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1/2008

Urticaria and urticaria related skin condition/disease in children

Forecasting the onset of an allergic risk to poaceae in Nancy and Strasbourg

Sublingual immunotherapy for allergic respiratory disease in elderly patients

Severe respiratory syndrome induced by allergic mono-sensitization to European hamster

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The new edition

After some months we resume the publication of European Annals of Allergy and Clinical Immunology, the official journal of AAITO. In the meantime the property as well as the Publisher of the journal have changed. The journal is going to become officially a property of AAITO (Associazione Allergologi Immunologi Territoriali e Ospedalieri) and is now published by Mattioli 1885 SpA sited in Fidenza, near Parma. The new publisher has got a long experience in publishing and distributing indexed medical journals and, importantly, is able to work using a PDF format (which was not the case before). We believe that all this will represent a significant improvement for both the readership and the authors. You will also notice some changes in the graphics and in the general outlook of the journal, including the title of the published articles on the front page of each issue. We hope that these changes as well will be appreciated. Further, we are preparing a section reporting on the main articles published on other allergy journals that are likely to change our clinical practice. Such section, that is scheduled to appear regularly up from one of the next issues, will be based upon expert reviews and we really hope that it will be appreciated by our readership for its practical usefulness.

Finally, the journal is presently mainly read in Italy and France. It is our intention to spread the diffusion of European Annals of Allergy and Clinical Immunology to other European countries in order to turn it into a relevant forum for novel ideas and clinical research in all fields of allergy and clinical immunology. In this sense your suggestions and criticisms will be essential.

We hope that you will appreciate our effort and that European Annals of Allergy and Clinical Immunology may become a useful support to your daily practice as well as a tool for your educational activities.

Sincerely

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Urticaria and urticaria related skin condition/disease in children

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Key words

UA = Urticaria-angioedema,
AST = autologous serum test,
VU = vasculitic urticaria,
HAE = hereditary angioedema

Summary

Urticaria is a rash, that typically involves skin and mucosa, and is characterized by lesions known as hives or wheals. In some cases there is an involvement of deep dermis and subcutaneous tissue that causes a skin/mucosa manifestation called angioedema. Urticaria and angioedema are very often associated: urticaria-angioedema syndrome. The acute episodic form is the most prevalent in the pediatric population, and it is often a recurrent phenomenon (recurrent urticaria). Acute episodic urticaria it is usually triggered by viruses, allergic reactions to foods and drugs, contact with chemicals and irritants, or physical stimuli. In many instances it is not possible to identify a specific cause (idiopathic urticaria). Chronic urticaria is a condition that can be very disambling when severe. In children is caused by physical factors in 5-10% of cases. Other trigger factors are infections, foods, additives, aeroallergens and drugs. The causative factor for chronic urticaria is identified in about 20% of cases. About one-third of children with chronic urticaria have circulating functional autoantibodies against the high affinity IgE receptor or against IgE. (chronic urticaria with autoantibodies or "autoimmune" urticaria). It is not known why such antibodies are produced, or if the presence of these antibodies alter the course of the disease or influence the response to treatment. Urticaria and angioedema can be symptoms of systemic diseases (collagenopathies, endocrinopathies, tumors, hemolytic diseases, celiachia) or can be congenital (cold induced familiar urticaria, hereditary angioedema). The diagnosis is based on patient personal history and it is very important to spend time documenting this in detail. Different urticaria clinical features must guide the diagnostic work-up and there is no need to use the same blood tests for all cases of urticaria. The urticaria treatment includes identification of the triggering agent and its removal, reduction of aspecific factors that may contribute to the urticaria or can increase the itch, and use of anti-H1 antihistamines (and/or steroids for short periods if antihistamines are not effective). In some instances an anti-H2 antihistamine can be added to the anti-H1 antihistamines, even if the benefits of such practice are not clear. The antileucotriens can be beneficial in a small subgroup of patients with chronic urticaria. In case of chronic urticaria resistant to all the aforementioned treatments, cyclosporine and tacrolimus have been used with good success. When urticaria is associated to anaphylaxis, i.m epinephrine needs to be used, together with antihistamines and steroids (in addition to fluids and bronchodilatators if required).

Corrigendum. Article previously published in incomplete pattern.

Definition

Urticaria is a rash, that typically involves skin and mucosa, and is characterized by lesions known as hives or wheals. A hive is a pruritic plaque usually erythematous and edematous; the edematous, central area (wheal) can be pale in comparison to the erythematous surrounding area (flare). These lesions blanch with pressure, and are the result of dilation of small venules and capillaries located in the superficial dermis. Similar pathologic alterations that occur in the deep dermis and subcutaneous tissue cause a skin/mucosa manifestation called angioedema. Urticaria and angioedema are very often associated: urticaria-angioedema syndrome (UA). UA is a skin condition with a very high prevalence among the general population, 10-20% of the general population experiences UA at least once in life. In children the prevalence is 2-6% (1).

Pathophysiology

The cells responsible for causing urticaria include mast cells and basophils. These cells are able to release histamine, the most important mediator in the urticaria pathogenesis.
Mast cell and basophiles produce many other factors that may also play a role in the UA pathogenesis.
Mast cells mainly reside in tissues, and in addition to histamine, produce other preformed mediators, such as tryptase, proteoglicans, heparin and chondroitin sulphate A and B. Basophiles are usually found both in the circulation and in tissues during an active allergic inflammation process, and express chondroitin sulphate A as well as histamine and preformed mediators. Upon stimulation mast cells and basophiles are able to synthesize leukotriens (LTB_4 and LTC_4), whereas only mast cells are able to secrete prostaglandin D_2 (PGD_2). Both mast cell and basophils can express IL-4, IL-13, but, in addition, mast cells express IL-5, IL-6, GM-CSF and TNF-alfa (2).

Classification

A classification of urticaria for clinical use has been recently published in a EAACI guideline (3). Spontaneous urticaria is defined as acute if wheals last less than 6 weeks, and chronic if wheals last 6 weeks or more. Physical urticaria includes cold contact, delayed pressure, heat contact, solar, dermographic, and vibratory urticaria. Other urticaria disorders include acquagenic, cholinergic, contact and exercise induced urticaria (Tab. 1).

Table 1 - Classification of urticaria

Spontaneous urticaria	- acute urticaria - chronic urticaria
Physical urticaria	- cold contact urticaria - delayed pressure urticaria - heat contact urticaria - solar urticaria - urticaria factitia - vibratory urticaria
Other urticaria disorders	- acquagenic urticaria - cholinergic urticaria - contact urticaria - exercise induced urticaria

The acute episodic form is the most prevalent in the pediatric population, and it is often a recurrent phenomenon (recurrent urticaria). Acute episodic urticaria is usually triggered by viruses, allergic reactions to foods and drugs, contact with chemicals and irritants, or physical stimuli. In many instances it is not possible to identify a specific cause (idiopathic urticaria) (4).
Chronic urticaria in children is caused by physical factors in at least 6% of cases (5, 6). Less often, infections (4%), foods (4%), additives (2.6%), aeroallergens (2.2%) and drugs (1.6%), are found to be the trigger factors.
In some patients with chronic urticaria, auto-reactivity functional auto-antibodies directed against the immunoglobulin E (IgE) receptors have been described in both adults and children (chronic urticaria with auto-antibodies or autoimmune urticaria) (7, 8). Nevertheless, the causative factor for chronic urticaria is identified in only 22% of cases (5). Urticaria and angioedema can be a symptom of systemic diseases (collagenopathies, endocrinopathies, neoplasias, hemolytic diseases, celiachia). (4). Syndromes that include urticaria/angioedema are: Muckle-Well syndrome, Schnitzler's syndrome, Gleich syndrome, Well's syndrome (3). In other cases, urticaria is related to other diseases as a result of the patient's history (urticaria pigmentosa, urticarial vasculitis, cold induced familiar urticaria, hereditary angioedema) (3).

Urticaria "Management"

Urticaria management should start with a check list to adequately characterize the clinical and anamnestic features of the episode (9) (Tab. 2).

Table 2 - Anamnestic and clinical features of the urticaria episodes

1)	Lesion first appeared: _____		
2)	Duration of urticaria:	☐ < weeks	☐ ≥ 6 weeks
3)	Duration of individual wheals:	☐ < 24 hours	☐ ≥ 24 hours
4)	Size of wheals: _____		
5)	Colour: _____		
6)	Skin's appearance after wheals have faded: _____		
7)	Frequency of whealing: _____		
8)	Diurnal variations? _____		
9)	Particular parts of body affected? If yes, which? _____	☐ YES	☐ NO
10)	Swelling of:	☐ eyelids ☐ tongue	☐ lips ☐ face ☐ throat
11)	Are lesions brought on by:	☐ rubbing ☐ exercise ☐ cold ☐ immersion in cold and warm water	☐ pressure ☐ heat ☐ exposure to UV light
12)	Are there associated symptoms?	☐ fever ☐ weight loss	☐ joint pain ☐ abdominal pain
13)	Are initiating or provoking factors (food or emotions) present?: _____		
14)	History of injections, insect bites or recent illness: _____		
15)	History of drug use: _____		

Once episodic or chronic urticaria has been established, a specific diagnostic algorithm can be followed (Tab. 3-4). Different urticaria clinical features must guide the specific diagnostic test, especially if a physical factor is suspected (Tab. 5). There is no need to use the same blood tests for all cases of urticaria (Tab. 6)! Blood examinations (blood cell count with differential, ESR, CRP hepatic and thyroid function, BUN and glicemia, antistrept titer, complement, total and specific IgE), skin tests for common inhalants, food or drug allergens, food or additive challenges, elimination diets, auto-antibodies, infectious disease work-up (hepatitis B e C, TORCH, Epstein-Barr, urea-breath test for the diagnosis Helicobacter Pylori infection, urine culture, stool culture, nasal or pharyngeal or vaginal culture beta hemolytic streptococcus and staphylococcus) should be considered part of an extended diagnostic programme only in the case of chronic spontaneous urticaria and according to the patient's history (3, 4) (Tab. 6).

Infection induced urticaria

Infections can trigger acute urticaria and exacerbations of chronic urticaria. Infections do not seem to be the cause, per se, of chronic urticaria.

Viruses, such as HBV, HCV, HAV, EBV, and in particular adenovirus and rhinovirus have been reported to be causes of acute urticaria and exacerbations of the chronic form. Little is known of the pathogenetic mechanism responsible for virus induced urticaria. The most likely explanation is that the virus induced release of pro-inflammatory lymphokines and cytokines may increase mast cell and basophile "releasability", facilitating their degranulation (6,2).

Chronic persistent bacterial infections such as H.Pylori, streptococci, staphylococci, or Yersinia can also trigger urticarial symptoms (10). Bacterial infection (streptococcus and staphylococcus) may induce acute urticaria that often evolves into the chronic type.

Table 3 - Acute urticaria: diagnostici algorythm

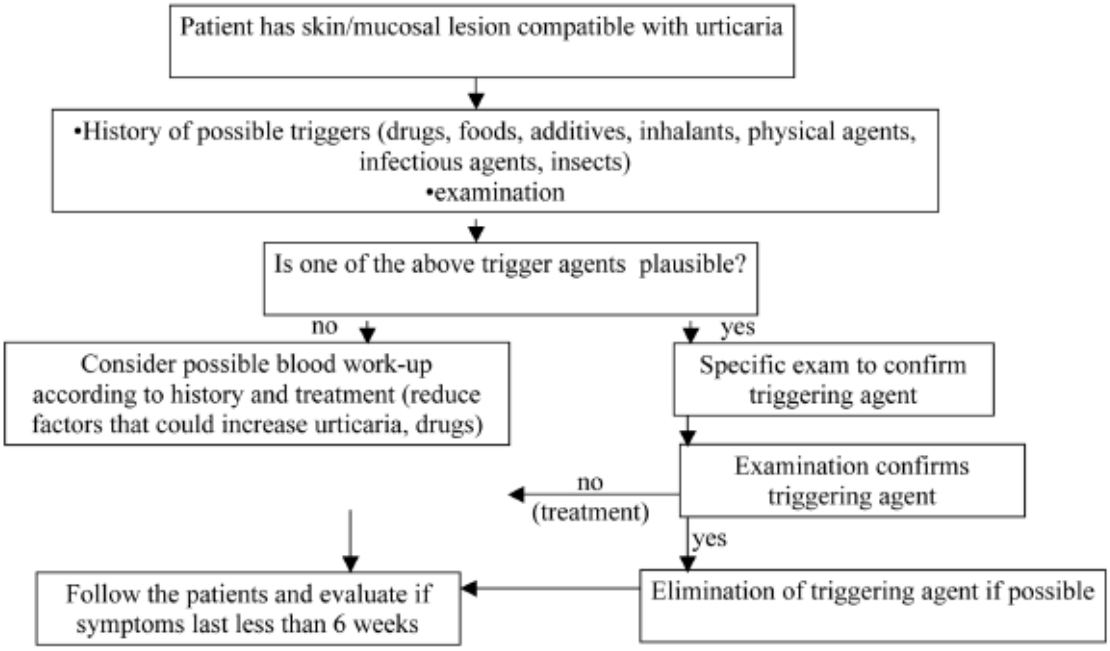

Table 4 - Chronic urticaria: diagnostici algorythm

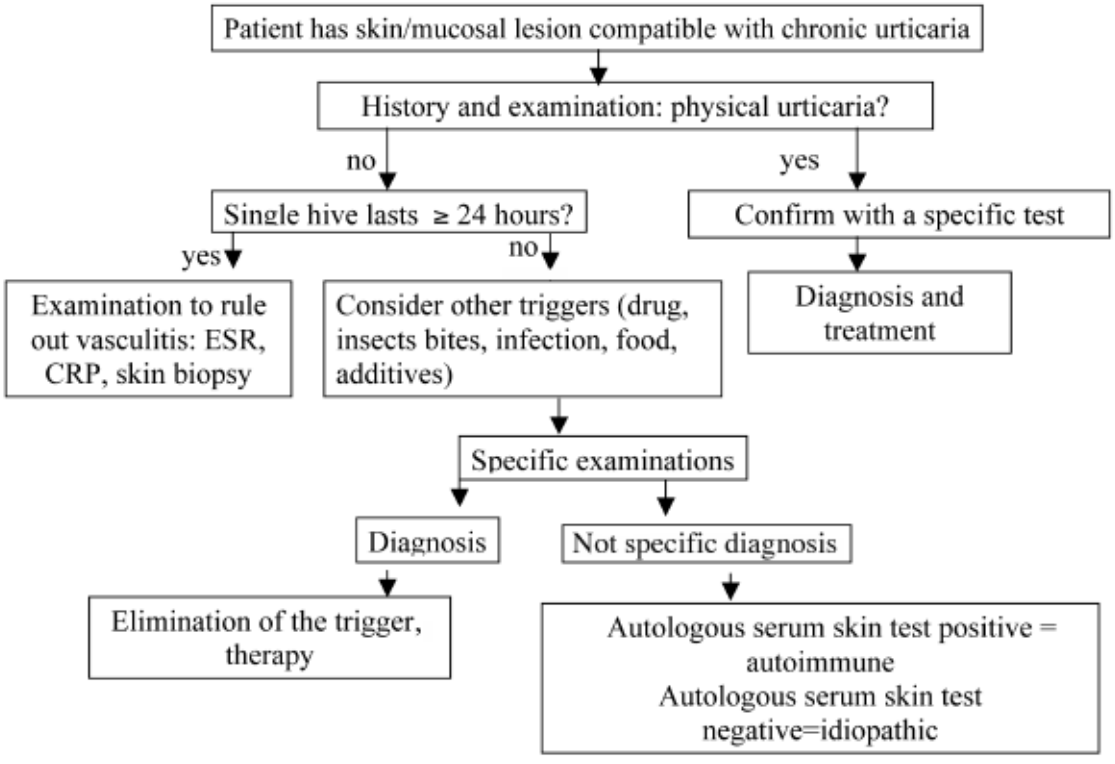

Table 5 - Clinical features and specific tests in some types of urticaria

Urticaria type	Clinical features	Test
Pressure	Erythematous, edematous, painful and itchy lesion, often big in size, at the site of pressure (soles of feet, palms of hands, waist) that last ≥ 24 hours, not associated with angioedema	Apply pressure for 10 minutes increasing pressure (500 g/cm^2, 1000 g/cm^2 1500 g/cm^2) at 90 degrees on the skin or a weight (6 kg) for 20 minutes on the extensor aspect of the thigh ("reading" at 30 minutes, 3 hours, 6 hours, 24 hours): positive test = lesion erythematous and persistent
Cold	Erythematous, edematous, itchy lesion in the area in contact with cold liquid or cold object. Can be generalized. Can be associated with angioedema.	Apply an ice cube for 10 minutes on the forearm, within 5 - 10 minutes after removing the ice a wheal should appear. Stay in a cold room (4 C°) for 10 - 30 minutes
Colinergic	Small, monomorphic, pruritic, pallid or pink wheal, mostly on trunk, neck and limbs associated with angioedema.	Excercise Intradermal test with methacolin
Autoimmune	Without specific clinical feature can be chronic	Autoinjection: intradermal with 50 μl of patient serum (positive if wheal volume is ≥ 9 mm^3 compared to the control after 60 minutes, positive if the wheal diameter is ≥ 1,5 mm compared to the control after 30 minutes). Reduction in peripheral basophils. Histamine release from basophils
Dermografism	Immediate (starts 2-5 minutes after the stimulus, and lasts 30 minutes), intermediate (starts after 30 minutes-2 hours and lasts 3-9 hours), delayed (starts after 4-6 hours and lasts 24-48 hours).	Scratch (back or forearm) with dulled point or nail with moderate pressure (from 3200 to 4900 g/cm^2) for a length of 10 cm

As antibiotics and NSAIDs are often prescribed during viral or bacterial infections, the infection-induced urticaria is often mistakenly attributed to the drug instead of the infective agent.

The most common skin manifestation associated with infection or reactions to drugs are maculopapular or erythematous exanthemas, which typically start at the trunk or areas of pressure, and subsequently spread to the limbs. Itch and fever may or may not be present. Occasionally drug-induced erythematous exanthemas may progress into far more severe skin manifestations (erithrodermia, Stevens, Jhonson Syndrome). For an accurate diagnosis of adverse reaction to drugs, the patient's history is the most useful tool available, such as cause-effect relationship between drug administration and beginning of symptoms, morphology and distribution of lesions. For example, an episode of hives shortly after administration of an antibiotic or angioedema shortly after NSAIDs intake is highly indicative of an allergic reaction. The presence of a sign not involving the skin is suggestive of an adverse drug reaction (fever, malaise, lymphoadenopathy, diarrhea, arthralgia, tachycardia, hypotension, dyspnea); the correct use of lab tests (i.e. eosinophil count, hepatic function, viral tests) may offer some assistance in the differential diagnosis between viral exanthema and adverse reactions to drugs (11). However, very often the viral exanthema and the drug reaction cannot be differentiated, and a prudent change of antibiotic or suspension of treatment may be warranted.

The role of H. pylori (Hp) in chronic urticaria is debated (7).

Even if the rate of Hp infection in patients with chronic urticaria is similar to that found in the general population, the immune response to Hp in patients with chronic urticaria seems to be different and characterized by a higher IgE secretion. Moreover, in some papers eradication of Hp was associated with a resolution of urticaria (10). However, no convincing demonstration of a causative role of Hp in chronic urticaria is presently available.

Table 6 - Laboratory evaluation of urticaria and angioedema

Suspected etiology	Procedures
General screening:	Complete blood count, sedimentation rate urinalysis
Vasculitis:	Ig, antinuclear factor, immune complexes skin biopsy
Infections:	Cultures, serological studies, liver function tests, stool for ova and parasites, x-ray
Allergic:	IgE, skin tests, eosinophil count, challenge, elimination diet, tryptase
Physical:	
Cholinergic	Metacholin test, running
Dermatographism	Spring-loaded dermographometer
Cold	Ice cube test
Solar	Light exposure
Heat	Warm water immersion
Hereditary angioedema	C3-C4, C1 esterase inhibitor
Other	T3-T4-TSH, skin biopsy, urea breath-test

Table 7 - Therapeutic management of urticaria

Remove identifiable	
Non-drug	Drug therapy
Explanation and information Avoid FANS	First line- all patients: - anti-H1 Second line- special indications: - anti-LT, anti-H2, Corticosteroids
Minimize stress, over-heatingalcohol	- Adrenaline
Exclusion diet when indicated	Third line- specialist use only: - Cyclosporin and tacrolimus - Ig - Cyclophoshamide

The role of parasitic infections in the pathogenesis of chronic urticaria is very uncertain (10).
In conclusion, even if the relationship between urticaria and infection is often suspected clinically, the lack of double blind studies makes it difficult to prove such an association, especially in a setting of different stimuli that can induce urticaria.

Allergic Urticaria

Allergic urticaria is the best known urticaria type. The pathogenetic mechanism is well known. Affected individuals are sensitized to specific allergens (most often foods, penicillins, cephalosporins or inhalant allergens), towards which they produce specific antibody of IgE class (6). Such antibodies bind to the IgE high affinity receptor present on mast cells and basophiles. The allergen binds to the IgE attached to the receptor, induces the cross linking of receptors, and subsequent degranulation of mast cells and basophiles. Examples of this urticaria type are: food induced urticaria/angioedema in subjects with food allergy, penicillins or cephalosporin induced urticaria in subjects that produce IgE against such drugs.
The patient's history establishes a temporal relationship between food or drug intake and the onset of urticaria. All types of food can induce urticaria in sensitized individuals, however the foods most often involved are eggs, milk, seafood and fruit. The drugs that most often cause urticaria are the beta lactams. Non-steroidal-antinflammatory drugs (NSAIDs) can cause urticaria by inducing degranulation of mast cells and basophiles, but not in an IgE mediated fashion. NSAID induced urticaria is typically associated with angioedema. These episodes are most often acute, recurrent and only seldomly chronic.
The most useful tools for diagnosis are skin tests (prick test), measurement of serum specific IgE, challenge and occasionally elimination diets (12).

Pseudo food allergy and urticaria

Pseudo food allergies are quite prevalent and seem to be re-

sponsible for chronic urticaria more often than food allergy (13). Pseudo food allergies are due to histamine release from skin mast cells and seem to be triggered by several agents (NSAIDs, additives such as salicylates and benzoates, and food colours such as tartrazine) (14). In rare cases urticaria can be the consequence of inhalation of volatile aromatic compounds found in white wine and tomatoes (15).
Diagnosis in these cases is based only on challenges and elimination diets, as in these instances skin tests are often not reliable.

Insect bite induced urticaria

This is probably the most common type of urticaria in children. It is characterized by groups of pruritic hives or papules on the exposed parts of the body (arms, legs). Several insects, including mosquitoes and fleas, can cause hives or papules. The pathogenetic mechanism can be either immuno-mediated (an IgE mediated response is followed by a delayed response) or, most often, irritative. After several insect bites, children may develop tolerance.
Hymenoptera sting-related allergic reactions can be more severe. In sensitized subjects hymenoptera stings can induce urticaria and angioedema either at the site of injection or systemically, and they can also cause anaphylaxis. Venom immunotherapy is recommended not only for life-threatening reactions, but also for urticaria if risk factors or quality of life impairment are present (16).

Contact urticaria

Contact urticaria can be immune mediated or not immune mediated.
The non immune-mediated form does not require prior exposure to the trigger agent, appears usually within 45 minutes after exposure, and is caused mainly by artificial or natural chemicals. The diagnosis is carried out with application tests.
The immunologic form needs a prior exposure to the offending agent, appears within 10-20 minutes after the exposure, and is caused by protein (animal, vegetal, plant etc). The diagnosis is carried out with the use of skin tests (prick test) or measurement of specific serum IgE (CAP) (1). Occasionally the same substance (as for example in the case of the Thaumetopeoa pityocampa- pine tree parasite-) can cause urticaria in a toxic/irritative manner and/or with a immunomediated mechanism (17).

Physical urticaria

Physical urticaria can be triggered by mechanical, thermal or light stimuli (Tab. 5).
Dermatographism is the most common type of physical urticaria, and it can be elicited by applying pressure to the skin by scratching it with a dull point at a pressure point of 3200-4900 g/cm^2 (18).
Cholinergic urticaria is usually triggered by warmth, exercise, or emotions. It can be localized or generalized. It is rare in children; in fact, it only represented 2.7% in a pediatric series (5). Usually it is localized on the neck, flexor aspect of elbow and knee, and arm pits. Typically the eruption lasts 30-60 minutes.
Cold induced urticaria can be typical or atypical. This form is very rare in children .

Autoimmune urticaria

The presence of histamine releasing factors was first reported in patients with chronic idiopathic urticaria, in whom the intradermic injection of autologous serum determined a wheal and flare response (19). These histamine releasing factors were recently identified as auto-antibodies against IgE or IgE receptors (1).
Auto-antibodies are found in up to 30-40% of children with chronic urticaria (8), but in none of those with other allergic diseases such as atopic dermatitis. Such auto-antibodies are found in other autoimmune diseases such as bullous pemphigous, vulgar pemphigous and dermatomyositis. Such auto-antibodies are often present in allergic or drug induced urticaria, and in children and adults (mostly women) with similar-allergic respiratory symptoms (20).
Although the effect of urticaria therapy does not change according to the presence of a positive or negative autologous- skin test (4), it has been reported that adult patients with positive AST tend to have a more severe disease (21). Therefore in these cases a more aggressive treatment could be justified.
Indeed it could be even hypothesized that auto-antibodies are not actually pathogenetic, but are secondary to the presence of urticaria in individuals with a predisposition to develop autoimmunity. Moreover, their presence does not change the therapeutic approach or the prognosis of the disease, therefore their presence does not have a high clinical significance.
Autoimmune urticaria is characterized by hives that last at least 8-12 hours (but always < 24 hours), with daily re-

currence, to which angioedema can be associated. From a diagnostic point of view, other causes of chronic urticaria (particularly the physical urticaria), must be excluded.
The diagnosis is based on the autologous serum -skin test that must be performed during the acute phase of the urticaria. Another useful test is the histamine release from basophiles induced by the serum from the affected patient. The concordance between those 2 tests is about 80% (8). There are no clinical features that can help in distinguishing between chronic urticaria with auto-antibodies as opposed to the one without auto-antibodies. Moreover children, as opposed to adults with chronic autoimmune urticaria, do not have other autoimmune diseases associated or sign of autoimmune thyroid disease, celiac syndrome or HP infection (21). On the other hand, chronic urticaria in children can be associated with other autoimmune diseases, mostly of the thyroid (22).

Vasculitic Urticaria (VU)

Vasculitic urticaria is rare in children; it can be associated with an immunocomplex disease, such as serum sickness or autoimmune disease such as sistemic lupus erithematosus or Henoch-Schoenlein purpura, or can be idiopathic. The skin biopsy, which is necessary for the diagnosis, typically shows a necrotizing vasculitis of small vessels, and immunocomplexes and complement deposits.
Hives last more than 24 hours, and leave purpuric signs. VU is often associated with arthalgias, abdominal symptoms, and elevated inflammatory markers. It does not respond to antihistamine treatment (1).

Urticaria Pigmentosa (cutaneous mastocitosis)

Cutaneous mastocitosis, is a rare disease in children. It usually appears in the first 2 years of life, and the most common manifestation is an isolated mastocitoma, a brownish lesion, sometimes mistakenly considered a mole, that can become red or can be itchy. Cutaneous mastocitosis can occur also as pigmentosa urticaria, i.e as an itchy generalized maculopapular rash. Scratching the lesion may cause a wheal and flare reaction (Darier sign).
The diagnosis of systemic mastocitosis needs the help of highly specialized laboratories, and is based on the presence of a major sign (multifocal dense infiltrates of > 15 mast cells in the bone marrow or in other extracutaneus organs) + one minor sign (serum alfa- tryptase levels > di 20 microgram/mL, CD2 o CD25 expression in bone marrow or other c-kit positive tissues mast cells, c-kit mutations in mast cells, presence of > 25% spindle-shaped bone marrow or other c-kit positive tissues mast cells) o three minor signs (23). Urticaria pigmentosa has a benign prognosis in most patients. Rarely, more severe symptoms can be present (rash, diarrhea, gastrointestinal bleeding and bronchospasm).

Hereditary Angioedema (HAE)

HAE is not a real form of urticaria. It can be congenital or acquired. The hereditary form (Quincke edema) is due to a reduced level or reduced function of C1 esterase inhibitor. This is a very rare type of angioedema, with a prevalence of 1/50.000 in the general population, and is transmitted in an autosomical dominant way. Only 10% of cases are new mutations. The clinical picture of this rare disease is characterized by recurrent angioedema attacks that can be potentially lethal if they involve the submucosal tissue of the glottis. Those patients need an adequate clinical and diagnostic follow up. The treatment of the severe attacks is based on the administration of the concentrated purified inhibitor. Intubation and mechanical ventilation of patients may be needed (24).

Skin diseases similar to urticaria

Scabies, especially in small children, can be similar to urticaria particularly the urticaria pigmentosa (25).
Herpetiform dermatitis (bullous skin disease very pruritic, which mainly involves the extensor aspect of limbs and is associated with celiac disease) can be similar to urticaria (26).
Other skin conditions similar to urticaria are psoriasis guttata, pitiriasi rosae, erithema nodosum, and eritmema multiforme. On the other hand, the angioedema can be similar to hypoproteinemic edema, due to erroneous diets (27), periorbital cellulitis, contact dermatitis, Gleich syndrome.

Therapy

The urticaria treatment includes (4, 28)(Tab. 6)
1. Identification (if possible) of the triggering agent and its removal
2. Reduction of nonspecific factors that may contribute to the urticaria or increase the itch

3. Use of antihistamines (and/or steroids for short periods if antihistamines are not effective). Second –generation antihistamines must be considered as first line symptomatic treatment for urticaria (29).
   All patients must choose between 2 antihistamines as the effectiveness and tolerance are different among different individuals.
   Before considering alternative treatment, higher dosages should be used. (29). Before increasing the dosage, a careful evaluation of risk/benefit ratio should be carried out, as higher doses of antihistamines certainly expose the patient to an increased risk of side effects (30).
   It is also possible to combine a non-sedative antihistamine with a sedative one in unresponsive cases.
   In some instances an antiH2 antihistamine can be used, even if the benefits of such practice are not clear. The antileucotriens can be beneficial in a small subgroup of patients with chronic urticaria (18).
4. In cases of insect related urticaria, treatment includes prevention (removal of possible sources of insects, such as pets, use of repellents), antihistamines, use of topical antibacterial drugs if there are signs of infection.
5. In cases where urticaria is associated with anaphylaxis i.m epinephrine needs to be used, together with antihistamines and steroids (+ fluids and bronchodilatators if required).
6. In case of chronic urticaria resistant to all the aforementioned treatments, cyclosporine and tacrolimus have been used with good success (28).
7. In case of HAE due to C1 esterase inhibitor deficiency the elective treatment is with anabolic steroids (stanazolol and danazol) or tranexamic acid. During acute episodes fresh frozen plasma and purified concentrated inhibitor can be used (31).

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Forecasting the onset of an allergic risk to poaceae in Nancy and Strasbourg (France) with different methods

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Key words

Poaceae, Forecast method, Meteorological data, Allergic risk

Summary

Pollens of Poaceae are among the most allergenic pollen in Europe with pollen of birch. It is therefore useful to elaborate models to help pollen allergy sufferers. The objective of this study was to construct forecast models that could predict the first day characterized by a certain level of allergic risk called here the Starting Date of the Allergic Risk (SDAR). Models result from four forecast methods (three summing and one multiple regression analysis) used in the literature. They were applied on Nancy and Strasbourg from 1988 to 2005 and were tested on 2006. Mean Absolute Error and Actual forecast ability test are the parameters used to choose best models, assess and compare their accuracy. It was found, on the whole, that all the models presented a good forecast accuracy which was equivalent. They were all reliable and were used in order to forecast the SDAR in 2006 with contrasting results in forecasting precision.

Introduction

Grass pollen is considered to be one of the most important aeroallergens in Europe (1) affecting, for example, 20% of pollen-allergic people in Denmark and 80% of pollen-allergic people in France or in the Netherlands (2). A calendar of the pollen average season is often used for forecasting the Starting Date of the Allergic Risk linked to Poaceae (SDAR). Because of the high variability of the SDAR from one year to the next, one this calendar is not suitable for an accurate prediction. Many models were produced to forecast the SDAR using only temperatures like the Growing Degree Days (GDD), the Lejoly-Gabriel and the Q_{10} sum methods presented in this paper. But, in the case of Poaceae, rainfall is also a significant factor in the prediction of the starting date of pollination (3) and this parameter is generally associated with temperature in a multiple regression analysis (4). This last method is chosen in order to predict the SDAR in Nancy and Strasbourg. With regression analysis, in addition to temperature and rainfall, we can introduce relative humidity, sunshine duration and underground temperature. These three last meteorological data were previously used to forecast the starting date of pollination of other herbaceous plants like ragweed (5).

Materials and methods

Climate and pollen monitoring sites

Nancy and Strasbourg are located in the north-eastern part of France; they are characterized by a climate with continental influences. Nancy is situated at 212 m above

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sea level (48°41' N, 6°11' E) and Strasbourg at 142 m (48°35' N, 7°45' E). In Nancy, mean temperatures for January and July are approximately 1.2°C and 18°C respectively, mean annual rainfall is about 759.3 mm and mean annual duration of sunshine is 1651.5 hours (1961-1990 average). With regard to Strasbourg mean temperatures are 0.9°C for January and 19.1°C for July; mean annual rainfall and the amount of sunshine recorded annually are lower than Nancy values (610.5 mm and 1636.9 hours respectively).

The pollen grains were sampled by Lanzoni-Hirst-type (6) volumetric traps placed on the roof of the Faculties of Medicine of Nancy and Strasbourg, 18 and 50 m above ground level respectively. They were calibrated to handle a flow of 10 litres of air a minute, which roughly corresponds to human breathing, and a built-in vane ensured that they were permanently oriented in the direction of the wind. Pollen grains sucked into the trap impacted on a cylindrical drum covered by a plastic film coated with a uniform layer of silicone solution and rotated by 7-day clockwork at a speed of 2 mm/h (7, 8). The methodology employed is common for this type of sampling. Every week, the strip was removed and cut into seven equal segments corresponding to the 7 days of the week. Each segment was mounted between slide and coverglass. Then it was examined by light microscopy and pollens were counted on 2 or 3 equal-distanced horizontal lines. The results were expressed as the number of pollen grains per cubic metre of air.

Grass pollen data

Grass pollen data were supplied by the French aerobiological network (RNSA) which managed 59 pollen traps in 2006. This study used two historical databases of 19 years for Nancy and Strasbourg; the dataset ranged from 1988 to 2005.

Various thresholds were found in literature in order to define the starting date of pollen season. For example Laaidi (4) used a relative threshold those origin is graphical (9). It corresponds to the day when the daily pollen concentration first reaches 1% of the annual sum, the accumulated concentration up to this day being at least 5% of the same annual sum. This procedure eliminates the long tails of very low values at the start of the season, which may not accord with local phenology (4). But these relative thresholds, inevitably, correspond to different counts according to the inter-annual variability of pollen amounts. This method is, therefore, not very suitable for a forecast intended for allergy sufferers. Furthermore missing values were found in the Nancy and Strasbourg datasets during the grass pollen season, so total grass pollen amounts could not be known for some years. In England, a Threshold 30 method was used (10) which is defined as the first day when the pollen count is greater than or equal to 30 grains/m^3. This method is based on the results of several clinical studies that indicate that this is the average concentration at which hay fever patients are likely to experience symptoms (11, 12).

In France, the RNSA has developed a risk index for each allergenic pollen (13, 14). This index ranges from 0 (no risk) to 5 (very high level of risk). For Nancy and Strasbourg, we chose the first day when the daily average Poaceae pollen count reached 10 grains/m^3 followed by a four-day period which reached, at least, 40 grains/m^3. Moreover, three days of the total five-day period had to reach the daily average threshold. Ten grains/m^3 correspond to level 3 in the risk index applied to Poaceae (medium risk) and the following conditions have the advantage of eliminating isolated days when the daily average grass pollen count reached the medium risk level.

Meteorological data

Meteorological data were supplied by Météo France. The following variables, from the sites of Nancy-Essey and Strasbourg-Entzheim, were used for this study:

- minimum, maximum and mean daily temperatures.
- daily rainfall.
- daily sunshine duration (in minutes).
- minimum, maximum and mean daily relative humidity.

In addition to these classical meteorological parameters, the number of days with rainfall (above or equal 0.1, 1 and 5 mm respectively), the number of days where minimum, maximum and mean temperatures were lower than 0°C and the temperature 10 cm and 20 cm under ground were included.

In literature the use of 10-day periods or decade-of-days is a standard method employed in meteorological and aerobiological works (15-20) but many of these periods are overlapping two months; the reading is, consequently, not very practical. To a straightforward reading we chose fortnightly periods, based on monthly division, which are the followings: 1 to 15 January (symbolized by 01a), 16 to 31 January (01b), 1 to 14 February (02a), 14 to 28 or 29 February (02b), 1 to 15 March (03a), 16-31 March (03b), 1 to 15 April (04a) and 16-30 April (04b). Variables were taken from 1 January because this is the onset date used

in papers about grass pollen forecast (10, 21). The earliest SDAR occurred at the beginning of May, therefore meteorological parameters recorded after the 30 April were excluded.
Because of the different lengths of these periods, all the factors were converted in fortnightly and monthly averages. Because of the variable length of the second fortnight of February, the number of rainfall days and negative temperatures days were taken over from the frequency of these days during the under consideration period.

Forecasting methods

Three temperature accumulation methods are presented in here part:

- Growing Degree Days (GDD) method was developed, originally, for the calculation of heat units in pest management (22). Degree-days are calculated by a single triangle and a single sine method. Minimum and maximum temperatures are accumulated depending on an upper and a lower threshold. Many combinations are therefore possible according to the position of minima and maxima in relation to values of the two thresholds. Many papers used the triangle method, or the sine one, in order to predict the starting date of pollen season of different species like olive tree (23) and oak (24, 25). But authors only used the lower threshold, according to a paper of Snyder et al., because: "it was assumed that development is negligible when the temperature is below the lower threshold and that there is no further increase in developmental rate when air temperature is above an upper threshold temperature" (26). GDD are calculated as following:

  $GDD = 0$ when $x \geq Tx$

  $GDD = [(Tx - x)/2]\,[(Tx - x) / (Tx - Tn)]$ when $Tn < x < Tx$

  $GDD = Tm - x$ when $x \leq Tn$

  Tn, Tx, Tm = minimum, maximum, mean temperature; x = threshold temperature

- Lejoly-Gabriel method (9) is a simpler version of GDD method. Originally, mean temperatures are accumulated above a certain threshold, but the use of maximum temperature appeared to be more efficient to predict the beginning of the pollen season linked to the appearance of an allergic risk. This method is, above all, used in French publications (4, 27, 28). The formula is the next one:

  Lejoly = when $Tx > x$

  Tx = maximum temperature; x = threshold temperature

- Q_{10} is, originally, a notion which corresponds to a constant for given vegetal specie. Analogically with Van't Hoff's law in chemical kinetic, Q_{10} (t) is identified to the existing link between the growth speed for T temperature and those would be observed for the temperature T+10°C. Q_{10} sum method, which results from it, allows the growth and development of a plant to be adjusted to an exponential temperature law (4). It corresponds, there, to the "Warm Effect" (WE) method (29), generally used in French articles notably for the Poaceae forecast (4, 30), which formula is the next one:

  $$WE = Q_{10}^{Tn/10} + Q_{10}^{Tx/10}$$

  Tn, Tx = minimum, maximum temperature

Contrary to GDD and Lejoly-Gabriel methods, where temperatures are summed above a certain threshold, the Q_{10} sum method gives us the ability of using all the temperatures of the period preceding SDAR.
In order to forecast the SDAR from many meteorological data like temperature, rainfall or relative humidity, linear multiple regression analysis is the most appropriate method (4, 5). A forward stepwise multiple regression was applied on all the meteorological data of each fortnightly period; the most non-colinear significant correlated variables with SDAR, at a p level of 0.05, were established. The operation was therefore repeated eight times (once for each fortnightly period from the 1st January to the 30th April).
Variables selected by each forward stepwise regression were included in a standard linear multiple regression as the next example:

$$SDAR = a_1x_1 + a_2x_2 + \ldots + b$$

Standards of choice of best models

GDD and Lejoly-Gabriel methods consists of cumulatively summing the daily average values, peculiar to each method, from a statistically determined date, above a

thermal threshold and until the SDAR previously calculated. Several dates were tested in order to determine the best one for starting the sum calculation. These dates ranged from 1 January to 30 April, in steps of one day. Different thermal thresholds, above which the daily temperature is effective, were also tested, from 0 to 20°C, in steps of 0.5°C. The same process was applied for the Q_{10} sum method but, instead of thermal thresholds, different Q_{10} coefficients were tested from 1 to 12, in steps of 0.1.

The best starting date and the more appropriate threshold were those that minimized the Mean Absolute Error (MAE) which is a good indicator of mean errors of prediction. The MAE is calculated as:

$$\left|MAE\right| = \frac{1}{N}\sum_{i=1}^{N}\left|x_i - \hat{x}_i\right|$$

N = Number of observations; x_1= estimated value;
$\hat{x}_1$ = predicted value

In the case of several date/threshold combinations with the same MAE value, those that minimized the Root Mean Square Error (RMSE) were chosen.

As regards linear multiple regression analysis, variables selected by each forward stepwise regression were included in a standard linear multiple regression. They were resulted from different periods and therefore they were physically independent because maximum temperatures of the second fortnight of April, for example, could not be predicted according to mean relative humidity of the first fortnight of February. But, in most cases, a statistical multi-colinearity, which affects the quality of models, exists between these variables. In order to compensate for this, the use of an Actual forecast ability test (Af test) is appropriate. This test is stemmed from the coefficient of determination (R^2) which takes into account the number of variables used and the number of available observations. Smaller the gap between Af value and R? is, better the model is.

The Af test is calculated as:

$$Af = R^2 - 2\left[(M/N) + (1 - R^2)\right](1 - M + N)$$

R^2 = coefficient of determination; M = number of variables in the equation; N = number of observations

Therefore, only the variables without multi-colinearity were kept in the equations of regression. These variables were, of course, significantly correlated with SDAR at a *p* level of 0.05.

Results

SDAR for each town and each year are presented in Table 1 in number of days from 1st January. In Nancy the average SDAR is approximately on 10th May (day 130 from 1st January) for a no-leap year (9th May therefore for a leap year). The standard deviation reaches 5.96 days. The earliest SDAR occurred on 2nd May in 1999 and 2003 and the latest in 1991 (23rd May).

The average SDAR occurs 3 days later in Strasbourg i.e. the 13th May for a no-bissextile year which corresponds to the 133rd day from 1st January. The standard deviation reaches 5.20 days. The earliest SDAR took place on 4th May in 2003 and the latest in 1996 on the 142nd day of the year (21st May).

According to the *W* test of Shapiro-Wilks, which evaluates the normality of a distribution, the series of SDAR of Nancy and Strasbourg presented a Gaussian distribution with *p* values of 0.1454 and 0.6611 respectively. So, in this case, the comparison between the two series could be done with the *t* test of Student, and linear correlation between data of Nancy and Strasbourg could be realized. The *p* value of the *t* test were 0.162 and the coefficient of

Table 1 - Starting Dates of the Allergic Risk in Nancy and Strasbourg (number of days from 1st January): annual values, average and standard deviation

Year	Nancy	Strasbourg
1988	128	127
1989	134	132
1990	133	133
1991	143	141
1992	134	135
1993	125	135
1994	129	128
1995	125	127
1996	142	142
1997	131	135
1998	129	130
1999	122	130
2000	123	126
2001	128	131
2002	127	133
2003	122	124
2004	132	136
2005	130	140
Average	129,83	132,5
σ	5,96	5,2

correlation reached a value of 0.78 ($p<0.001$). So SDAR of Nancy and Strasbourg were statistically similar, despite a gap of 2.7 days between both averages, and followed the same trend during the 1988-2005 period.

Following the determination of the Starting Date of the Allergic Risk for each station, the next results presented were resulted from models established from 1988 to 2005. The year 2006 was deliberately removed of the development of models in order to test the accuracy of the different models in a forecasting context.

The best combinations between date and threshold in order to minimize the mean absolute error for the three cumulative methods are given in Table 2.

We can notice that the starting dates are late and all occur during the second part of April except for Q_{10} method in Nancy. The latter we start the summing, the better are the forecasts in Strasbourg, but it is not the case in Nancy. Thresholds are various but they are almost identical for the Lejoly-Gabriel method.

Mean Absolute Error (MAE) and Root Mean Square Error (RMSE) associated to the date/threshold emerging from Table 2 are presented in Table 3.

All the models present a good accuracy with a mean absolute error lower than 2.6 days. We can notice, here, that Lejoly-Gabriel is the best cumulative method to predict the SDAR in Strasbourg and Q_{10} method is the most accurate for Nancy. But, overall, the results are equivalent; all the methods are valid even they were elaborated according to different processes and hypothesis.

As regards linear multiple regression analysis, variables significantly correlated with SDAR at a *p* level of 0.05 are collected on Table 4.

Table 2 - Starting dates of summing temperatures, thresholds and sums to reach in order to forecast the Starting Date of the Allergic Risk of the most accurate models for each cumulative method and each station (1988-2005)

	Method	Date	Threshold	Sum
Nancy	GDD	25 april	7.5°C	77.62°D
	Lejoly-Gabriel	29 april	16.5°C	135.57°C
	Q_{10}	4 january	3.2	734.83 unités
Strasbourg	GDD	30 april	8.5°C	73.36°D
	Lejoly-Gabriel	30 april	17°C	183.94°C
	Q_{10}	30 april	3.2	224.51 unités

GDD = Growing Degree Days method. Lejoly-Gabriel and Q_{10} are the name of the other ones

Table 3 - Mean Absolute Error (MAE) and Root Mean Square Error (RMSE), in days, corresponding to date/threshold combinations of each cumulative method presented in Table 2 (1988-2005)

	Method	MAE	RMSE
Nancy	GDD	2.50	3.34
	Lejoly-Gabriel	2.56	3.38
	Q_{10}	2.33	3.25
Strasbourg	GDD	2.39	3.34
	Lejoly-Gabriel	1.94	2.66
	Q_{10}	2.28	3.36

GDD = Growing Degree Days method. Lejoly-Gabriel and Q_{10} are the name of the other ones

The main characteristic of this table is the important rule played by the variables of the second fortnight of January in Nancy and Strasbourg. Temperature and rainfall are significantly and negatively correlated with SDAR. Early SDAR seems to be linked to mild temperatures and rainy weather during this period. Temperature is the most recurrent variable and has the same influence for all the periods where it appears:

- negative correlations with thermal values.
- positive correlations with number of days where temperature (minimum, maximum or mean) are lower than 0°C.

Two equations, where the gap between R^2 and *Af* test values are minimized, are resulted from these correlations:

$SDAR_{NANCY} = 1.059*\mathbf{T0\_01b} - 1.308*\mathbf{Tn\_04b} + 131.622$
$R^2 = 0.7724$ ($p < 0.001$) $Af = 0.7326$ MAE = 2.28 RMSE = 2.77

$SDAR_{STRASBOURG} = 0.798*\mathbf{T0\_01b} + 1.120*\mathbf{T0\_03a} + 127.790$
$R2 = 0.5794$ ($p = 0.0015$) $Af = 0.5168$ MAE = 2.82 RMSE = 3.30

T0 = number of days where mean temperature is lower than 0°C; Tn = minimum temperature; 01b = 16-31 January; 03a = 01-15 March; 04b = 16-30 April

Mean Absolute Error associated to these equations is a little upper than MAE of models resulted from cumulative methods. However, the accuracy is good especially for Nancy. We can notice that the use of the Actual forecast

Table 4 - Significant correlations between fortnightly meteorological variables and the Starting Date of the Allergic Risk at the 0.05 level

Station	Variable	Period	Significance
Nancy	rainfall	16-31 January	-0.4715
	rainfall days > 0 mm		-0.5299
	rainfall days > 0.9 mm		-0.4733
	rainfall days > 4.9 mm		-0.5357
	minimum temperature		-0.6466
	maximum temperature		-0.7063
	mean temperature		-0.6874
	number of days where minimum temperature < 0°C		0.6998
	number of days where maximum temperature < 0°C		0.6526
	number of days where mean temperature < 0°C		0.7727
	ground temperature (-10 cm)		-0.5765
	ground temperature (-20 cm)		-0.5413
	minimum relative humidity		0.4864
	number of days where minimum temperature < 0°C	01-14 February	0.5114
	number of days where mean temperature < 0°C		0.4731
	ground temperature (-10 cm)		0.479
	ground temperature (-20 cm)		0.4973
	minimum temperature	16-30 April	-0.5772
Strasbourg	rainfall days > 0 mm	16-31 January	-0.4883
	rainfall days > 0.9 mm		-0.5531
	maximum temperature		-0.5025
	mean temperature		-0.4905
	number of days where minimum temperature < 0°C		0.6166
	number of days where maximum temperature < 0°C		0.5457
	number of days where mean temperature < 0°C		0.6443
	number of days where minimum temperature < 0°C	15-28 (29) February	0.5172
	minimum temperature	01-15 March	-0.4743
	number of days where mean temperature < 0°C		0.5475

ability test conducts to equations with only two predictive variables which are not affected by multi-colinearity.

2006 forecasts

In 2006, the Starting Date of the Allergic Risk (SDAR) occurred on the 12th of May in Strasbourg and on the 15th of May in Nancy. The different models presented before are used to predict the SDAR for this year. Results are presented in Table 5.

The SDAR forecasted in Strasbourg always occurs before the observed SDAR with a very small gap for models re-

Table 5 - Predicted Starting Date of the Allergic Risk in 2006 and gap, in days, between predicted and observed value for each cumulative method presented in Table 2 and the linear multiple regression

Year	Nancy	Strasbourg
GDD method	6 may (-9)	11 may (-1)
Lejoly-Gabriel method	7 may (-8)	10 may (-2)
Q_{10} method	14 may (-1)	11 may (-1)
Linear multiple regression	11 may (-4)	20 may (+8)

sulting from cumulative methods. Results are contrasting in Nancy with very accurate forecasts using model of Q_{10} method, while the SDAR predicted by the three others occur later than the real one. In order to initiate a preventive treatment against pollen allergy, too earlier forecasts (however without large gaps) are less prejudicial than too later ones.

Discussion and conclusion

We presented different methods: their main characteristic was their equivalent forecast ability with a similar accuracy demonstrated by the use of the Mean Absolute Error. Recently, a study of Laaidi was done on the forecast of Poaceae for four Burgundian stations (4) during the periods 1996-1998 (Montbard, Dijon and Mâcon) and 1995-1998 (Chalon-sur-Saône) where forward stepwise regression analysis, Lejoly-Gabriel and Q_{10} methods were used. With regard to models which result from Lejoly-Gabriel method, Mean Absolute Error values ranges from 0.33 day (Montbard and Mâcon) to 3 days (Dijon). As for Q_{10} method, models give the exactly starting date of Poaceae season for three sites except for Chalon-sur-Saône where MAE is equal to 3 days. The comparison between these and Nancy and Strasbourg data is impossible because of the differences in series lengths and geographical location. However, for the four sites taken as a whole, MAE linked to each cumulative method is globally similar and shows their equivalent ability in forecasting the SDAR; a fact which is confirmed in the present paper. Multiple regression analysis was performed with 10-day meteorological data and the four periods were grouped together in a fictive 13-year dataset because of the small size of the samples in each site (4). MAE of the equation resulting from this dataset is 4.54 days. These quite bad results might come from the process used and put forward that model accuracies are better when they are elaborated from dataset of one site.

The parallel established between our results and the study upon Burgundian sites allows verifying that different types of forecast methods can be used with similar results. Multiple regression is as reliable as the more classical cumulative methods but its approach is different using other meteorological data than air temperature.

The main objective of this paper was to construct forecast models from different methods and several meteorological variables. Using underground temperature, number of days of rainfall or number of days where air temperature is below 0°C is an uncommon approach. The use of winter averages of the NAO (Northern Atlantic Oscillation), not tested here, seems as well to be useful in the forecast of pollen counts (10, 12). There is probably a place here for further investigation in the SDAR forecast.

The ability to predict the first day when occurs a medium-level allergic risk for Poaceae up to one month and half before the SDAR will be of assistance to the medical profession, including allergists planning treatment and physicians scheduling clinical trials. Such information will also be useful for pharmaceutical companies and the health care industry that market and stock hay fever treatments (19).

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Sublingual immunotherapy for allergic respiratory disease in elderly patients: a retrospective study

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Key words

Elderly patients, Monosensitized, Sublingual immunotherapy, House dust mite, Respiratory allergy

Summary

Background: *Very few studies have evaluated the effects of sublingual immunotherapy (SLIT) in elderly adults with either rhinitis or bronchial asthma. The aim of this study was to ascertain whether SLIT is effective in these patients.* ***Methods:*** *One hundred and sixty seven patients (aged 18-65 years) with persistent rhinitis and mild asthma, selected from 573 subjects allergic to house-dust mites, were treated with either standard chronic pharmacotherapy or SLIT plus drugs on demand. Monthly symptom/drug scores, respiratory function, methacholine (MCh) challenge and eosinophil count were scheduled at the beginning and end of the study.* ***Results:*** *We analysed two age groups (18-28 years, 49 patients) and 55-65 years, 40 patients). There were no differences between the groups at baseline but MCh sensitivity was lower in the older patients. At the end of treatment, SLIT achieved improvement in all variables ($p<0.001$) in both age groups, but the global symptoms were lower in the younger patients ($p=0.002$). There were also fewer new sensitizations in the SLIT groups ($p=0.03$) than in the "control" patients given standard pharmacotherapy, but with no relation to age. Asthma became worse only in the control groups, regardless of age.* ***Conclusions:*** *SLIT reduces symptoms, drug consumption and the progression of the disease in both young and elderly subjects allergic to house-dust mites, with persistent rhinitis and mild bronchial asthma.*

Introduction

Rhinitis and allergic bronchial asthma are very common in people of all ages, with a prevalence of approximately 10% in western countries (1). During the last 15 years, it has gradually become clear that rhinitis and asthma are two distinct clinical aspects of a single disease that involves the entire respiratory system (2). The progression from atopic dermatitis to asthma is generally known as the atopic march (3): in atopic children the disease initially arises as atopic dermatitis and food allergies, which subsequently evolve into rhinitis and asthma. Skin manifestations are less frequent in patients whose symptoms started during adulthood, but the march from rhinitis to asthma proceeds nevertheless, together with the possibility of new sensitizations (4-7).

The natural history of the disease has changed significantly over the last few decades, especially with emerging pollinoses from allergens such as birch (8, 9) and ragweed (10, 11). Often the patient does not present with a background of atopic constitution, the average age is higher than for other pollinoses, and the onset is after 45 years of age in up to 20% of cases; in some patients the symptoms first appear even after the age of 70 (12). These patients

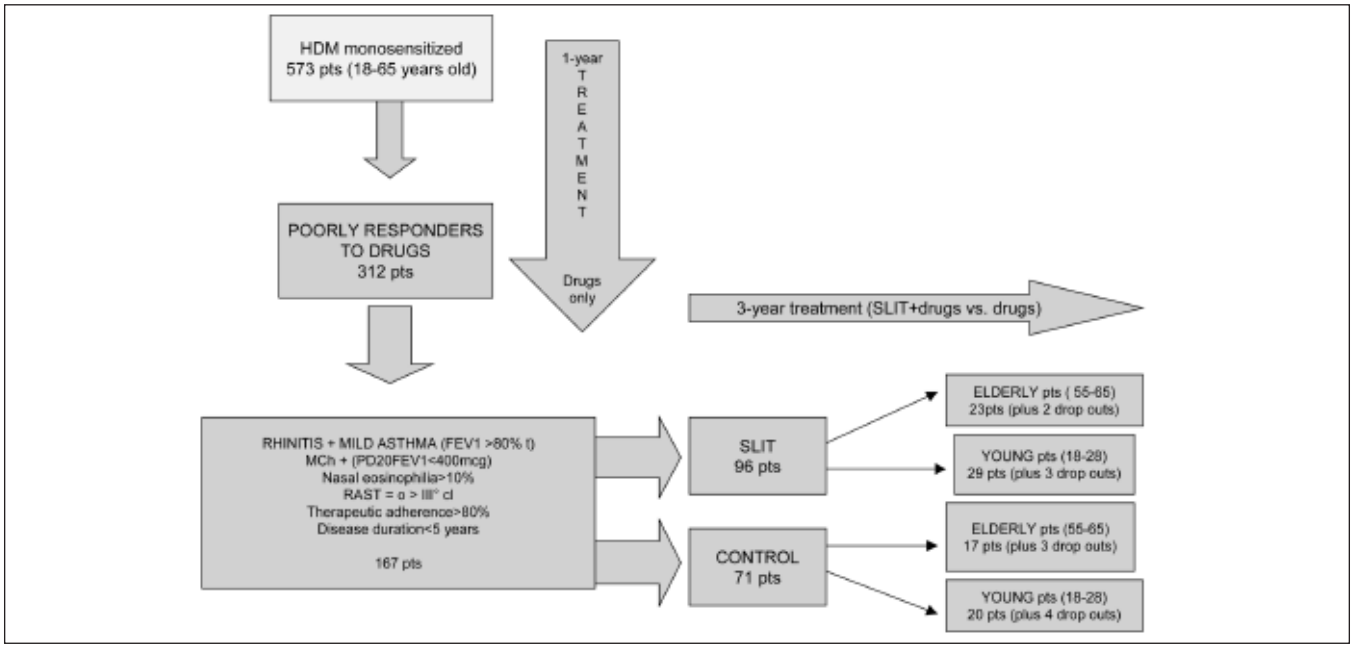
often started an allergen-specific immunotherapy (SIT) on account of the severity of the symptoms and inadequacy of control with standard drug therapy.
Although SIT is deemed the only treatment that can at least partly modify the natural course of the disease during its initial stages, its use in elderly patients is still debated. There are only few studies for injective SIT (13, 14), and none at all for non-injective SIT, or sublingual SIT (SLIT) in particular.
It is obvious that SIT is less indicated for elderly patients with a long history of allergic respiratory disease due to remodelling of the respiratory tract, which produces chronic and irreversible ultrastructural changes. However, elderly patients with a recent history of allergies seem to be ideal candidates for investigating the efficacy of SIT during their last decades.
Presented here are the findings of an observational, retrospective study regarding the use of SLIT in patients aged 55-65 years with respiratory disease (rhinitis and asthma) caused by *Dermatophagoides*, compared to younger patients (aged 18-28 years) with similar allergic and functional characteristics, who were also treated with SLIT, and two other groups of patients (of the same ages) who were given drugs alone.
The main purpose of the study was to establish whether SLIT plus drugs on demand provided control of symptoms and helped to prevent the progression of the respiratory disease and the onset of new sensitizations in these patients better than the standard chronic pharmacotherapy plus drugs on demand. The study also looked for any differences in the effect of SLIT in younger and elderly patients.

Materials and methods

Patients

We retrospectively evaluated 167 adult patients who had had persistent rhinitis and mild asthma for no more than five years, selected from a total of 573 patients monosensitive to *Dermatophagoides* and receiving medical care between 1994 and 2006 (Figure 1). Sixty-six patients (39 assigned to the active group and 27 controls) were not included because they were aged between 29 and 54 years. Among the 101 eligible patients (aged 18-28 or 55-65 years old) there were 12 spontaneous drop-outs, five from the active group (n=57) and seven from the control group (n=44). None were because of side effects.
The following diagnostic-therapeutic protocol has been implemented in the respiratory Allergology Clinic at the Cuasso al Monte Hospital (VA) since the early 1990s:

Figure 1 - Study design



1) At the first visit (admission): skin prick tests, full spirometry with body plethysmography, methacholine (MCh) challenge, assays of specific IgE for the main pneumoallergens, eosinophil count in nasal secretions.
2) During the first year: treatment with drugs and monitoring based on clinical diaries of the symptoms and drugs consumed.
3) During the next three years patients who had not responded to standard treatment with drugs after the first year were asked for informed consent, and were given SLIT, usually for moderate-to-severe rhinitis and for rhinitis with asthma.
4) Re-evaluation of the immunoallergic profile after three years of SLIT.

After receiving only scant clinical benefit from treatment with drugs alone for one year, these 312 "poor responders" were also given the option of SLIT for three years plus drugs only on demand.

All the patients presented as follows at baseline:

1) Clinical profile of rhinitis and mild asthma (FEV_1 >80% of the expected value);
2) Positive MCh challenge for $PD_{20}FEV_1$ (or $PD_{35}Sgaw$) <400 μg;
3) Moderate-to-severe nasal eosinophilia (>10%);
4) RAST/CAP for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* Class II or more;
5) Duration of disease less than five years.

Treatment

After one year of treatment with drugs patients had two options: to continue standard pharmacotherapy alone, i.e. cetirizine 10 mg/day and cromolyn sodium nasal 10 mg/day chronically plus inhaled salbutamol (100 μg 1-2 puffs) and nasal steroids (beclomethasone dipropionate, 1 puff per nostril once or twice per day) on demand, or else to select SLIT, based on a carbamylated monomeric allergoid in tablet form (Lais®, Lofarma S.p.A., Milan, Italy), plus drug therapy on demand. Ninety-six patients moved to SLIT and 71 preferred to continue with the drugs alone. The main reasons were: the higher cost of SLIT in comparison to the drugs, the patient's GP's opinion about immunotherapy, and the patient's own opinion.

SLIT was administered in accordance with the latest Position Paper (15, 16), using the therapeutic protocol recommended by the manufacturer. The therapy involved a mixture of monomeric allergenic extracts (50% *Dermatophagoides pteronyssinus*, 50% *Dermatophagoides farinae*) at the following allergy unit (AU) doses: 25, 100, 300, 1000. The extract was standardized by EAST-inhibition in comparison with an internal standard.

The treatment was designed with a dose-increasing phase of 14 weeks during which each dose was taken three times a week in accordance with a schedule provided by the manufacturer, and a maintenance phase during which the maximum dose of 1000 AU was taken once a week for the next three years. The cumulative annual average dose taken was approximately 60,000 AU.

After three years we re-evaluated the 89 patients to compare the results of SLIT + drug on demand with the schedule of drug alone taken chronically + drug on demand, in the two age groups, to verify whether SLIT gave better control of the symptoms than drugs alone, and whether there was any age-related difference in clinical and preventive efficacy with SLIT.

Table 1 - Clinical parameter values at baseline (mean and Standard Error of Mean, SEM) of younger (18-28 years) and older (55-65 years) patients in treated (SLIT) and control group (NO SLIT)

	NO SLIT				SLIT			
	18-28 yy		55-65 yy		18-28 yy		55-65 yy	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
SMS BAS	393.6	17.1	422.2	16.4	384.4	11.8	415.0	14.9
FEV1 BAS	86.9	.8	86.8	.7	86.7	.7	87.5	.6
MEF25 BAS	55.4	1.6	57.4	2.8	59.1	1.2	57.3	1.3
MCh BAS	204.8	23.6	149.8	24.4	151.2	16.3	253.6	20.4
EOS BAS	32.1	2.0	27.6	2.4	29.4	1.7	26.0	1.9
B2 BAS	18.8	1.1	21.7	1.1	21.3	.8	20.9	1.4
NCS BAS	27.3	1.3	23.8	2.0	17.0	.9	21.4	1.7

Diagnosis

Prick tests were done in accordance with international guidelines (17) using standardized commercial extracts (ALK Abellò, Lainate, Milan, Italy) for the following allergens: *Dermatophagoides pteronyssinus* and *farinae*, grass, *Artemisia*, ragweed, pellitory, dog and cat dander, birch, olive, *Alternaria* and *Cladosporium*.
Respiratory function was tested by computerized spirometry with plethysmography to study specific conductance and resistance (Masterlab Yaeger, Wurtzburg, Germany). The MCh challenge was done using a dosimeter (Yaeger) activated by inhalatory effort in response to increasing doses of MCh: 30, 60, 120, 240, 390, 690, 1290 μg (18, 19). Patients observed a 48-h wash-out period for beta-stimulants before the test.
Eosinophils in the nasal secretions were counted using a nasal tampon from the front nasal cavity. The material collected was smeared onto glass slides and dried, stained using the May Grünwald-Giemsa method, and read under an optical microscope with an immersion lens. The eosinophil count (number of eosinophils per 100 white blood cells in the nasal secretion) was classified as mild (<10%) or moderate-severe (>10%). Patients gave informed consent to the prick test and the MCh challenge.

Patients' diaries

Patients were instructed how to keep a clinical diary recording their symptoms and drug consumption each month during the period November-February from the beginning to end of treatment (three years), for SLIT or chronic standard drug therapy plus drug on demand for both groups. The clinical efficacy of the treatment was assessed on the basis of the following parameters: coughing, wheezing, dyspnea, nasal obstruction, nasal itching, rhinorrhea, sneezing, conjunctival itching, conjunctival redness, watery eyes. Each symptom was rated using the following scale: 0=absent, 1=mild, 2=moderate, 3=severe.
Both groups recorded the consumption of symptomatic drugs taken on demand (salbutamol 1 puff=1 point, beclomethasone dipropionate 1 puff per nostril=1 point).

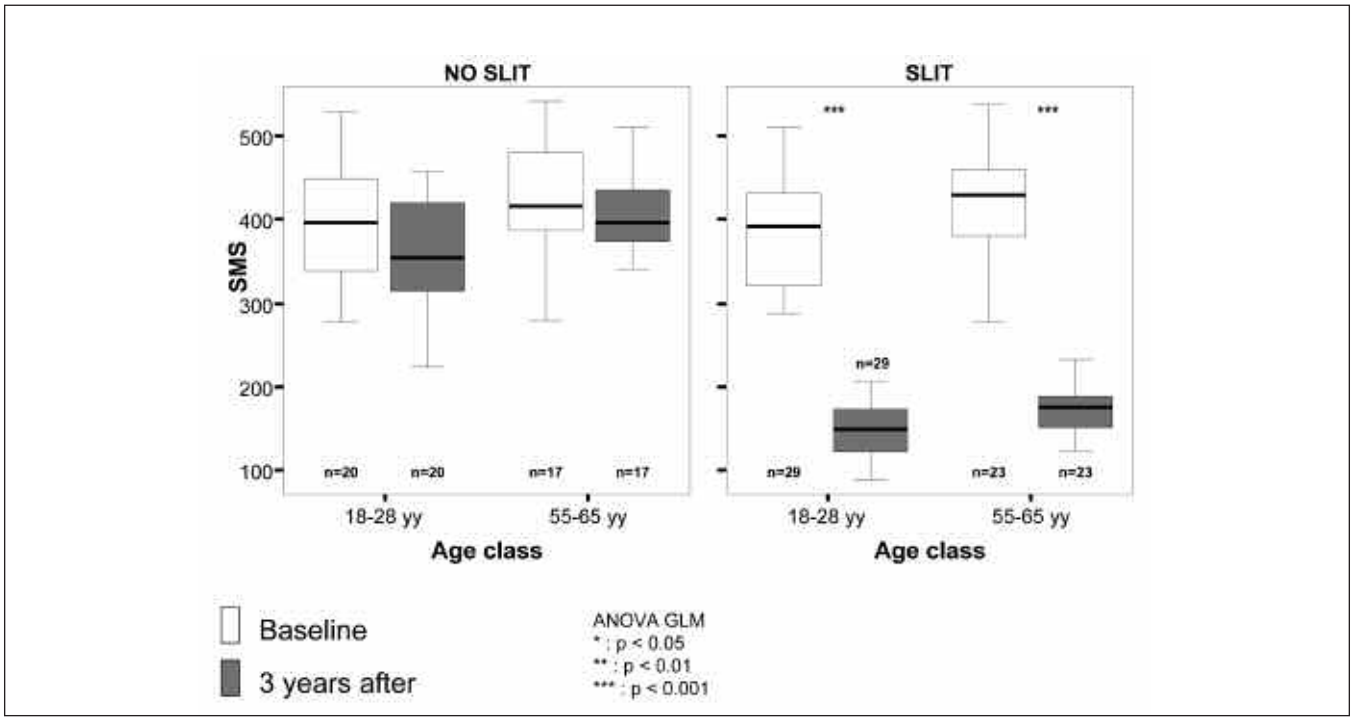
Statistical analysis

The sex ratios in the two treatment groups at baseline were compared by Fisher's exact test (20, 21), and differences in the clinical parameters at baseline were tested by GLM MULTI-way ANOVA (analysis of variance by a general linear model), using treatment and sex as fixed factors.
The effect of the treatments and the course of the parameters from baseline over the three years were then modelled using a modified ANOVA for repeated measures (repeated measures GLM) (22). The multivariate effects (overall clinical changes in all parameters) were tested by using Pillai's trace, and the within- subject effects were tested by the Greenhouse and Geisser method (23).
The probability levels for Pearson's Chi-Square were computed using a complete randomization method (permutation or exact test; P_{Exact}) or by a Monte Carlo simulation based on 100,000 sampled tables (P_{MC}) (24, 25) when the permutation method was not feasible.
All statistical analyses were done using the Statistical Package for Social Sciences version 13.01 (SPSS®).

Results

There was no difference in the sex ratios at baseline in the SLIT groups and the No-SLIT groups (respectively X^2 = 0.009, df = 1, P_{Exact} = 1.000 and X^2 = 0.187, df = 1, P_{Exact} = 0.746). Similarly, there were no differences in sex ratio when grouped by age (young, old) and comparing SLIT with No-SLIT (old, X^2 = 0.051, df = 1, P_{Exact} = 1.000 and young, X^2 = 0.113, df = 1, P_{Exact} = 0.777).
There were no differences in treatment, sex, and age class in the groups at baseline as regards the Symptom Medication Score (SMS), FEV_1, and MEF_{25} (Figures 2, 3), but there were differences in MCh when treatment and age groups were combined (F = 13.311, df = 1, P < 0.001), with the older patients in the No-SLIT group showing lower MCh sensitivity than the younger ones (Figure 4A; 151.7 ± 23.8 and 203.5 ± 22.4), while the opposite was seen in the SLIT group (254.7 ± 20.6 and 150.4 ± 18.3). The EOS count also differed at baseline between the two age classes (F = 4.984, df = 1, P = 0.028) with the younger patients having significantly more eosinophils than the older patients (Figure 4B; 31.2 ± 1.3 and 26.8 ± 1.5). Finally, the use of nasal corticosteroids (NCS) differed significantly between the two groups at baseline (F = 17.872, df = 1, P<0.001), with the SLIT group using NCS less than the controls (Figure 5B; 19.1 ± 0.9 and 25.4 ± 1.1).
The effect of treatment significantly affected the overall clinical scenario (multivariate effect; Pillai's trace, $F_{7, 79}$ = 68.590, P < 0.001), as did age ($F_{7, 79}$ = 2.243, P = 0.039), but the effect of age was no longer detectable after three

Figure 2 - Symptom medication scores (SMS) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment with drugs (NO-SLIT) or allergoid SLIT (SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$



years (Age*Time, $F_{7, 79} = 1.262$, $P = 0.101$). Individually, all the parameters showed significant changes after three years (Figures 2-5) ($P < 0.001$), with a consistent change due to treatment ($P < 0.001$), but irrespective of age ($P > 0.050$), except for the eosinophil count ($F = 5.280$, $P = 0.024$) which was higher in younger patients (Figure 4B). Analysing the effects on each single parameter, treatment affected all parameters ($P < 0.050$), while age affected only the global symptoms (SMS, Figure 2; $F = 10.310$, $P = 0.002$). A combination effect of age and treatment was also detected for β_2 (Figure 5A; $F = 7.148$, $P = 0.009$) and NCS ($F = 6.247$, $P = 0.014$).

The rate of new sensitizations differed significantly between the treated and control subjects for both the older ($X^2 = 5.673$, df = 1, $P_{Exact} = 0.030$) and the younger patients ($X^2 = 5.979$, df = 1, $P_{Exact} = 0.020$), but there were no differences due to age in either group (controls $X^2 = 0.187$, df = 1, $P_{Exact} = 0.746$; SLIT $X^2 = 0.092$, df = 1, $P_{Exact} = 1.000$).

Some worsening of asthma (mild progressed to moderate asthma) was detected only in the controls, not in the SLIT patients. No age-related differences were detected in the control groups ($X^2 = 0.011$, df = 1, $P_{Exact} = 1.000$).

No noteworthy side effects were reported during the study. This is probably explained by the kind of SLIT employed (a modified allergoid) and the relatively low dosage.

Discussion

The medical literature reports no studies specifically evaluating the efficacy of SIT in general or, in particular, in elderly patients. This is probably for two reasons: firstly, most patients attending the reference allergy centers are children, adolescents and young adults and, secondly, many of the older patients who come in for an allergy evaluation have a history of allergic respiratory disease that has persisted for many years which – it is generally held - renders them ineligible for allergen-specific immunotherapy (26, 27).

In our retrospective evaluation, we found that SLIT was equally effective in both young and elderly patients as long as the disease had started fairly recently. Long-term compliance (three years) to this SLIT schedule (tablets to be taken once a week) was also very good (only five spontaneous drop-outs out of 57 patients). We also did not

find any appreciable side effects. This can probably be ascribed to the type of SLIT utilised (a modified allergoid) and the relatively low dosage.

A double-blind, placebo-controlled trial would certainly have been a more appropriate tool to assess the indication for SLIT in elderly patients. However, a similar real-life evaluation during normal clinical practice in our allergy center would create ethical problems, particularly as regards the randomization of active treatments and placebo, and also because of the need to conduct the study for at least three years in order to verify specific changes in the patients' clinical, immunological, cytological and functional profiles (6, 28, 29). We therefore believe that a rigorously conducted retrospective evaluation comparing two treatments (SLIT *versus* chronic standard drug therapy) can nevertheless provide useful information on a practical allergological level to define the benefits of SLIT in elderly patients.

Like the younger patients, elderly patients treated with SLIT enjoyed significant improvement in their symptoms and a reduction in the use of drugs on demand. We also observed a tendency to improvement in respiratory function parameters and a decrease in eosinophil infiltration in the nasal mucosa, as well as a higher aspecific bronchoreactivity threshold to MCh challenge.

Figure 3 - Functional expiratory volume (FEV_1, A) , and MEF_{25} (MEF_{25}, B) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (No-SLIT and SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$

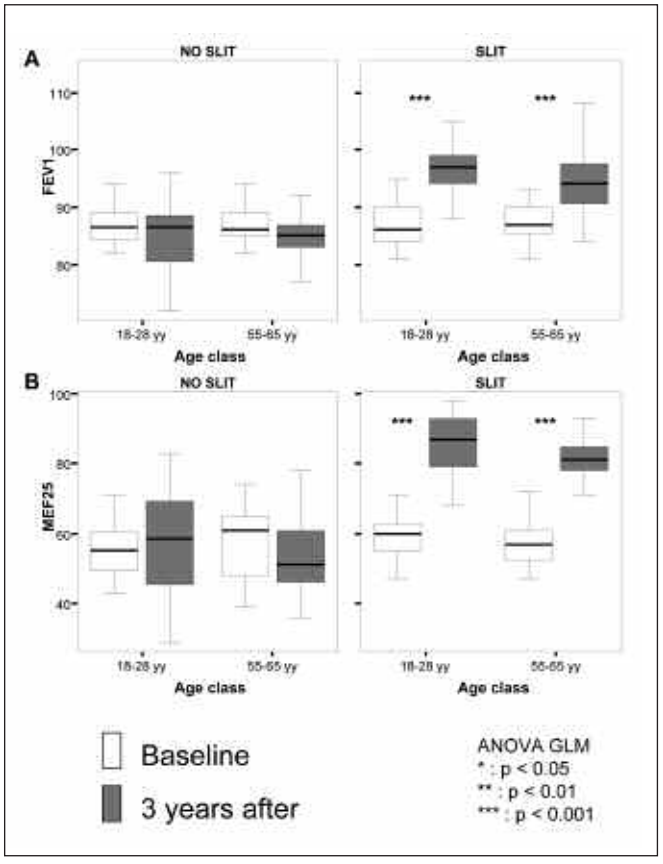


Figure 4 - Methacholine sensitivity (MCh, A), and eosinophils count (EOS, B) in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (NO-SLIT and SLIT) during a four-year study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers indicate the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$

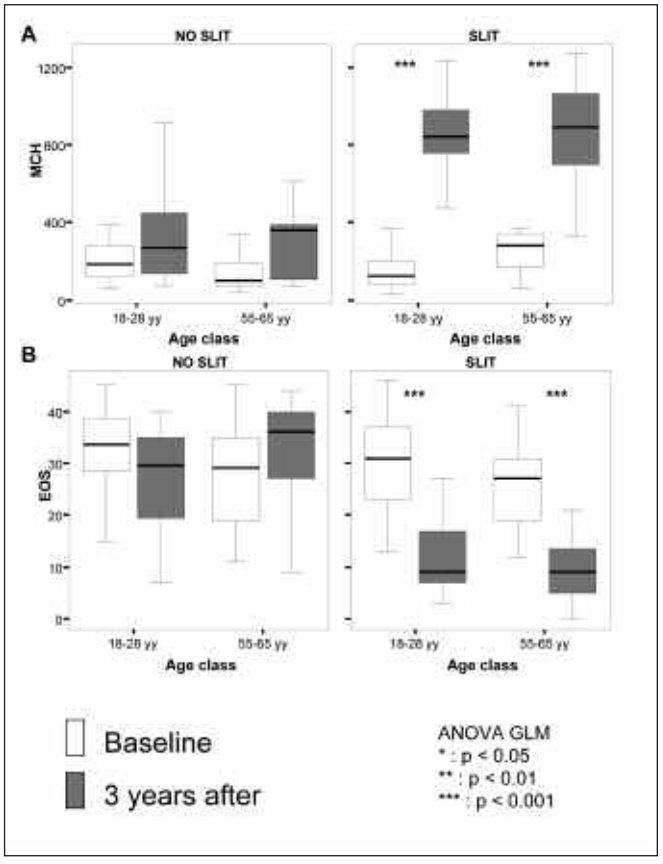
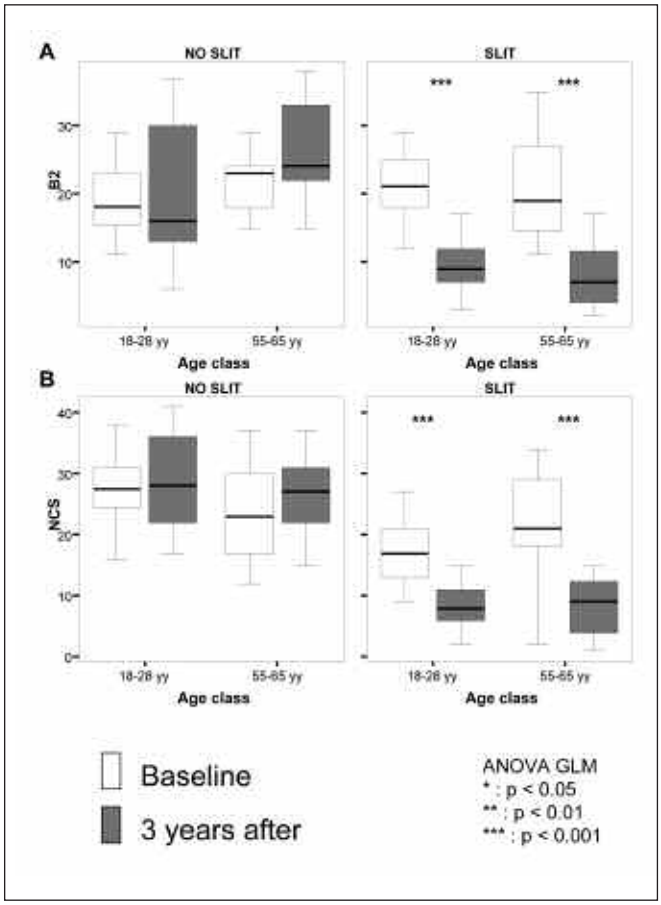


Figure 5 - Beta-2 (β_2, A), and nasal corticosteroids (NCS, B) use in young patients (18-28 yrs) and elderly patients (55-65 yrs) at baseline (white boxes) and after three years of treatment (NO-SLIT and SLIT) during a four-year term study in Cuasso al Monte Hospital, Italy. Boxes represent the first quartile (25%, lower box extreme), second quartile (median, thick bar), and third quartile (75%, upper box extreme), and whiskers represent the extreme values. GLM ANOVA results are reported: *** = $P < 0.001$



Lastly, like in the younger patients, there was some prevention of the progression of the respiratory allergic disease, with fewer new sensitizations and less worsening of asthma. On the other hand, and again without any significant differences between young and elderly patients, many of the patients in the two control groups showed no real changes in the severity of their respiratory allergy profile, with many patients reporting some worsening of their clinical condition. Based on these considerations, SLIT can probably be considered a valid therapeutic option in elderly patients, as long as their history of disease is relatively short.

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Severe respiratory syndrome induced by allergic mono-sensitization to European hamster (*Cricetus cricetus*) in a older woman

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Key words

Allergic rhinitis, Allergic sensitization, Bronchial asthma, Cricetus cricetus, European hamster, Hamster allergy, Hypersensitivity, Respiratory allergy

Summary

Although the increase in the rate of hamster ownership, no report of allergic sensitization to common hamster (Cricetus cricetus)-derived allergens as a consequence of domestic exposure has been published in Italy. A 64-year-old woman was referred to our Allergy Centre for the recent onset of conjunctival and severe respiratory symptoms (rhinitis, cough, wheezing and dyspnea). About three months ago she had purchased a common hamster as home pet. Another hamster had lived at patient's home for about four months nine years ago. The results of SPT revealed allergic sensitization to Cricetus cricetus dander only (wheal 6x7 mm, positive control 7x7 mm). Total IgE were 59,3 kU/L. Specific IgE only to Cricetus cricetus epithelia (2,10 kUA/L), were also detected. Spirometry revealed a moderate degree of bronchial obstruction. Some important considerations can be drawn from our report: a) few months of hamster ownership are probably sufficient to induce an allergic sensitization and clinical symptoms, b) older age of sensitization in comparison to other studies, c) rapid remission of clinical symptoms after the removal of hamster d) skin prick tests and/or evaluation of specific IgE for hamster allergens should be performed in all potentially susceptible individuals.

Exposure to common hamster (*Cricetus cricetus*) – derived materials is well recognized as an occupational hazard for people who are in contact with this animal in laboratory or other occupational settings (1, 2). In the recent years, hamsters became more and more popular as pets to have at home, like dogs and cats, in Italy and in other countries. For instance, in Japan, hamster ownership has largely increased in the 1990s (about 20% of all pets) (3, 4), as a consequence of this, a number of patients started to suffer from respiratory symptoms related to hamster ownership (5). Although in Italy there are no official data on the overall number of hamsters living in domestic environments, some indirect indexes suggest a significant increase in the rate of hamster ownership. In fact, commercial sources indicate an increasing business in hamster breeding as well as in production of hamster-related materials such as food, accessories etc. Nevertheless, no report of allergic sensitization to common hamster–derived allergens as a consequence of domestic exposure has been published in Italy so far.

Case report

A 64-year-old woman was seen at our Unit for the recent onset (about two weeks) of conjunctival and severe respi-

ratory symptoms (rhinitis, cough, wheezing and dyspnea). Although family history was positive for atopy, her personal history was negative for previous cutaneous and/or respiratory symptoms of a suspected IgE aetiology. She had a dog at home since three years. About three months ago she had purchased a common hamster to be kept as pet. Another hamster had lived at patient's home for about four months nine years before. The patient reported a strict contact with this animal (hamster was allowed to enter also the bedroom) and a worsening of respiratory symptoms after hamster exposure.

Methods

Skin-prick-test (SPT) was performed with commercial standardized extracts and prickers (ALK- Abello Group, Milan, Italy). The panel included the following allergenic extracts : house dust mites, *Parietaria* species, grasses, cat, common hamster (*Cricetus* cricetus) and dog dander, olive, birch, *Alternaria alternata, Cladosporium herbarum* and mugwort, plus a positive (1% histamine hydrochloride) and negative (glycerinate solution) control. The SPT was carried out and interpreted according to international guidelines (6), the result was read after 10 min and expressed as the major diameter of the wheal and its orthogonal. A skin reaction of 3 mm or greater was considered positive. A blood sample was taken for the measurement of total IgE and specific IgE to the same allergens of SPT panel (CAP System, Phadia, Uppsala, Sweden). A standard spirometric evaluation was also carried out. As monoclonal antibodies-based methods to measure the amount of hamster allergen are not available, we could not evaluate the degree of hamster allergen contamination in patient's indoor environments.

Results

The SPT showed an allergic sensitization only to *Cricetus cricetus* dander with a wheal diameter of 6x7 mm, compared to 7x7 mm of the positive control. Total IgE were 59,3 kU/L. Specific IgE only to *Cricetus cricetus* epithelia (2,10 kUA/L), were also detected. Spirometry revealed a moderate degree of bronchial obstruction. The removal of hamster from patient's home as well as an intensive cleaning of indoor environments resulted in a reduction and, after about three months, a complete disappearance of all respiratory symptoms

Discussion

At the best of our knowledge, this is the first documented report of a severe respiratory allergy induced by single-sensitization to European hamster in Italy. Some important considerations can be drawn from our report:

1) A total of seven months (four + three with an interval of nine years) of indoor exposure to hamster epithelia was sufficient enough to induce allergic sensitization and then to trigger respiratory allergic symptoms. It is likely that the short term period necessary to induce allergic sensitization and development of symptoms might be due to the high sensitizing capacities of hamster allergens. This finding has been observed also by other authors (5, 7-10).
2) The age of our patient was higher in comparison to those found in other studies (5, 7-10).
3) The rapid remission of clinical symptoms after the cessation of hamster keeping demonstrates the exclusive role of hamster sensitization in determining respiratory allergy in our patient.
4) A progressive increase in hamster sensitization may be expected in the future as a consequence of the increase of hamster ownership such as observed for rabbit allergy (11, 12).
5) Skin prick tests and/or evaluation of specific IgE for hamster allergens should be performed in all potentially susceptible individuals (for example those sensitized to several animal allergens) before the introduction of an hamster indoors also in the absence of respiratory symptoms after previous occasional hamster contact (13, 14).

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