions (7%). SLIT was used in 806 patients, 173 of whom (21.4%) were noncompliant, with a highly significant difference for a better compliance in hospital setting (90.5%) compared to private office setting (61.2%); the most common reasons of withdrawal were the cost of treatment, reported globally in 36.4% of cases, inconvenience, feeling of in-

efficacy, and side effects. Still, the good compliance to SLIT was not confirmed when the data from manufactures were analyzed. In fact, calculating the rate of spontaneous discontinuations by the sales data of two large manufacturers in Italy over a 3-year period, a decrease from 100% to 43.7% in the first year, to 27.7% in the second year, and to 13.2% in the third year, was found (3). We aimed the present real-life study at evaluating the compliance to SLIT and to SCIT administered by a short-course of four injections during a 3-year period of observation.

Patients and methods

Patients

During the pollen season 2010-2011, 145 patients (79 males, 66 females, age ranging from 14 to 69 years), suffering from pollen-induced moderate to severe rhino-conjunctivitis with or without mild asthma were enrolled in the study. To be included, patients must have homogeneous characteristics according to allergic disease severity. As reported in a previous article (4), we proposed either SCIT with Pollinex 4 (Allergy Therapeutics, Worthing, UK), a product based on a short administration in 4 injections, or SLIT with extracts from different manufacturers, namely Allergy Therapeutics, ALK Abellò (Horsholm, Denmark), Stallergenes (Antony, France), Allergopharma (Reinbek, Germany) and Lofarma (Milan, Italy). For each kind of SIT, the major practical advantages or burdens were highlighted. Of 145 patients, 72 chose Pollinex 4 SCIT and 73 chose SLIT. SCIT-treated patients received a total of 90 treatments (18 patients had double course of SCIT). SLIT-treated patients received a total of 87 treatments (14 patients had double course of SLIT). The pollens used for AIT were as follows: birch pollen or tree mix pollens, 28 SLIT and 20 SLIT; grass pollen, 56 SCIT and 47 SLIT; *Parietaria* pollen, 3 SCIT and 2 SLIT, ragweed pollen, 2 SCIT and 0 SLIT; mixed birch and grass pollen, 0 SCIT and 10 SLIT; mixed grass and *Parietaria* pollen, 1 SCIT and 4 SLIT; mixed grass and ragweed pollen, 0 SCIT and 4 SLIT. In the SCIT group, there were 49 males and 23 females; in the SLIT group, there were 30 males and 43 females. Mean age was 36.5 years in SCIT group and 28.5 years in SLIT group. Here we present the data from three years of follow-up in patients treated with SCIT or SLIT. All patients received written information and had to refer every year to the Allergy service to renew the prescription of SCIT or SLIT; during this visit, the data regarding safety and tolerability of the treatments were obtained. All patients were instructed to contact us in case of problems with the treatment.

Educational forms

Two kinds of written forms were given to patients, concerning SLIT and SCIT, respectively. The SLIT form reported:

1. How to take the treatment (number of days per week, time to assume SLIT during the day, up-dosing modality, how to storage the AIT).
2. The possible local adverse event (oral or gastro-enteric) and how to deal with them.
3. The outpatient clinic phone number to call if the patient needed explanation from doctor or nurse or to inform the doctor in case of interruption.
4. The remind to schedule another visit to order the allergen extracts for AIT at the 2nd and 3rd year. The form indicated the month of the year the patient had to visit the clinic to be in time for the re-order.

The SCIT form reported:

1. The number, date and time of visits to perform the injections course.
2. The possible local adverse event after the injection and how to deal with them.
3. The outpatient clinic phone number to call if the patient needed explanation from doctor or nurse or to inform the doctor in case of interruption or troubles with the injection visits.
4. The remind to schedule another visit to order the allergen extracts for AIT at the 2nd and 3rd year, with the same instructions as for the SLIT form

The objective was to educate the patient to have an active role in the AIT process and to increase the compliance.
All data from the two groups of patients were compared by the chi square test, a significant difference being stated at a p value < 0.05.

Results

SCIT was chosen by a number significantly higher ($p < 0.05$) of males, this significant difference was confirmed after 1, 2 and 3 years of treatment (**table 1**). SLIT was chosen by more females than males, but the difference was not significant. No patient discontinued SCIT or SLIT during the first cycle of treatment. **Table 1** shows the number of patients continuing the treatment after 1, 2, and 3 years. The withdrawal after 1 year concerned 11 grass pollen and 3 birch pollen SCIT treatments, and 19 grass pollen and 7 birch pollen SLIT treatments (including one double treatment with both pollens). After 2 years it concerned 7 grass pollen and 2 *Parietaria* pollen SCIT treatments, 7 grass pollen and 3 birch pollen SLIT treatments and 2 *Parietaria* pollen SCIT treatment (including 2 double treatments, one grass / birch and the other grass / *Parietaria*). After 3 years, it concerned one grass pollen treatment both for SCIT and SLIT. There was no significant difference in the rate of withdrawal between males and females, while the mean age of patients who

Table 1 *- Number of SCIT and SLIT treatments continued during the follow-up.*

	After 1 year (%)	**After 2 years (%)**	**After 3 years (%)**
SCIT (90) 59 males, 31 females	76 (84.4) 50 males, 26 females	67 (74.4) 44 males, 23 females	66 (73.3) 43 males, 22 females
SLIT (87) 35 males, 52 females	58 (66.6) 23 males, 35 females	48 (55.2) 17 males, 31 females	47 (54) 16 males, 31 females

withdrew was 40 years after one year (higher than the mean age of 36.5 years in SCIT group and 28.5 years in SLIT group at baseline), this higher age being confirmed for SCIT at the study end for females (mean 40 years compared to 35 years at baseline) but not for males (mean age 33 years compared to 35 years at baseline). All these differences were not significant. The reasons for withdrawal were missed visits for all patients interrupting SCIT, while were local reactions for 20 patients (8 males and 12 females) and missed visits in the other patients. Regarding the safety, no systemic reaction requiring medical treatment was observed either in SCIT or SLIT group.

Discussion

A poor compliance is a general issue for prolonged medical treatments, but is particularly detrimental for AIT, because an insufficient duration prevents the occurrence of the immunological changes that underlie the clinical efficacy and, especially, the persistence of the clinical effects after stopping AIT (5), that must be administered for at least three years (6). This makes the achievement of a good compliance of critical importance. Actually, in the rigid organization of controlled trials, the compliance to both SCIT and SLIT was good in most cases (7), and also the first real-life studies reported, particularly for SLIT, compliance and adherence rates often higher than 80% (1). However, the data based on manufacturers sales reported by Senna et al (3) changed the landscape and were confirmed by recent surveys. For example, in a recent retrospective analysis by Dutch authors of data from 6486 patients starting immunotherapy between 1994 and 2009, 2796 patients receiving SCIT and 3690 received SLIT, only 18% reached the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively. These findings were, according to the authors' suggestion, a sign for "an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance" (8). In another study, German sales data for different preparations of a single allergen manufacturer were retrospectively evaluated for 5 consecutive years, based on prescriptions per patient. Pollen SLIT and high-dose hypoallergenic (allergoid or unmodified depot pollen and mite preparations for SCIT) were used, 85,241 patients receiving pollen or mite SCIT and 706 patients receiving pollen SLIT. Prescriptions for at least 3 years were done for 42% of patients with pollen SCIT and for 45% of patients with mite SCIT. Compliance with SLIT concerned only 16% of patients receiving prescriptions for at least 3 treatment years (9). The approaches to improve compliance to AIT, and particularly to SLIT, that were proposed when the available data were more positive, remain valid. They include patients' education and appropriate timing of control visits. Concerning education, a better compliance was reported in patients receiving a complete educational program on SLIT with written instructions compared with patients receiving verbal standard information (10). This was confirmed in a study based on an educational / follow-up plan applied on 149 patients treated with SLIT compared to 90 patients not participating to the plan. In the first group, discontinuations at 4 months were 5% vs. 18% in the controls and after one year they concerned 12% of patients in the first group and 35% in the control group. The authors concluded that "An adequate education and a strict follow-up can significantly reduce SLIT discontinuations" (11). Regarding the timing, Vita et al. performed a study on three groups of SLIT treated patients, the first with a control visit scheduled at 3-months interval, the second at 6-months interval, and the third with only one visit / year. The best compliance was found in patients called for visits four times per year (18.5% of withdrawals), while children of other two groups abandoned SLIT with a rate of 32.3% in patients with two visits and 70.4% in patients with one visit / year, respectively (12).

In the present study we used the innovative approach to involve the patient in the treatment choice. Following extensive information and written instructions on the two treatments for seasonal allergy, 49.6% of patients chose SCIT and 50.3% chose SLIT (4), This suggests that when the SCIT schedule is short (only 4 injections / year with the product we employed) choosing SLIT is not so obvious. Sixty-eight per cent of male patients preferred SCIT (a rate significantly higher than females), while 58.9% of female patients preferred SLIT, this difference being not significant compared with males). The results of the follow-up showed that the higher rate of withdrawal occurred at the first year (15.6% and 33.4% for SCIT and SLIT, respectively), with a rate increase at the second year of 10% for SCIT and 11.4% for SLIT, and a further but small increase of withdrawal of about 1% at the

third year. Very recently, a study based on the same approach was published. Patients underwent to SLIT or SCIT according to their preference (active group) or to physician's choice (control group). After 6 months, there was no difference in adherence to SLIT or SCIT in the active group, while a significant difference was detected between the rate of non-adherence in the active group (11%) compared with the control group (21%), this being a good outcome, though limited by the short follow-up duration (13). In a recent review, Antico discussed the large differences of compliance and adherence observed in the available studies. He suggested that the better outcome in placebo-controlled studies may depend on the patient's motivation, and particularly on the patient's decision to participate in the trial and to meet the researcher's expectations, defining a condition conceptually similar to concordance, that is a consultation process, based on the patient's belief and needs, that tends to establish a therapeutic alliance between the physician and patient (14). This is in agreement with the role of patient's values and preferences in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to medical treatments (15). Our study, as well as the study by Sanchez discussed above, supports the importance of this concept.

In conclusion, the findings from this real-life study show that when patients are involved in the choice of the kind of AIT, a satisfactory compliance to the treatment is observed. In particular, more than 70% of patients treated with a short schedule of SCIT completed the three-years course of treatment that is recommended for AIT, while this goal was reached by 54% of SLIT treated patients. This rate of compliance to SLIT, though lower than to SCIT, is much better than those reported in recent studies (3,7,8) and is comparable to the compliance commonly observed with prolonged drug treatments by oral administration (16).

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Monitoring the hospital management of acute asthma: the Italian Pediatric Network experience

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Summary
Background. *The Study Group on Accreditation and Quality Improvement of the Italian Society of Pediatrics has developed an observational study about the hospital management of pediatric patients affected by severe asthma, in order to evaluate how the Guidelines for severe asthma in childhood are applied in the daily practice.* ***Methods.*** *This study included patients between 2 and 17 years, hospitalized or under short intensive observation for acute asthma. The data collection was carried out through the compilation of on-line forms. The statistical technique used was the Chi Square test.* ***Results****. 409 forms were filled in by 32 Italian Centers. 17% of the patients showed severe asthma, 59% moderate and 24% mild. On arrival at the Emergency Room the oximetry was measured in 95% of the patients, the respiratory rate in 64% while the heart rate in 88% of them. 48% of the children were exposed to chest X-ray. More than half of the children received oxygen therapy, 98.5% received short-acting beta-2 agonists and systemic steroid therapy was given to 82% of children, mainly orally. At discharge only half of the children were provided with written instructions for the management of any subsequent asthmatic episode. The analysis of the collected data highlights that not all the children had their oxygen saturation measured, although this parameter is one of the main indicators of disease severity, as well as the respiratory rate, which was detected in a minimal percentage of cases. The frequency of chest X-ray was extremely high, even though it does not have any indication in the majority of asthma cases. The evaluation of the therapeutic treatment denotes an adequate use of the oxygen therapy according to the oximetry values found on arrival, but an abuse of steroid therapy. Critical issues emerge at discharge: children are not always educated about the home management of the disease and the self-evaluation of the illness seriousness.* ***Conclusions.*** *The pediatric network has become an excellent system of monitoring of the clinical management of asthmatic children, highlighting strengths and weaknesses on which to focus actions of improvement.*

Background

During the past years there has been a significant increase in pediatric asthma cases worldwide (1). This epidemiological evaluation was mainly directed by the ISAAC International Study (2,3) through computerized and hard-copy standard questionnaires, with detection of higher prevalence of asthmatic symptoms in developed countries, but greater symptom severity in developing countries.

This trend prompted the need to draft more and more updated National and International Guidelines for the treatment

and the diagnosis of asthma and to monitor the adherence of pediatricians to the optimal indications in the management of childhood asthma. While many documents (4,5,6) have been published suggesting the various steps to the diagnosis and therapy of asthma and indicating the parameters to evaluate the patient adherence to the medical instructions, little is known on how the national and international Guidelines of pediatric acute asthma management are applied in everyday clinical practice. Since Italy is not exempt from this evident lack of data, the Study Group on Accreditation and Quality Improvement (GSAQ) of the Italian Society of Pediatrics (SIP), in the context of a network of analysis of the various pediatric pathologies, issued an observational study on the hospital management of the pediatric patients with acute asthma.

Methods

From 2009 to 2013, 2 to 17-year-old patients, either hospitalized or under short intensive observation were recruited. The patients with positive or suspected post-infectious wheezing were excluded, on the basis of medical history and clinical signs of recent or concomitant infection on physical examination.
The data were gathered through the compilation of on-line forms accessible after registration on the Network website (7). The sheet was designed by a team of experts, on the basis of the Italian Guidelines for acute asthma in children (4), directly available at the dedicated link of the Network website. The sheet included several sections, referring to each of the diagnostic-therapeutic steps, starting from the collection of the anamnesis, the vital signs, the clinical management, to the procedures of hospitalization and discharge. To limit the bias raised by the subjective clinical interpretation of any physician, the form included impartial parameters, favoring quantifiable information (blood oxygen saturation, respiratory rate). For the same reason the questions that were not requiring the input of numeric data, in almost all the cases, required simple answers as YES/NO, preventing the possibility of entering free text. In addition, the Network tool offered the Centers the possibility to view the statistical analysis of their own data, and compare them to the ones collected at Regional or National level.
For each Center participating, one or more pediatricians, mainly allergists, were identified, and trained on how to fill in the sheets. They were responsible of data loading both of their own patients and of the ones managed by their colleagues from the same hospital organization, taking the information from the medical records of hospitalization or from short intensive observation. The export of the data from the Network sheets was performed through the portal. The information normalization and the variables definition under examination was carried out using the Microsoft Access database.

Statistical Analysis

The study was set up as an exploratory investigation, preliminary to further studies focused on specific clinical aspects. The purpose was to identify significant connections between variables that regarded the following aspects: personal data, anamnesis, description of the acute event, therapy and the procedures of hospitalization and discharge. It was possible to represent the variables through contingency tables, since they were measured on nominal range. The proper statistical technique in this case is the Chi Square test for the independence of categorical variables. This test evaluates the general hypothesis that the considered variables are mutually independent, or, in other words, that the correlation between them is equal to zero. This is the null hypothesis, to falsify. First the following assumptions were verified: independence of the observations (meaning to reject variables representing repeated measures in the same patients); presence of not more than 20% of expected frequencies less than 5; no observed frequency equal to zero. In the first stage, the contingency tables were submitted to the Chi Square test as they appeared, without handling the original frequencies. In the following stage, in some cases the variables were aggregated, in order to delete the cells lacking informative content. In the tetrachoric tables, the significance was evaluated also through the Fisher exact test. In the relations showing a p-value < 0.05 the following factors were also evaluated: the strength of the association between the variables, by the Cramér's V coefficient, and the falsity degree of the null hypothesis, utilizing an index of the effect size (Pearson's Phi). Furthermore, the adjusted standardized residuals were analyzed, in order to identify the cells of the contingency table mainly responsible of the association between the variables. With the information referred to a sample of 409 patients and collected into 71 variables, 39 connections were found, on which the analysis was focused.

Results

Anamnesis

409 completed forms were collected from 32 Italian Centers. The population considered in the study was 55% males and 45% females; 57% of the patients were in their preschool age (< 6 years) and 43% were 6 to 17 years old. About 48% showed positive personal history of allergic diseases and 66% of asthma. 11% of the patients referred a hospitalization for asthma in the past 12 months. Only a small percentage (16%) was already taking a controller anti-asthmatic medication, while 49% was already under a home therapy for acute episodes before the access to the hospital. 81% of the patients (87.7% in preschool age and 75.3% in school age) arrived to the hospital without a previous consultation with their own Pediatrician or Family Doctor.

Parameters at entrance

The parameters collected at entrance are shown in **table 1**. An oximetry value below 92% was found in 29% of the cases, above 95% in 22% and an intermediate value in 44% of the cases. 5% of the patients did not have their oximetry value measured at entrance.
The classification of the asthma severity level identified 17% of the cases as severe, 59% as moderate, and the remaining 24% as mild.

Table 1 *- Parameters collection at entrance.*

	YES	NO
Oximetry	95%	5%
Respiratory rate	64%	36%
Heart rate	88%	12%

Clinical management

The data about the clinical management of asthma are summarized in **table 2**. The bronchodilator therapy was administered in 77% of the cases via nebulizer and only in 33% through puff with spacer. The systemic cortisone therapy was mainly administered orally. The children treated with an antibiotic therapy took mainly macrolides.

Table 2 *- Clinical management.*

	YES	NO
Oxygen therapy	54%	46%
Short-acting beta 2 agonist	98.5%	1.5%
Systemic steroids	82%	18%
Inhaled steroids	37%	63%
Antibiotic therapy	30%	70%
Chest X-ray	48%	52%

Discharge and follow up

At discharge (**table 3**) half of the children received written instructions on how to follow the clinical management at home and about the self-assessment of the disease: most of them were patients with a known diagnosis of asthma.

Table 3 *- Discharge and follow up.*

	YES	NO
Written instructions	51%	49%
Prophylaxis at discharge	37%	63%

Discussion

Anamnesis

In a country like Italy, in which the territorial Family Pediatrician has been available for several years now, the analyzed data still show an excessive number of spontaneous accesses to the Emergency Room (ER) without a previous consultation with the Family Doctor. There seems to be a correlation between the spontaneous entry in ER and the patients' age ($p < 0.022$), in other words the youngest children (3-5 years) are more frequently brought to the hospital without a previous evaluation of the Family Pediatrician.
This issue, in our opinion, is due to the fact that the parents of the youngest children have less experience in the management of this pathology: often it is the first time they have to deal with it, and consequently their greater concern prompts them to look for immediate support at ER. The literature also outlines that in children of pre-school age it is more difficult to classify the type and the severity of acute asthma attacks (8): if it is hard for clinicians, it would be even more difficult for parents. The analyzed data do not point out a significant connection between asthma severity and age range of occurrence: at any age the asthma attack diagnosed at ER could be mild, intermediate or severe.

Parameters at entrance

The respiratory rate and the oximetry, as stressed in the Guidelines (4), are the fundamental parameters to define the severity of a clinical episode. The analysis of the collected data highlights that the oximetry was not measured in all the cases; even more important is the missing measurement of the respiratory rate in about one third of the patients. However, the allocation in the classification of asthma severity based on the oximetry values, heart and respiratory rate was found to be correct, in accordance with the Guidelines (4).

Clinical management

Although the frequency of oxygen administration increased with asthma seriousness, our data point out how the oxygen therapy was used not only, as indicated by the Guidelines (4), in the cases with oximetry values below 92%, but also in about

half of the children with oximetry between 92 and 95% and in a fifth of the children with values above 95%.
Similarly, although the frequency of use of systemic corticosteroids increased with asthma severity, the study showed an abuse of this therapy, that should be reserved only to patients with moderate and severe asthma: even if not optimal, our data outlined an adequate administration of systemic steroids to the patients with moderate and severe asthma, but an excessive use in those with mild asthma. Frequent use of steroids therapy by nebulizer was reported as well, which is not suggested by the Guidelines (4) for acute asthma treatment. The adequacy of the correlation of the severity classification with the oxygen saturation values has already been verified, so we do not believe that excessive corticosteroid prescription could be linked to a wrong clinical evaluation but, as for oxygen therapy, to an excessively aggressive approach to the management of this pathology by physicians.
Our data, in line with the literature (9,10), indicate a very high frequency of chest X-ray use, even though this procedure is not indicated for the initial management of an asthmatic patient, but should be reserved to the severe asthma cases not responsive to the therapy. On the contrary, no connection was found between the chest X-ray use and greater asthma severity. The X-ray abuse exposes children to unnecessary radiations and increases the costs of health expenditure. However, we noticed that the chest X-ray at entrance in patients with a diagnosis of asthma is highly diffused, especially in some hospitals compared to others. It is not known if those Centers have specific internal protocols which require this exam: anyway, those indications should be updated as soon as possible.
The spirometry is generally not performed, probably due to objective difficulties, the need of highly qualified personnel, an available instrument, adequate patient compliance, and enough time to dedicate to the exam. This consideration is in accordance with what described in literature (11). However, it is crucial for the patient to be offered specialist assessment and ambulatory spirometry, even after some time (11,12).
Our data show, in any case, that the spirometry during the hospitalization, when carried out, was reserved to the most severe asthma cases.
In line with the American data (9), 30% of the patients received an antibiotic therapy, generally with a drug belonging to the macrolides class. Comparing these data with those related to the chest X-ray it appears clear that the majority of the patients who were not submitted to an X-ray did not receive any antibiotic therapy, while almost half of those who had an X-ray were subsequently given an antibiotic therapy. Since the radiographic reports are lacking, it is not possible to define if the decision of setting up an antibiotic therapy was linked to a specific X-ray result that modified the diagnosis or to another therapeutic abuse. It is common knowledge that the abuse of antibiotic therapy, in addition to being a useless healthcare resources waste, also favors the development of resistance in the population.

Discharge and follow up

Our data demonstrate the existence of critical issues at discharge too: only half of the children received written instructions and clear explanations on the home management and about the self-assessment of the pathology. Such information was supplied mainly to family of patients with known asthma and thus already partially educated.
In literature there are some international studies that tried to point out the best and most effective follow up options in the post-discharge period and long term follow up (14). In Indiana, they carried out a trial which provided home visits within few days from the discharge by adequately trained paramedic personnel, in order to avoid new hospitalization within a short time of the newly discharged patients but also to evaluate the effectiveness of the therapy and/or prophylaxis prescribed (15).
Other studies outline the patients' difficulty in understanding the instructions received at discharge; benefit could be provided by the use of informative videos to be viewed during the hospitalization and/or at pre-discharge stage to help with the communication, often limited by the lack of time to dedicate to this activity (16,17,18). The hospitalization time could be advantageously used also for health education and instructions, even if the improper hospitalizations for asthma should be reduced through a more adequate outpatient and home management of the patients (19).

Conclusions

The Pediatric Network has become an excellent system of monitoring of the clinical management of childhood asthma, highlighting strengths and weaknesses on which to focus actions of improvement.
On the basis of the data collected, our purpose is now to propose strategies focused on the health personnel training and indications to support the implementation of the Guidelines in their own local reality by means of specific care pathways creation.
Some time from now, a new data collection will provide a feedback on the real effectiveness of the implemented strategies. For the future, we would like to improve the form with some alerts insertion, that on the basis of the loaded data will alarm the compiler on the possible mistakes made in the management of the patient, thus making the compiling task a formative moment, too. These preliminary data could be enriched through wider children case histories entries, thanks to the participation of other pediatric centers as well, that did not take part part in this first edition of the study.

List of abbreviations

GSAQ: Study Group on Accreditation and Quality Improvement
SIP: Italian Society of Pediatrics
ER: emergency room

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Author Contributions

LP AFD GG RL MTO conceived and designed the trial
LP gave access to the Pediatric Network and provided the clinical registration form
AGM MB RB BB analyzed the data and wrote the manuscript
ADV performed the statistical analysis
All authors read and approved the final manuscript.

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A pilot study to assess relationship between total IgE and 95% predictive decision points of food specific IgE concentration

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Key words
food allergy; IgE

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Summary
Background*. False positive test results in children who are tested for food allergies may lead to inappropriate dietary restrictions.* ***Objective.*** *The aim of this study was to report our experience with a 3 year-old boy, who presented with "multiple food allergies" and, however, passed the food challenges, and to review our experience regarding management of children with high specific food IgEs with high total IgE.* ***Methods****. Medical records of 16 children with food challenges were reviewed. Median age of subjects was 39 months, with a history of adverse clinical reaction to a food, a specific IgE greater than the decision point, and an elevated total serum IgE level of 500 IU, underwent challenges to the offending food.* ***Results.*** *13 out of 16 subjects were successfully re-exposed to the suspected foods and continued to tolerate these foods well.* ***Conclusion.*** *Our finding suggests a much lower clinical risk with previously defined specific IgE decision points in children with very high levels of total IgE (> 6000 IU/ml).*

The prevalence of food allergy approaches 8% in children in the United States. It poses a significant morbidity and mortality burden with 30 000 anaphylactic reactions, 2000 hospitalizations, and 200 deaths reported (1). While double-blind, placebo-controlled food challenges remain the gold standard for food-allergy diagnosis, their use is limited by the risk of severe reactions as well as time, cost, and patient anxiety. Skin testing has a high negative predictive value but a poor positive predictive value, so its use is limited (2). Elimination diets, while vital in the management of true food allergy, can have significant and sometimes devastating consequences, which underscores the need for accurate predictive tools. Daily clinical practice calls for tools in assessing the risk-benefit ratio before making recommending double-blind, placebo-controlled food challenges.
Previous investigators have attempted to investigate correlation between specific and total IgE levels (8-9). Some researchers have established 90% and 95% positive predictive values for milk, egg, peanut, and fish, and 73-74% predictive values for wheat and soy that serve as decision points (3-7).
The utility of these values in a population with markedly elevated serum IgE is not clear, which poses a clinical dilemma. Purpose of our study was to investigate if very high level affects previously established predictive decision points of food-specific IgE antibody concentration.

Methods

Case Report

A 3 years old boy presented for evaluation of multiple food allergies and eczema. His medical history was significant for severe eczema since the age of 6 months with a remission and relapse course. He was avoiding dairy, egg, soy and wheat in his diet due to history of "severe eczema flare ups" after consuming these foods. Child was

seen by his primary care physician who obtained specific IgE testing. Result of Immuno CAP RAST for the suspected foods revealed high values; 56 KU/L for milk, 78.8 KU/L for egg, 56 KU/L for soy and 76 KU/L for wheat. He was given a diagnosis of "food allergies" and referred to a local allergist. He had skin testing done at the allergist's office. Skin prick testing revealed positive reactions to the above mentioned 4 foods plus several other foods. Considering positive skin testing and specific IgEs above "90-95% values for predicted challenge failure", the allergist decided to continue with suspected food avoidance and advised to carry Epinephrine injection for emergency needs. He was also placed on amino acid based formula however; it was changed to almond milk due to high cost. Mother also started giving him "Gluten free diet", some fruits and vegetables. Child started losing weight and was referred to a nutritionist who put him on hydrolyzed formula, adjusted his diet based on required daily caloric intake and referred him to an allergy practice at a tertiary care center where total IgE was obtained in addition to the specific IgE. His total IgE was 6229 IU. There was no significant change in specific IgEs levels. Although his specific IgE levels were "way higher" than "90-95% values for predicted challenge failure", however, considering poor nutritional status, significantly high total IgE level and history of mild reaction to the suspected foods (eczema flare up / mild urticaria) it was decided to proceed with food challenge in a controlled setting. He passed challenges to all 4 major foods (milk, soy, wheat and egg). Eczema management was revised with significant improvement in his skin condition. He continued to tolerate these foods without urticaria, eczema or any other reactions.

Retrospective study to determine the relationship between total IgE and previously established 95% predictive decision points of food specific IgE concentration

The finding in this case led us to perform a retrospective medical records review study approved by our Nemours institutional review board. We identified sixteen children and adolescents, median age 39 months, with a history of adverse clinical reaction to a food, a specific IgE greater than the decision point, and an elevated total serum IgE level of 500 IU, underwent challenges to the offending food.

Inclusion criteria

All patients had a history of food allergy based on the following criteria: 1) adverse reaction to one or more common foods (egg, milk, peanut, fish, soybean, wheat and tree nuts) and 2) food-specific IgE levels greater than previously defined positive predictive value to the food.
3) The patient should have both a food-specific IgE and a total IgE within 6 month preceding challenge.
4) Documented evidence of re-exposure (home challenge, office food challenge) with documented outcome. The target dose for re-exposure was determined based on previously established target doses (8-10 gram for dry foods and 100 ml for wet foods (10). Food challenge was considered positive if one or more was noted: urticaria, angioedema, cough, wheezing, abdominal pain, emesis, shock or worsening of atopic dermatitis (AD) lesions. We followed our subjects for up to 2 years and confirmed that continued ingestion of previously suspected foods in the diet of these children was well tolerated.

Exclusion criteria

Increased total IgE due any other conditions besides atopic conditions. Patient serum was analyzed for concentrations of total

Table 1 *- Demographics of the study population.*

Characteristic	**Study Population (n = 16)**
Male sex	10 (62.5)
Median age at challenge (months)	39
Race	
Caucasian	4 (25)
African American	11 (68.7)
Asian	1 (6.25)
Atopic History	
Atopic dermatitis (Physician diagnosed)	14 (87.5)
Asthma (Physician diagnosed)	12 (75)
Allergic rhinitis (Physician diagnosed)	14 (87.5)

IgE and sIgE to wheat, soy, cow's milk, hen's egg, or peanut as per history of food allergy using the Pharmacia CAP-System FEIA® (Pharmacia-Diagnostics, Uppsala, Sweden). The upper and lower detection limit of the CAP-System was 100 and 0.35 kU/L respectively.
A total of 16 challenges were completed: 6 to wheat, 4 to soy, 4 to milk, 1 to egg and peanut. Study demographics are listed in **table 1**.

Results (table 2)

All of the 6 wheat challenge patients had specific IgE levels greater than 26 kU/L with a mean value of 44.7 kU/L and a mean total IgE of 8460 IU/ml. None of these challenges were positive. The 4 soy challenge patients had specific IgE levels greater than 30 kU/L with a mean value of 47.4 kU/L and a mean total IgE of 16,144 IU/ml. None of these challenges were positive. Similarly, all of the 4 milk challenge patients had specific IgE levels greater than 15 kU/L with a mean value of 73.7 kU/L and a mean total IgE of 4,444 IU/ml. Two of the 4 milk challenges were positive. One patient with an egg specific IgE > 100 kU/L and a total IgE of 6,229 IU/ml had a negative egg challenge. Finally, one patient with a peanut specific IgE > 100 kU/L and a total IgE of 663 IU/L had a positive challenge.
For soy, wheat, and egg, the observed PPV of the previously defined cut-off values of 30, 26, and 7 kU/L, respectively, was "zero" rather than 73-98%. For milk, the observed PPV of the previously defined cut-off of 15 kU/L was 50% rather than 95%. For peanut, the observed PPV of the previously defined cut-off value of 14 kU/L was 100%, consistent with previous findings (**table 2**).

Table 2 *- Study results.*

Type of Food	**Factors at the time of Diagnosis**		**Factors at the time of Challenges**	
Wheat	Initial reaction	Skin rash	# of positive challenges	0
	Skin test	5 mm (mean)	Skin test	4 mm (mean)
	SIgE	50.1 (kU/L) (mean)	SIgE	44.7(kU/L) (mean)
	Total IgE	5518 (IU/ml) (mean)	Total IgE	8460 (IU/ml)
Soy	Initial reaction	AD /Skin rash	# of positive challenges	0
	Skin test	5 mm mean)	Skin test	3 mm (mean)
	SIgE	43.51 (kU/L) (mean)	SIgE	47.4 (kU/L) (mean)
	Total IgE	12,372 (IU/ml) (mean)	Total IgE	16,144(IU/ml) (mean)
Milk	Initial reaction	Skin rash/Eczema flare	# of positive challenges	2
	Skin test	13 mm mean)	Skin test	10 mm (mean)
	SIgE	64.2 (kU/L) (mean)	SIgE	73.7 (kU/L) (mean)
	Total IgE	1458 (IU/ml) (mean)	Total IgE	4444(IU/ml) (mean)
Egg	Initial reaction	AD/Urticaria	# of positive challenges	0
	Skin test	n/a	Skin test	0 mm
	SIgE	78.8 (kU/L)	SIgE	>100 (kU/L)
	Total IgE	3154 (IU/ml)	Total IgE	6229 (IU/ml)
Peanut	Initial reaction	anaphylaxis	# of positive challenges	1
	Skin test	30 mm	Skin test	20 mm
	SIgE	27.8 (kU/L)	SIgE	>100 (kU/L)
	Total IgE		Total IgE	663 (IU/ml)

Discussion

There is significant confusion on the topic of relationship between total and food specific IgEs, specifically among the non Allergy / Immunology (A/I) physicians. Allergists often see children who underwent a specific IgE immune cap tests run by their primary care physicians and other non A/I specialists. Often the results reveal 8-9 foods that are positive in vitro, and automatically these provides advice to them to avoid those foods. This could lead to malnutrition due to unnecessary exclusion of all the foods that are positive on in vitro testing. While the previously established decision points would have predicted challenge failures in 73-95% of these subjects, in our study only 3/16 (18.75%) failed the challenge, indicating a noticeable lower clinical risk than predicted. We observed much lower clinical risk with previously defined specific IgE decision points in our small sample population. This may be attributed to the total IgE level confounding these values.

Most of our successful challenges were in patients with relatively mild food reactions (i.e., AD flare) rather than life threatening reactions yielding conclusions that may not be applicable in patients with a history of anaphylaxis to foods. Also, it is quite possible that our observation regarding the lower clinical risk with previously defined specific IgE decision is applicable only to a subset of patients with AD. We found the greatest discordance from expected outcomes in soy and wheat challenges. Prior studies noted that the predictive power of specific IgE for these foods was weak compared to other foods (4).

Interestingly, the patient with a positive peanut challenge had the lowest total IgE level in our sample and a history of a severe reaction (anaphylaxis). Our findings suggest a much lower clinical risk with previously defined specific IgE decision points in children with very high levels of total IgE > 6000 IU/ml).

Conclusions

Our findings suggest a possibility of link between total serum IgE levels and specific food IgEs and how the serum total IgE affects true predictive specific IgE values in patient with possibility of food allergy. Further investigation in a larger population may support less restrictive use of decision points in a subset of the population with markedly elevated serum IgE levels. Further data focusing on relationship between total IgE, specific IgE and the persistence / transience of food allergy may aid in the use of decision points and identify subsets of patients that are more likely to be clinically tolerant of certain foods.

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Trends of asthma hospitalization and hospital mortality in mainland Portugal

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asthma; epidemiology; hospitalization; mortality; trend

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Summary
Aim. *To evaluate nationwide asthma hospitalizations and hospital mortality from the year 2000 to 2010.* ***Methods.*** *Data from the Health Services Central Administration of the Portuguese Ministry of Health on hospital admissions and hospital mortality in the National Health Service in mainland Portugal, from January 1st 2000 to December 31st 2010, were analysed. Cases with bronchial asthma as a main diagnosis were selected.* ***Results.*** *We found a mean frequency of asthma hospitalizations of 2.5 / 1000 hospital admissions, 28.1 / 100,000 inhabitants (66.6/100,000 in < 19 years old). The global frequency of hospital admissions decreased 18.6% from 2000 to 2010 ($r = -0.85$, $p = 0.002$), and 47.0% in those aged 0 to 2 years old ($r = -0.77$, $p = 0.008$). There were 261 hospital deaths attributed to asthma (68.5% > 65 years old), accounting for an in-hospital mortality of 8.0 / 1000 asthma hospitalizations and 2.4 / 1,000,000 inhabitants, with no change throughout the years.* ***Conclusions.*** *Asthma hospitalization rates have decreased, especially in younger children. Mortality remained unchanged, particularly in the elderly; this might be explained by deficient control in this age group.*

Introduction

Asthma is a chronic inflammatory disorder of the airways associated with widespread, but variable, airflow obstruction within the lung, that is often reversible either spontaneously or with treatment (1). There are over 300 million people with asthma worldwide (1) and an estimated 695,000 Portuguese with current asthma (defined as "self-report of asthma and one of the following: at least one medical appointment due to asthma in the last 12 months; current use of asthma medication; or asthma symptoms in the last 12 months), with a prevalence of 6.8% in this population (2). Of Portuguese preschool children, 9.4% had four or more episodes of wheezing in the previous year (3). The World Health Organization has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden; moreover, annual worldwide deaths from asthma have been estimated at 250,000 (1).

Awareness of this gave rise to the 2001 National Asthma Control Programme (PNCA) of the Portuguese National Health Authority. This was inspired by the Global Initiative for Asthma (GINA) and set up to reduce asthma morbidity and mortality and improve asthmatics' quality of life and well-being (4). Two of the PNCA evaluation parameters were the number of hospitalizations due to asthma and the annual mortality.
As a previous study has depicted the regional differences of hospital admissions and mortality from asthma (5), our aim was to evaluate nationwide asthma hospitalizations and hospital mortality from the year 2000 to 2010, with a particular focus on the evolution of these parameters in different age groups.

Methods

Data from the Health Services Central Administration of the Portuguese Ministry of Health on global and asthma hospital

admissions and hospital mortality in the National Health Service in mainland Portugal, from January 1st 2000 to December 31st 2010, were analysed.

Cases with bronchial asthma as a main diagnosis (ICD, ninth revision, 493x) were selected, excluding all those in which bronchial asthma was recorded in a secondary position.

Hospital admissions, hospital stay days, days spent in intensive care units (ICU), mortality and costs are reported according to year and age group, in crude frequency and adjusted to the number of inhabitants.

Data on year and age-adjusted population resident in mainland Portugal were retrieved from the National Institute of Statistics (6). Spearman Rank Correlation (7) was used to evaluate yearly variation and considered statistically significant for a p-value < 0.05.

Results

Hospital admissions

From January 1st 2000 to December 31st 2010 there were 32,504 asthma hospitalizations, with a mean of 2955 hospitalizations per year, 2.5 per 1000 hospital admissions, and a mean annual asthma hospitalization rate of 28.1 per 100,000 inhabitants living in mainland Portugal.

Asthma hospitalization frequency was higher in children aged 5 years old or younger (134.9 per 100.000 inhabitants), with an age-specific frequency of 66.6 per 100,000 children and adolescents aged under 19 years old (**table 1**). Females accounted for 18,112 (55.7%) of asthma hospitalizations. Asthma hospitalization rates in children aged 0 to 5 years old was 1.6 higher in boys (172.9 vs. 110.8 per 100,000 girls aged under 6 years old), while in those aged 66 or older it was 2.1 times more frequent in women (42.1 vs. 19.7 per 100,000 men aged over 65 years old) (**figure 1**). Hospitalizations were consistently less frequent during the summer, peaking in the months of December and January (**figure 2**).

Table 1 *- Age-specific asthma hospitalization frequency and mean annual asthma hospitalization rate per 100,000 inhabitants in mainland Portugal.*

Age (years)	Total frequency	Mean annual frequency	Per 100,000 inhabitants
0-2	4668	424.4	131.3
3-5	4946	449.6	138.4
6-12	4953	450.3	59.1
13-18	911	82.8	11.8
19-40	4078	370.7	11.0
41-65	6677	607.1	18.9
> 65	5909	537.2	29.7

Figure 1 *- Age and gender-specific mean annual hospitalization rate per 100,000 inhabitants.*

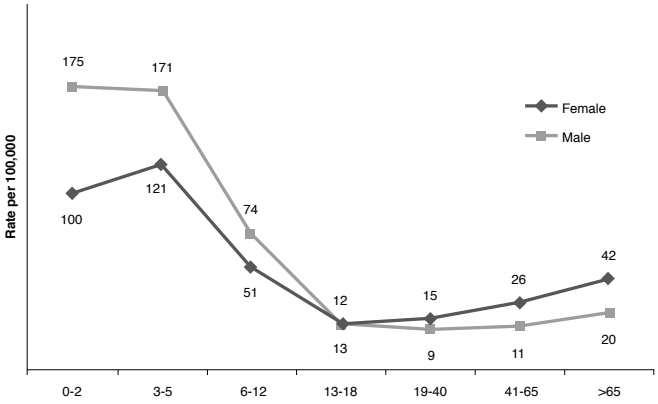
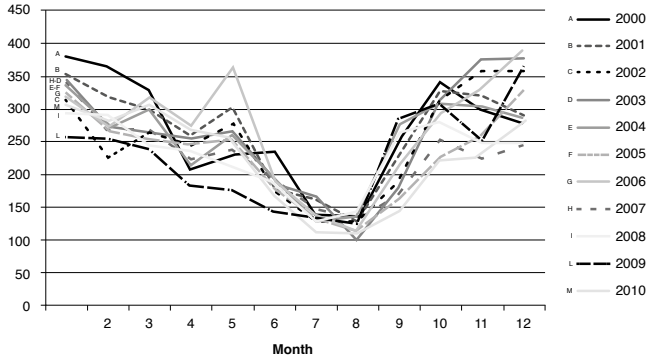


Figure 2 *- Asthma hospitalization frequency according to month of discharge.*



Hospital stay days

The total number of hospital stay days was 185,146, with a mean (SD) stay of 5.9 (0.29) days, which increased with age (r = 0.89, p = 0.01), ranging from 2.9 days in the 3 to 5-year-old group to 9.7 days in those aged over 65 years old.

Days spent in an intensive care unit (ICU) comprised a total of 5122 days, representing 2.8% of all asthma hospital stay days, ranging from 2.2% in those aged 41 to 65 years old to 4.2% of all asthma stay days in children 3 to 5 years old.

Mortality

During this 11 year period there were 261 deaths attributed to asthma in hospitalized patients, 149 (57.1%) in females, with a frequency of 8.0 per 1000 asthma hospitalizations and a mean

annual asthma hospital mortality of 2.4 per 1,000,000 inhabitants. People aged older than 65 accounted for 68.5% of asthma hospital mortality, while the paediatric age group accounted for 1.9% (**table 2**).

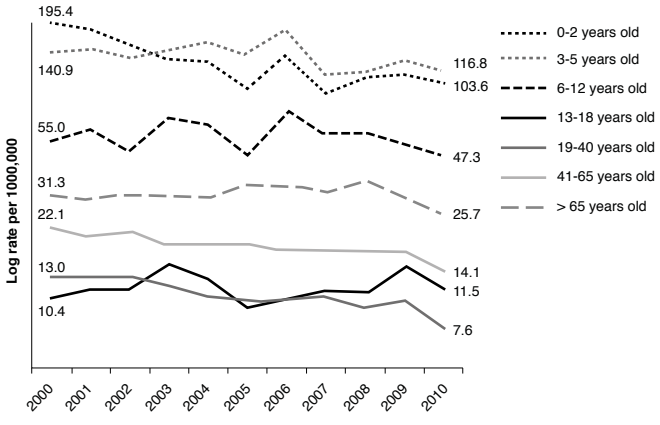
Table 2 *- Age-specific asthma hospital mortality frequency and mean annual asthma hospital mortality rates per 1,000 asthma hospitalizations and per 1,000,000 inhabitants in mainland Portugal.*

Age (years)	Total frequency	Mean annual frequency	Per 1,000 Hospitalizations	Per 1,000,000 inhabitants
0-2	1	0.1	0.2	0.3
3-5	0	0.0	0.0	0.0
6-12	2	0.2	0.4	0.3
13-18	2	0.2	2.2	0.3
19-40	25	2.3	6.1	0.7
41-65	52	4.7	7.8	1.5
> 65	178	16.1	30.1	8.9

Costs

A total 36,602,995 € was spent in asthma hospitalizations, with a mean cost of 1184 € per hospitalization and of 198 € per hospital stay day, ranging from 117 € in those aged 41 to 65 years old, to 285 € in adults between 19 and 40 years old.

Figure 3 *- Yearly variation in age-specific asthma hospitalization rate per 100,000 inhabitants.*



Yearly variation

Throughout the years, there has been an overall decrease in asthma hospitalization rate (r = -0.85, p = 0.002), with 18.6% less hospitalizations in 2010 compared to the year 2000 and a more important decrease in those aged 0 to 2 years old (r = -0.77, p = 0.008, -47.0%), 19 to 40 years old (r = -0.87, p < 0.001, -41.5%) and 41 to 65 years old (r = -0.98, p < 0.001, -36.2%) (**figure 3**). There were no significant timeline changes in overall mortality rate (r = 0.19, p = 0.578), mortality rate in the oldest age group (r = 0.40, p = 0.225), mean hospital stay days (r = 0.07, p = 0.838) or mean cost per patient (r = 0.35, p = 0.286) (**table 3**).

Table 3 *- Yearly variation (2000-2010) in asthma hospitalization rate per 100,000 inhabitants, asthma hospital mortality rate per 1,000,000 inhabitants, mean hospital stay days and mean cost per patient (€).*

Year	Hospitalization rate	Mortalitity rate	Hospital stay days	Cost per patient
2000	31.2	2.1	5.69	1,108
2001	30.8	2.1	5.86	1,122
2002	29.1	1.5	6.21	1,181
2003	29.8	2.9	5.51	1,218
2004	28.7	2.3	6.03	1,277
2005	26.2	3.0	6.39	1,192
2006	30.5	2.0	5.61	1,105
2007	25.6	2.1	6.31	1,252
2008	26.4	2.2	5.95	1,198
2009	25.7	1.6	5.67	1,155
2010	25.4	3.0	5.87	1,230

Discussion

This study describes hospitalization rates attributed to asthma in mainland Portugal from the year 2000 to 2010. We found a mean frequency of asthma hospitalizations of 2.5 per 1000 hospital admissions, 28.1 per 100,000 inhabitants and 66.6 per 100,000 inhabitants aged under 19 years old, which was lower than the one reported from 1995 to 1999 in the United States (76 per 100,000 Caucasian inhabitants) using a similar methodology (8).

The seasonal predominance of asthma hospitalizations during winter is in agreement with other northern hemisphere countries (9) and is probably related to a higher frequency of respiratory infections as a cause for asthma exacerbation in all age groups.

The frequency of hospital admissions from asthma decreased 18.6% from the year 2000 to 2010, in accordance with the trend for decrease in asthma hospitalizations worldwide (8). We found a particularly important decrease in the number of hospital admissions in younger children, where hospitalizations remain the highest. In the study by *Brandão et al* (10), severe asthma was the only predictive factor for hospital admission in children aged 4 to 19 years old. In 124 Portuguese children with asthma, the three most significant independent risk factors for hospital admission were previous hospitalization, environmental tobacco exposure and atopy (11). We have previously reported in a nationwide population-based study that 24.5% of Portuguese preschool children had current wheezing and 9.4% had four or more episodes of wheezing in the previous year, while only 5% referred an asthma diagnosis and 4% of these were treated with inhaled corticosteroids (3,12). This underdiagnosis and undertreatment of asthma in preschool children, along with recurrent hospitalizations (13), might explain the higher rates of asthma-related hospital admissions in this age group. On the other hand, tobacco smoke restrictions in Portugal since 2008 might be a positive factor influencing the decrease in hospitalizations.

During this 11-year period there were 261 deaths attributed to asthma in hospitalized patients, accounting for an in-hospital asthma mortality of 8.0 per 1000 asthma hospitalizations (0.8%) and 2.4 per 1,000,000 inhabitants. This frequency is in accordance with the reported < 1% found in other studies, namely in the United Kingdom (0.4%) (14), United States (0.5%) (15) and Spain and Latin America (0.8%) (16). The former study (16) showed that female gender, out of hospital cardiopulmonary arrest and arterial pH < 7.3 during hospitalization were strongly associated with asthma mortality. *Watson et al* (14) found that women and those over 45 years old had the highest rate of death, possibly reflecting asthma prevalence, while *Woods et al* (17) reported worse outcomes in men. In our study, 55.7% of asthma hospitalizations and 57.1% of asthma deaths occurred in women, which is not in favour of a higher risk for mortality in the female gender, although a comparative study was not possible. However, while only 24.9% of asthma hospital admissions occurred in those aged over 65 years old, 68.5% of in-hospital mortality were in this age group, which might be related to other frequent comorbidities in the elderly, namely cardiovascular disease and diabetes, decreased asthma control and deficient awareness of their asthma control level. This is in line with results found in the Portuguese National Asthma Survey, performed in 2010, where lack of asthma control was significantly more frequent in females and in the elderly (18,19). Despite previous studies showing a downward trend in asthma deaths, less significant in those aged 65 or older (20), we could not find an improvement in mortality either in the total or elderly population.

The main limitation of this study is the fact that we excluded patients with asthma as a secondary diagnosis, even when the main diagnosis was respiratory insufficiency, failure or arrest (possible complications of an asthma exacerbation) or respiratory infection (a frequent cause for exacerbation). This methodology probably leads to an underreporting of asthma hospitalizations, which is much lower than the 3.9% prevalence of lifelong hospitalization in children aged 6 to 17 years old from a population-based nationwide *Portuguese* survey (21). However, including other diagnosis would introduce distorting factors in the analysis and hamper comparability with other studies. Another limitation results from the confidentiality of data supplied by the Health Services Central Administration, from which it is not possible to assess if one given patient has been hospitalized more than once. It would have been interesting to evaluate if the high frequency of hospital admissions in children is due to recurrent hospitalization, as suggested in other studies (10), as this information would impact on future strategies for decreasing hospitalization rates in these age groups.

The strengths of the study are the inclusion of nationwide data on asthma hospitalization and mortality over a period of 11 years, the categorization in different age groups and the analysis according to the population for a given age group and year, which allowed for the calculation of rates per 100,000 inhabitants and comparability with other studies in different populations.

As asthma hospitalization rates vary inversely with inhaled corticosteroid use, implying that most hospitalizations are preventable (22,23), the Portuguese National Health Service in 2011 produced a recommendation for physicians focusing on asthma control (24), with frequency of prescription of inhaled corticosteroid per diagnosed asthma patient being an evaluation parameter of the implementation of this recommendation. Despite the observed reduction in asthma hospitalizations, possibly due to the impact of the National Asthma Control Programme started in 2001 (4), an effort to further reduce hospitalization rates and especially mortality needs to be pursued, with particular attention to the older patients with asthma (25).

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Use of omalizumab in the treatment of chronic urticaria

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Key words

chronic spontaneous urticaria; omalizumab; treatment; anti-immunoglobulin E; wheal

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Summary

Background. *Omalizumab is indicated to treat chronic spontaneous urticaria (CSU) refractory to antihistamines. We aim to describe the experience of our department in the treatment of CSU with omalizumab.* ***Materials and Methods.*** *Retrospective review of the clinical records of patients.* ***Results.*** *Six patients (5 females, median age 33 years) treated with omalizumab for a median of 17.5 months were evaluated. All patients had improvement of symptoms after the first dose. In one case, the treatment was suspended after 7 months, but in 9 weeks there was recurrence of symptoms. The main side effect was headache in the drug administration's day. Currently, all patients maintain therapy with omalizumab and are clinically stable.* ***Conclusion.*** *Omalizumab proved to be an effective and safe drug for the treatment of patients with refractory CSU.*

Background

Urticaria is a disease characterized by the development of wheals (hives), angioedema or both, and is divided into acute and chronic forms (≥ 6 weeks), with chronic urticaria being further classified into chronic spontaneous urticaria (CSU) and inducible urticaria (1). CSU is the spontaneous development of symptoms with no external specific trigger (2), and inducible urticaria may coexist with CSU (3).

The exact prevalence of chronic urticaria depends on the population studied, but reports suggest that globally it can affect up to 1% of the population at any given time (2). CSU accounts for approximately two-thirds of the cases of chronic urticaria (4), with the peak incidence in working age (20-40 years-old) (5), and the duration of chronic urticaria in adults has been reported to be as follows: 6-12 weeks in 52.8%, 3-6 months in 18.5%, 7-12 months in 9.4%, 1-5 years in 8.7% and over 5 years in 11.3% (6).

CSU has a high overall impact on quality of life (2). Patients who suffer from this disease have a high disease burden, because of the associated impact on physical, emotional and social aspects of their life (2). Further, there is a high socioeconomic impact arising from both the direct costs (such as medication or healthcare visits) and indirect costs (such as absence or reduced efficiency at work) (2).

With respect to the treatment of urticaria, the international EAACI / GA2LEN / EDF / WAO guidelines state that the aim of therapy should be complete symptom control (1). In CSU, the recommended first-line treatment option is non-sedating H1-antihistamines, which are only effective in around half of the patients (3). The second-line treatment recommended is a trial of up to fourfold dose of second generation H1-antihistamines (1), which reduce symptoms in about 75% of patients with chronic urticaria (including patients with concomitant inducible urticaria) (7). In the remaining cases, third-line treat-

ments must be considered, namely the use of monoclonal antibodies, as omalizumab (1).
Based on Phase III clinical data in patients with CSU, omalizumab was approved in Europe in February 2014 as a third-line therapy for the treatment of CSU in adult and adolescent patients showing an inadequate response to H1-antihistamine treatment (2), being the dosage either 150 or 300 mg subcutaneously every 4 week.
Omalizumab is a recombinant, humanized, monoclonal, anti-IgE murine antibody that targets the C3 domain of the Fc region of IgE, reducing the levels of free IgE by sequestration what can also, indirectly, cause the downregulation of the cell-surface FcεRI receptors, which may reduce the potential for histamine release and the subsequent symptoms of CSU (2,8,9).
The aim of this study is to describe the experience of our department in the treatment of refractory chronic urticaria with omalizumab and to assess its efficacy and safety.

Materials and methods

We performed a retrospective review of the clinical records of patients treated with omalizumab in our department, from November 2012 to June 2015, in the context of severe chronic urticaria. The baseline characteristics of patients before starting the treatment and their clinical evolution were evaluated.
Prior to initiation of anti-IgE treatment all patients signed an informed written consent, and the administrations of omalizumab were performed under medical supervision, with a time of surveillance of 2 h after the first three administrations and 30 minutes thereafter.
After starting anti-IgE antibody, corticosteroids were weaned as tolerated. Response to the therapy was assessed based on the time until improvement of symptoms and the weaning of corticosteroids. The number of exacerbations after starting omalizumab that required treatment with corticosteroids was assessed as well as the side effects of anti-IgE therapy.

Results

We studied 6 patients (5 females and 1 male) with a median age of 32 years-old (range 22-61). The baseline characteristics of the patients and their clinical evolution are presented in **table 1**. They all had chronic spontaneous urticaria, that in one case was associated to inducible urticaria (dermographic, cholinergic and delayed pressure urticaria) and the median duration of symptoms was 8 years (range 2-20). All patients had recurrent attacks of generalized urticaria, with almost daily moderate to severe symptoms before starting omalizumab.
Patient 2 had a confirmed hypersensitivity to anti-histamines and corticosteroids. She referred development of urticaria lesions and angioedema when taking multiple antihistamines (loratadine, desloratadine, cetirizine and promethazine) and corticosteroids (hydrocortisone, methylprednisolone and deflazacort). We performed a single-blind drug challenge with placebo which was negative. and single-blind drug challenges with suspected and alternative antihistamines (desloratadine and dimethindene) that were both positive. It was also conducted a single-blind drug challenge with an alternative corticosteroid (dexamethasone) which was negative, but latter the patient was treated with dexamethasone and developed urticaria with angioedema. Therefore, patient 2 had no alternative medication to treat CSU and thus started treatment with omalizumab.
The other cases showed poor response to treatment with maximal doses of anti-histamines (four-time updosing) and required frequent cycles of daily oral corticosteroid to achieve symptomatic control. Additionally, patient 5 had previously been treated with cyclosporine (2 months, 0.6 mg/kg), and sulfasalazine (2 months, 1500 mg/daily) which were not effective.
Four patients were atopic and 3 had allergic asthma and rhinitis. The anti-thyroid antibodies were positive in 1 case (anti-thyroid peroxidase antibodies - 46 UI/mL) and the thyroid function test was compatible with hypothyroidism in another one. Total serum IgE was elevated in 5 patients (median value 316 IKU/L, range 28-1055). The autologous serum skin test was performed in 2 cases and it was positive in one.
In patient 6, who initiated anti-IgE antibody in the year of 2012, the initial dose of medication used was calculated according to the patient's bodyweight and total serum IgE (300 mg bimonthly), as performed in the cases of severe asthma. In the other patients, who started treatment between November 2013 and February 2014, after the publication of the likely optimal doses of omalizumab for treatment of chronic urticaria (10), the initial dose used was 300 mg monthly.
The median duration of treatment was 17.5 months (16-31) and there were no dropouts. All patients showed improvement of symptoms after the first administration of omalizumab and it was possible to discontinue corticosteroids before the second administration in 4 cases.
Two weeks after the first dose, patient 3 presented an exacerbation of urticaria lesions that required a cycle of corticosteroids for resolution. In the fourth, fifth and eleventh months of treatment, she presented other four symptomatic exacerbations, two of them in the context of antibiotic therapy used in the treatment of skin and urinary tract infections.
In patient 6, four months after adequate control of urticaria with administration of omalizumab 300 mg bimonthly, a decrease in the dose was held to 150 mg monthly, without symptoms recurrence. Three months later, the period between administrations was increased to 5 weeks, but in approximately 4 weeks the patient began experiencing lesions of urticaria. For this reason, administrations at 4 week intervals were resumed.

After 7 months of treatment without recurrence of symptoms, omalizumab was suspended in patient 1. Nine weeks later, she began experiencing lesions of urticaria with incomplete control, so the anti-IgE antibody was restarted with resolution of symptoms after the first administration.
The main side effect observed was headache in the drug administration's day that was found in 2 patients, who improved clinically with analgesics.
Currently, all patients maintain therapy with omalizumab and are clinically stable.

Discussion

In our study we report six patients with severe chronic urticaria who showed a good long-term response to treatment with omalizumab, being possible to discontinue the corticosteroid treatment in all patients.
As observed in other studies (11), the anti-IgE treatment had a rapid onset of action, with relief of urticaria lesions within days to few weeks after first administration. This rapid response may be a reflection of the binding of the omalizumab to free IgE antibodies, which occurs within a few hours of administration that reduces the binding of IgE to the high affinity receptor FcεRI on basophils and mast cells. It may also be related to the downregulation of the expression of FcεRI on blood basophils (within 2 weeks) and mast cells (within 8 weeks) (3,10).
Chronic urticaria patients frequently exhibit increased total IgE levels (12) and have autoimmune conditions, especially thyroid autoimmune disorders, such as Hashimoto thyroiditis (13). Several independent studies have reported that a significant number of patients with chronic urticaria (up to 33% in some studies) exhibit high level of autoantibodies to thyroid antigens (14). In fact, almost all of our patients (5 in 6) showed increased levels of total serum IgE and one also presented Hashimoto thyroiditis, but their response to anti-IgE treatment showed no differences from the other patients.
According to other published case reports and real-life retrospective observational studies, omalizumb has also been reported to be effective in cases of chronic inducible urticaria (1,2,11) such as cholinergic urticaria (15), cold urticaria (16,17), solar urticaria (17), heat urticaria (18), dermographic urticaria (17,19), and delayed pressure urticaria (20). Some of this indications are currently being evaluated in randomized clinical trials (21,22,23).
In our study, the anti-IgE treatment also showed effectiveness in one patient with severe chronic spontaneous urticaria associated to various subtypes of inducible urticaria (dermographic, cholinergic and delayed pressure urticaria). Thus, omalizumab may be a therapeutic alternative in some cases of refractory inducible urticaria.
Currently, the recommendations to guide the use of omalizumab in the treatment of chronic urticaria are a subject of controversy, so the authors' criteria to interrupt treatment, change the dose or increase the duration between doses were based on the clinical course of patients. When disease control was reached and patients were clinically stable, changes in the doses or suspension of the treatment were attempted in order to achieve the lowest effective dose.
In one patient, omalizumab was suspended after 7 months of successful treatment, but in nine weeks we verified recurrence of the urticaria lesions. These results are similar to those found in other studies. Silva PM, et al (24) suspended omalizumab in 3 patients, respectively after 12, 18 and 24 months of successful treatment and all of them, approximately six weeks later, had urticaria recurrence. Two phase III multicenter trials, with follow-up periods of 16 weeks, have also reported the reappearance of urticaria in an average of 10 weeks after discontinuation of omalizumab (10,25). In another study (7), with patients observed for additional 20 weeks after 3 administrations of anti-IgE antibody, at 8 weeks, there was a gradual return of pruritus and urticaria by week 20. This data suggests the need for long term treatment at least for some patients (3).
Since 2006, there have been a number of case reports with scarce number of patients on the use of omalizumab in chronic urticaria and also broader real-life studies (both retrospective and prospective) and some phase III studies (2). In all of them, the treatment was well tolerated and no safety issues or concerns were reported when they were compared with the well-established profile of the anti-IgE treatment use in allergic asthma (10,25,26).
In the six cases here described, only mild side effects were reported in 2 cases (headaches), none of them leading to treatment withdrawal.
The main limitation of this study is related to the limited dimension of our case series which makes it difficult to characterize patients' features that can provide different responses to anti-IgE treatment. However, the clinical improvement seemed to be independent of gender and age, duration of the disease, total serum IgE levels and presence of atopy.
Patient 3 had a less effective response to omalizumab, as she presented 5 exacerbations requiring corticosteroids during omalizumab treatment. The only feature that distinguishes her from the other patients is the presence of positive anti-thyroid antibodies, but other studies have shown efficacy of omalizumab also in cases with positivity to these antibodies (24,27).

Conclusions

Omalizumab seems to be a new effective and safe treatment for patients with chronic urticaria refractory to other treatments. However, some issues regarding its use needs to be addressed in the future and further studies will be necessary. The mechanisms of action of omalizumab have not been fully clarified

Table 1 *- Baseline characteristics of the studied patients and their clinical evolution.*

Patient	**1**	**2**	**3**	**4**	**5**	**6**
Gender	M	F	F	F	F	F
Age (at start of omalizumab treatment)	61	22	25	33	31	39
Duration of symptoms (years)	2	10	5	20	9	7
Angioedema	Yes	Yes	Yes	No	Yes	Yes
Association with inducible urticaria	No	No	No	No	No	Yes[1]
Previous treatments	AH, SC, LTRA	No	AH, SC	AH, SC	AH, SC	AH, SC, LTRA, Cy, Doxepin, Su
Total Serum IgE (IKU/L)	239	320	28	313	1055	548
ASST	NP	–	NP	NP	NP	+
Anti-thyroid antibodies	–	–	+	–	–	–
Atopy	Yes	Yes	No	Yes	No	Yes
Other diseases	Dyslipidemia, Diabetes and hypothyroidism	A+R, DH[2]	DH, Hashimoto thyroiditis	A+R	Adrenal adenoma	A+R, Hypertension
Start of treatment	Nov 2013	Feb 2014	Feb 2014	Dec 2013	Nov 2013	Nov 2012
Inicial omalizumab dose	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 4/4 week	300 mg 2/2 week
Duration of treatment (months)	16	17	17	18	19	31
Administrations required to clinical improvement	1	1	1	1	1	1
Administrations required to corticosteroid discontinuation	1	NA	1	1	3	1
Exacerbations requiring corticosteroid treatment	0	0	5	0	1	1
Current omalizumab dose	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	300 mg 4/4 w	150 mg 4/4 w
Current additional medication	AH on demand	AH on demand	AH 3xday	AH on demand	AH on demand	AH 4xday
Side effects	None	None	None	None	Headache	Headache

F - Female; M - Male; AH - anti-histamine, SC - systemic corticosteroid; LTRA - Leukotriene receptor antagonist; Cy - Cyclosporine; Su - Sulfasalazine; ASST - Autologous serum skin test; NP - Not performed; A+ R - Asthma and rhinits; DH - Drug hypersensitivity; NA - Not applicable; AH - Anti-histamine; w - Week.

[1]Dermographic, cholinergic and delayed pressure urticaria

[2]Hypersensitivity to anti-histamines and corticosteroids

and also the duration of treatment remains to be established (3). Similar to other medications and interventions, the decision to continue omalizumab for chronic urticaria should include assessing therapeutic benefit and any untoward effects (3).

During the treatment, attempts should be made to achieve the lowest dose that allows the control of symptoms. Instead of reducing the dose given every month, the authors consider a better alternative to increase the interval between the doses, since this approach allows more comfort to patients, reducing the hospital visits. Other reasons that justify trying to achieve the lowest effective dose are the high cost of omalizumab as well as the possible occurrence of long-term side effects not yet known.

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Urticarial vasculitis in the childhood with C2 hypocomplementenemia: a rare case

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Key words
urticaria; child; urticarial vasculitis; complement

Summary
We report a first case of hypocomplementemic urticarial vasculitis of C2 fraction in a child, with cutaneous manifestation only, with no reports in scientific literature.

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Introduction

Urticarial vasculitis (UV) is defined as recurrent episodes of urticaria persisting for more than 48 hours, with pain and burn sensations that have histopathological characteristics as leukocytoclastic vasculitis (1,2,3). The UV occurs in about 1.8% of the adult population, that corresponds to 5-10% of the chronical urticarias on adults, while the childhood prevalence is unknown (2,3,4,5).

Three types of UV have been described: the normocomplementemic form, responsible for 80% of the cases, self-limited and restricted to the skin (3); the hypocomplementemic form, frequently associated with systemic inflammatory diseases like arthritis (50%), intestinal diseases (20%), asthma and chronical obstructive pulmonary diseases (20%); and the hypocomplementemic vasculitis syndrome, a rare and potentially severe condition, characterized by the urticaria with hypocomplementenemia persisting for at least six months. This form is associated with systemic manifestations such as severe angioedema, laryngeal edema, lung diseases, arthritis, glomerulonephritis and recurrent abdominal pain (6,7,8).

Case report

The patient, a 5 years old male, reached the medical service complaining about recurrent urticarial episodes lasting 48-72 hours, and were relieved with anti-histaminic drugs without any other symptoms. Through the examination were found the presence of urticariform lesions on the trunk (**figure 1a**) and superior limbs, and as well residual hyperchromic lesions were found on proximal limbs and back (**figure 1b**).

The followed laboratorial exams were: complete blood count (CBC), renal function (urea, creatinine), hepatic function (Aspartate transaminase, Alanine transaminase, Gamaglu-

til transferase, alkaline phosphatase, coagulation profile), C reactive protein (CRP), hepatitis B and C serology, cryoglobulins, total and fraction bilirubins, anti-nuclear antibody (ANA), anti-DNA double stranded, Anti-SS-A (Ro), anti-SS-B(La), rheumatoid factor (RF), anti-thyroid antibodies, electrophorese of protein, Glucose-6-phosphate dehydrogenase (G6PD), Perinuclear Anti-Neutrophil Cytoplasmic Antibody (pANCA), Cytoplasmic Anti-Neutrophil Cytoplasmic Antibody (cANCA), C4 and urine-analysis. However, the complement fractions CH50 (50% haemolytic complement) was reduced (75 mg/dL; reference: 150-300 mg/dL) and C3 (89.3 mg/dL; reference: 90-180 mg/dL). C1 esterase dosage was normal, C1 was normal value and C2 fraction was diminished (57% Reference: higher than 67%), characterizing C2 deficiency.

The patient was also submitted to a cutaneous lumbar punch biopsy. This provided evidence of vasculitis of the superficial and profound vascular plexus with eosinophilia, and hystologically compatible with urticarial vasculitis.

To control the urticaria, therapies with anti-histaminic drugs and corticoids were used.

During follow-up, the patient showed diverse hives episodes, with 48-72 hours of duration, worsening when anti-histaminic use was stopped. After 4 years of segment and periodical exams (**table 1** and **figure 1b**) the patient returned with ANA reagent, nuclear fine speckled pattern (1⁄640) which was followed up until April of 2014. During that period, titles of ANA were rising (1⁄1280), nuclear fine speckled pattern, with no development of other diseases, with persistence of the cutaneous manifestation, but with notable improvement.

Discussion

The urticarial vasculitis typically manifests itself through painful hives with prolonged duration and residual hyperpigmentation (9). It affects mainly the trunk and extremities, having an average duration of three years (9) with higher prevalence among females and peaking in the fourth decade of life, being extremely rare in children (1,4,11,12,15). In hypocomplementemic form, which is observed most exclusively in female patients (16), other manifestations may occur such as gastrointestinal symptoms (abdominal pain, nausea, vomiting and diarrhea in approximately 17-30% of cases), musculoskeletal involvement (arthralgia and arthritis in 50-75%), renal involvement (proteinuria and hematuria in 20 to 30% of cases). Chronic obstructive pulmonary disease is present in 20 to 30% of patients while ophthalmic complications were present in less than 10% of patients (10).

The diagnosis of this entity should be considered in the presence of persistent hives with suggestive clinical, serologic or systemic diseases evidences. Histopathologically, as observed in our patient, the UV demonstrates leukocytoclastic vasculitis signals, such as endothelial damage of post-capillary venules, extravasation of red blood cells, fragmentation of leukocytes with nuclear debris, perivascular and infiltrated fibrin deposition with a predominance of neutrophils (3,8-10).

During the follow up, autoimmune diseases should be investigated, given the fact that its association with Sjögren's syndrome is 30% and with systemic lupus erythematosus (SLE) is 20% (1,3,8). These diseases were excluded in the diagnostic elucidation of the patient, even though it had progressing ANA titles with fine speckled pattern, once it didn't show any clinical laboratory changes that would close the diagnostic criteria for both conditions.

Figure 1a *- Urticariform lesions on the trunk (abdominal region).*

Figure 1b *- Residual hyperchromic lesions on the back.*

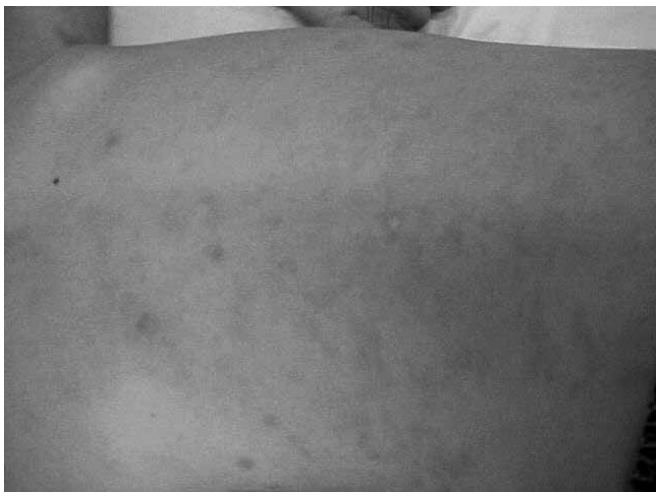

Tabella 1

Patient's data	Mar-06	Jan-07	dec-07	Mar-08	Jul-09	Mar-10	Jul-11	Jan-13	Jan-14
Hb (g/dl)	*	12,3	12,8	13	13,6	12,4	12,8	13,9	13
WBC (10E9/L)	*	5,9	5,8	5,3	6,22	4,9	4,5	5,07	5
Platelets (10E9/L)	*	368	281	313	354	259	294	228	240
CRP (mg/L)	< 5	0,1	0,1	*	< 0,10	< 5	< 5	< 0,3	< 0,3
ANA (1:n)	0	0	0	80	0	0	640	1280	1280
pattern				speckled			speckled	speckled	speckled
CH50 (mg/dL)	75	80,29	*	*	*	160	*	161	160
C2 (%)	57%	57%	58%	57%	56%	55%	55%	56%	55%
C3 (mg/dL)	98	89,3	*	*	108	88	86	98	*
C4 (mg/dL)	14	12,8	*	*	14	10	10	11	*
Urea (mmol/L)	31	22	28	*	*	*	29	*	*
Creatinine (umol/L)	0,4	0,38	*	*	0,5	0,72	0,4	*	*
RF	< 10	7,4	*	*	< 10	*	< 11	< 9,3	*
24 h urine protein (g/dL)	50,5	*	*	*	*	*	*	*	*

*Unknown values / Hb hemoglobin / WBC white blood cell count / CRP C reactive protein / ANA antinuclear antibody / CH50 50% haemolytic complement / RF rheumatoid factor

Elevated erythrocyte sedimentation rate and a drop in levels of complement are frequently observed (10), characterized by activation of the classical pathway with reduced C1, C2, C4, C3 and CH50 (11), and the C1q deficiency is associated to severe autoimmune disease in 95% of cases (13). Even though the complement fall is a sensitive marker for systemic disease (10) and the C2 loss is associated in 40% with autoimmune severe diseases (13), this situation was not observed in this case described of exclusively cutaneous presentation without any systemic manifestation.

It is an unwieldy condition, often guided by the severity of symptoms and the underlying systemic disease. Antihistamines are the first choice drug for the treatment of UV with only cutaneous involvement (e.g. Cinnarizine), even though they don't control inflammation caused by immune complexes, requiring oral corticosteroid, indomethacin, colchicine, dapsone and hydroxychloroquine. In cases of systemic involvement, patients may require treatment with immunosuppressants such as azathioprine or cyclophosphamide, or immunomodulators such as rituximab, or Immunoglobulin G intravenous (1,4,17).

This case illustrates an atypical presentation of urticarial vasculitis Hypocomplementaemic (C2 decrease) in a very young male patient with only cutaneous involvement, and no systemic manifestation until now, such fact not seen in the literature before. The diagnosis of this likely pathology systemic involvement from a cutaneous manifestation stresses the importance of further investigation of vascular lesions of the skin, resulting in early diagnosis that will provide greater care and attention to any systemic change, favoring a better prognosis and disease management.

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Febuxostat hypersensitivity: another cause of DRESS syndrome in chronic kidney disease?

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Key words
febuxostat; DRESS; chronic kidney disease

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Summary
Febuxostat is a xanthine oxidase inhibitor that during the last years has successfully replaced allopurinol treatment in patients with chronic kidney disease (CKD) and hyperuricemia. Several adverse events have been observed during therapy with febuxostat. DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome induced by febuxostat has been poorly described, mainly in patient with CKD who previously developed allopurinol hypersensitivity syndrome. DRESS syndrome is characterized by manifold cutaneous reactions and systemic disorders with potential devastating consequences. The underlying pathogenetic mechanisms remain unidentified, though immune responses are often complicated. P-i concept can partially explain the phenomenon. The role of renal insufficiency appears to be crucial and further investigation is required. The present article describes the case of a CKD patient that developed febuxostat-related DRESS syndrome.

Introduction

Febuxostat is a selective inhibitor of xanthine oxidase and it is recommended as urate-lowering therapy in patients with chronic kidney disease. Among post-market adverse events of febuxostat, the most deleterious are hypersensitivity type cutaneous vasculitis (1), interstitial granulomatous reaction (2), rhabdomyolysis (3, 4), hepatitis (5) and severe neutropenia (6).

Herein we aim to report the case of a patient under febuxostat treatment that presented with fever, impaired liver function and hypersensitivity reaction with eosinophilia. According to the European RegiSCAR scale (7) the case was characterized as a "definite" Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, while the Naranjo Adverse Drug Reaction Probability Scale (8) illustrated febuxostat as the "probable" cause of the syndrome.

Case Report

A 62-years-old Caucasian male presented to our Emergency Department complaining of fever and a three-day history of generalized, erythematous, maculopapular rash without erosive lesions, accompanied with pruritus. No mucosal involvement was observed. The patient had a medical history of hyperuricemia, complicated with several gout episodes and deregulated hypertension, that had led to chronic kidney disease (GFR 52 ml/ min/ 1.73 m^2) due to hypertensive nephrosclerosis. He was under regular follow-up every three months. His medication included furosemide (40 mg/day), diltiazem hydrochloride (180 mg/day), clopidogrel (75 mg/day), ranitidine hydrochloride (150 mg/day) and moxonidine (0.4 mg/day). The patient received urate-lowering therapy with allopurinol (100 mg/day) that had been interrupted two months ago due to exfoliative dermatitis with eosinophilia and

poor uric acid control. After allopurinol discontinuation, the hematological profile had been normalized and dermatitis had resolved. Due to severe hyperuricemia (uric acid 12.6 mg/dL), allopurinol had been switched to febuxostat (80 mg/day) two weeks before symptoms arose.

On admittance, patient's vital signs were: blood pressure 110/80 mmHg, temperature up to 38.6 °C, pulse 105 beats per minute. The ECG showed sinus tachycardia. During physical examination neither lymphadenopathy nor other pathological findings were observed apart from a generalized, pruritic skin rush. Hematological examination revealed normochromic normocytic anemia (Hct 31.2% and Hb 9.7 mg/dL) and leucocytosis ($16.22 \times 10^9 L^{-1}$) with eosinophilia (41.8%, total count $6.8 \times 10^9 L^{-1}$). Further laboratory tests showed moderate acute liver injury (AST 148 mg/dL, ALT 107 mg/dL, γGT 830 mg/dL) with normal values of bilirubin, renal insufficiency (serum creatinine 1.78 mg/ dL, urea 86 mg/dL) without electrolyte disturbances (serum potassium 3.8 mg/dL, sodium 137 mg/dL and calcium 9.75 mg/dL), increase of C-reactive protein levels (5.38 mg/ dL, normal ranges 0-0.5 mg/dL) and Erythrocyte Sedimentation Rate of 98 during the first hour. The chest radiography and urine examination were normal. Thyroid hormones were within normal ranges too.

In order to exclude possible causes of eosinophilia and transaminasemia, several examinations were carried out. Immunological parameters such as ANA, c-ANCA, p-ANCA, ASMA, AMA, C3 and C4 levels, tumor markers, virological immune tests for EBV, CMV, HAV, HBV, HCV and HIV as well as Brucella melithensis, Toxoplasma Gondii and Echinococcus granulosus serological tests were negative. Furthermore, blood and urine cultures were collected but they were also negative. Stool microscopy had no evidence of parasitic infection and cultures were negative as well.

Liver or biliary tract diseases were also excluded since an abdominal ultrasound, computed tomography and magnetic resonance image scan revealed no pathological entities. The peripheral blood smear and bone marrow aspiration were negative for hypereosinophilic syndromes or other hematologic malignancies (**figure 1**).

Due to great suspicion of DRESS syndrome, febuxostat was discontinued and the patient received intravenous therapy with dimethindene maleate and methylprednisolone in an initial dose of 125 mg/dL twice daily followed by 40 mg/dL three times daily for a total period of ten days. Within four days, body temperature became normal. Meanwhile, skin rush became exfoliative (**figure 2**) and transaminase levels decreased gradually. The patient was released on the tenth day of hospitalization. After three months in total, transaminase and eosinophil levels were normalized.

Figure 1

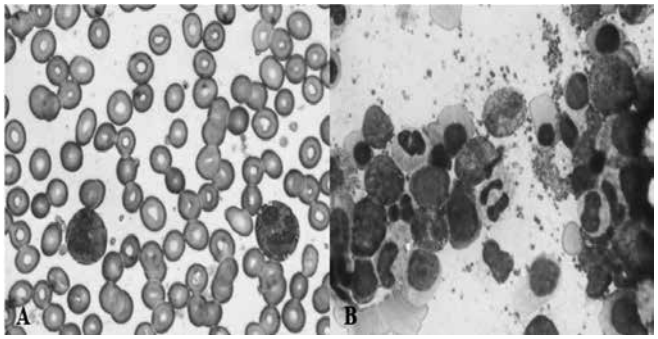
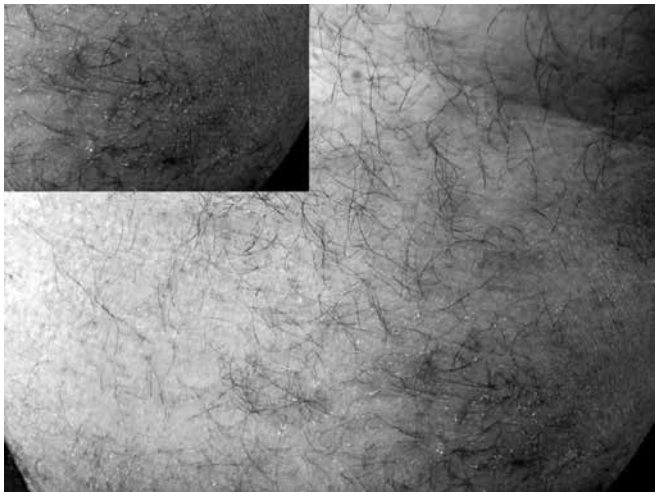


Figure 2



Discussion

Drug Rash (or Reaction) with Eosinophilia and Systemic Symptoms (DRESS) syndrome was first described in the 1950's by Chaiken et al (9), while in 1996 received its name by Bocquet et al (10) in an effort to clarify the vagueness of the terminology used to describe cutaneous drug reactions. Other similar nomenclature used for such reactions are drug-induced hypersensitivity syndrome, drug hypersensitivity syndrome or severe cutaneous adverse drug reactions (SCAR).

This syndrome represents a severe, potentially fatal, drug-induced hypersensitivity reaction. The estimated incidence ranges from 1 in 1,000 to 1 in 10,000 drug exposures without sex predilection (11), while adults are more affected than children (12). Its mortality has been calculated to 10 - 12% (13). The most frequent causative agents seem to be anticonvulsants, allopurinol (14) and sulfonamides (14). Other medication related to DRESS syndrome less frequently are dapsone (15), linezolide (16) and micocycline

(17). Cross-sensitivity among aromatic anticonvulsants in Chinese population has been referred to be almost 75% (18).

Apart from skin rash DRESS syndrome is characterized by fever, lymph node enlargement, hematologic disorders (eosinophilia, atypical lymphocytes, thrombocytopenia and lymphocytosis) and internal organ involvement, mainly liver but also kidneys, lungs, heart and pancreas (19). Systemic disorders partially come up as a result to eosinophilia. Eosinophils enter tissues and cause further damage by releasing toxic granule products or cytokines that may be involved in tissue remodeling and fibrosis (20). The reaction occurs within two to six weeks after drug initiation and may persist or even worsen upon drug discontinuation (21).

A plethora of pathogenetic mechanisms regarding DRESS syndrome have been proposed. Among them, the most important suggests an immunologically driven pathway. It seems that hypersensitivity induced by allopurinol is strongly associated with HLA-B*58:01 (22). In 2014, Yun J et al generated T cell lines that react to allopurinol (ALP) or oxypurinol (OXP) from HLA-B*58:01(+) and HLA-B*58:01(-) donors, and observed that ALP/OXP-specific T cells reacted immediately to the addition of the drugs and bypassed intracellular Ag processing, which is consistent with the "pharmacological interaction with immune receptors" (p-i) concept. They concluded that the drug-specific T cells are activated by OXP bound to HLA-B*58:01 through the p-i mechanism (23). Moreover, asymptomatic reactivation of chronically persistent viruses, such as Human Herpesvirus -6 and -7 (HHV-6/7), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), has been incriminated as possible pathogenetic mechanism. This reactivation leads to expansion of activated T lymphocytes in the blood, including both CD8+ and CD4 cells (22). Alternatively, it has also been suggested that predisposition to auto-immune disease may contribute to the development of a drug hypersensitivity syndrome (24).

Our patient presented with generalized rash, fever and systemic disorders such as severe eosinophilia and liver impairment. Several tests ruled out potential diseases: idiopathic eosinophilic syndrome, eosinophilic leukemia or other malignancies, parasitic infection or infection of hepatotropic viruses, Addison's disease or connective tissue disorders. As a result, DRESS syndrome due to febuxostat was considered probable.

In order to test our hypothesis, the RegiSCAR scoring system was used. This scale was designed to grade suspected cases of DRESS as "no" (score < 2), "possible" (score 2-3), "probable" (score 4-5), or "definite" (score > 5). DRESS is considered as "definite" in our case, given that other causes of febrile eruption with eosinophilia and liver involvement were excluded. Thus, our patient was classified as a "definite" case because of the presence of fever > 38 ^{o}C (0 points), eosinophils ≥ 1.5×10^{9} L^{-1} (2 points), skin involvement > 50% of body surface area (1 point), resolution past 15 days (0 points), internal organ involvement of liver (1 point) and exclusion of other possible causes (1 point). Furthermore, our patient's skin involvement, composed of maculopapular erythematous lesions, was consistent with the RegiSCAR description. According to Naranjo Adverse Drug Reaction Probability Scale (8), febuxostat was illustrated as the "probable" cause of the syndrome (score 5), even if alternative causes such as secondary allopurinol hypersensitivity reaction could have caused the events.

To our knowledge, there are only four possible cases of hypersensitivity syndrome due to febuxostat. All patients had previously experienced cutaneous reactions due to allopurinol hypersensitivity. In 2010, Mauck et al reported cross-sensitivity of allopurinol and febuxostat in a 44 years-old woman with chronic kidney disease (25). In 2012, Abeles AM described hypersensitivity due to febuxostat in a patient with moderate renal insufficiency that had previously developed allopurinol hypersensitivity syndrome (AHS) (26). Dore et al reported the case of an immunosuppressed patient with myopathy developing hypersensitivity syndrome in both combination of azathioprine-allopurinol and azathioprine-febuxostat (27). Recently, Lien and Logan referred another case of severe febuxostat - allopurinol cross reaction leading to DRESS syndrome in a 76-year-old woman with chronic kidney disease. The authors suggested a non-immunological mechanism related to the common pharmacological action of the drugs, inhibition of xanthine oxidase, as the possible cause of the syndrome (28). In a case series of thirteen patients with a history of allopurinol hypersensitivity syndrome who received febuxostat, one experienced a hypersensitivity type of cutaneous vasculitis (leukocytoclastic vasculitis) (1). The authors suggested careful dose escalation and close monitoring when febuxostat is prescribed in allopurinol-intolerant patients. Thus, there are indications that allopurinol and febuxostat share relative pathophysiological mechanisms leading to hypersensitivity syndromes. The fact that patients with history of AHS were excluded from phase III studies of febuxostat (26) suggests that further investigation needs to be conducted.

It is noteworthy that most patients experiencing cross-sensitivity of allopurinol and febuxostat suffered from chronic kidney disease. It is known that renal insufficiency represents an important risk factor of AHS since renal clearance of oxypurinol, the major metabolite of allopurinol, is directly correlated with glomerular filtration rate. As a result, serum half-life time of oxypurinol is prolonged leading to accumulation of oxypurinol in the serum of those patients (26). On the other hand, febuxostat is primarily metabolized in the liver while its metabolites are partially excreted to urine (29). Thus, in patients with chronic kidney disease, accumulation of febuxostat metabolites in serum could be a potential explanation of allopurinol-febuxostat cross sensitivity.

Conclusions

In April 2008, febuxostat obtained marketing approval from the European Medicines Agency as a new, promising urate-lowering therapy. It is widely used, particularly in patients with chronic kidney disease and pure uremic control. In these patients, hypersensitivity induced by febuxostat does exist, although it appears less frequently than allopurinol hypersensitivity syndrome. The precise mechanism remains unidentified. Cross-sensitivity between allopurinol and febuxostat may occur. We suggest that patients with renal insufficiency treated with febuxostat should be closely monitored especially when allopurinol intolerance pre-exists. Clinicians' awareness during febuxostat administration is necessary in order to identify systemic disorders of DRESS syndrome leading to potentially life-threatening consequences.

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