A THERAPEUTIC GUIDELINE OF URTICARIA

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Abstract:*For the treatmen tof urticaria is very important the identification and exclusion of all causes and triggers that could produce it, also improvement and disappear of the symptoms. We have to treat also any kind of associated diseases. Unfortunately the quality of life of these patients is low. The indicated therapy is the second generation antihistaminic H1 medications, corticotherapy and cyclosporine, and the first generation antihistaminic must be avoided. It is also important the information and education of the patients.*

Cuvinte cheie: *urticaria, antihistaminice, corticosteriozi*

Rezumat: *pentru tratamentul urticariei este important identificarea şi eliminarea cauzelor şi trigeerilor care o produc, respectiv ameliorarea şi dispariţia simptomelor. Trebuie tratată orice boală asociată. Din păcate calitatea vieţii acestor pacienţi este scăzută. Terapia indicată este medicaţia antihistaminică H1 de generaţia a doua, respectiv corticoterapie şi ciclosporină, cu evitarea antihistaminicelor de generaţia I. Este de asemenea importantă informarea şi educarea pacienţilor.*

SCIENTIFICAL ARTICLE OF THEORETICAL PREDOMINANCE

A new guideline of urticaria was elaborated at Charité Hospital in Berlin (1), where meet 200 specialists from 33 countries for a consensus about this problem. These are members of the following medical organizations: Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO).

The two basic lines of management are (1,2):

1. Identification and elimination of the underlying causes and/or eliciting triggers; we have to mention that stress is a trigger who made increase itching, but is not a causing factor.
2. Amelioration or disappearance of symptoms by inhibition of effects, caused by eliberation of mast cell mediators and other implicated mediators. In the pathogenesis of urticaria the mast cells are effector key cells for induction of urticaria symptoms, the most important mediator being histamine.

The quality of life is the main purpose in all clinical trials. Although in dermatologic and allergic diseases exist such studies, unfortunately in urticaria are only some few studies about quality of life and for the different subtypes of urticaria such studies don't exist (1,3). Itching is the principal debilitating symptom in chronic urticaria, which is associated with severe discomfort, sleep disorders and depression. School and professional performances are negative influenced and productivity at school and work falls with 25-30%. Patients are also alarmed about their physical aspect because of urticarian plaques and angioneurotic oedema. One of the few studies about this problem established that the quality of life in chronic urticaria is similar with that in coronary heart disease. At this meeting in Berlin was elaborated also a questionnair about quality of life, evaluating physical, emotional, social and practic aspects. It was translated and validated in Germany and Spain, and will be soon validated also in England, Greece, Turkey, Bulgaria and Poland (1).

The first objective in urticaria treatment is identification and elimination of the suspected causes and triggers (1,4). If remission, following elimination of the suspected agent, occurs, we have to made the double-blind placebo controlled provocation test, which confirm the causing agent. But, unfortunately, the identification of urticarias cause is not, possible in every case, an important percentage being idiopathic urticaria.

Drugs can be a cause of urticaria. In these case, drugs should be omitted, and if they are indispensable, it is recommanded the substitution by another class of therapeutic agents. Drugs causing nonallergic hypersensitivity reactions (the prototypes being nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors) can not only elicit, but can also aggravate preexisting chronic spontaneous urticaria.

In case of physical urticaria, physical stimuli must be avoided. In delayed pressure urticaria and in symptomatic dermographism must be avoided heavy bags or friction. In cold urticaria must be avoided the contact with cold products and cold water, and in solar urticaria we have to use sunscreens or for the selection of light bulbs with a UV-A filter. However, total avoidance of stimuli is virtually impossible. Severe dermographic urticaria is sometimes confused with chronic urticaria because seemingly spontaneous hives are observed where even loose-fitting clothing rubs on the patient's skin.

We must eradicate infectious agents and treat all inflammatory processes. Chronic spontaneous urticaria is often reported to be associated with a variety of inflammatory or

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infectious diseases, an important role having Helicobacter pylori or bacterial infections of the nasopharynx. We don't have to ignore the presence of bowel parasites. Intestinal candidiasis is not a causing factor.

Another objective is reduction of functional autoantibodies. In chronic urticaria direct reduction of functional autoantibodies is made by plasmapheresis, which has been shown to be of temporary benefit in individual and costs are very high. So, this therapy is suggested for autoantibody-positive chronic spontaneous urticaria patients, who are unresponsive to all other forms of treatment. There were reported good results with Ciclosporin as inhibitor of autoantibodies formation. Other immunomodulatory therapies include intravenous immunoglobulins, Methotrexate, Azathioprine, Mycophenolate, Mofetil, Cyclophosphamide, anti-IgE (Omalizumab), and Tacrolimus (1).

We must have also a dietary management. IgE-mediated food allergy is rare, and in this case omitting of type I allergens goes to rapid reductions to urticaria. But, in many cases are involved additives and food ingredients, pseudoallergens respectively, which through non-IgE-mediated hypersensitivity reactions can produce or aggravate chronic spontaneous urticaria. A diet at least 3–6 months produce a remission in 50% of patients.

Symptomatic therapy produce induction of tolerance in cold urticaria, cholinergic urticaria, and solar urticaria. The aim is to reduce the effect of mast cell mediators on the target organs by the action of histamine on H1-receptors. By action on endothelial cells it produce the wheal and on sensory nerves it produce neurogenic flare and pruritus.

Antihistaminics (AH) have been available since the 1950s, first generation antihistamines have pronounced anticholinergic effects and sedative which last longer than 12 h whereas the antipruritic effects last only for 4–6 h. These have many interactions with alcohol, analgesics, hypnotics, sedatives, and interfere with rapid eye movement (REM) sleep and impact on learning and performance. The worst side-effects are observed with Promethazine, Diphenhydramine and Chlorpheniramine. The guideline recommended very insistent to avoid them. The second generation antihistamines led to drugs which are minimally sedating and free of anticholinergic effects. Astemizole and Terfenadine had cardiotoxic effects and are not yet available, while Cetirizine, Desloratadine, Fexofenadine have non-sedating metabolites and they are usually used, most recently appear Levocetirizine, Ebastine, Mizolastine. These should be considered as the first line symptomatic treatment for urticaria. Some studies demonstrated that the increase for 4x of the Desloratadine, Levocetirizine and Rupatadine doses are significant beneficially, without adverse effects. The 4x increase of the Cetirizine dose was not beneficially. The guide recommends for urticaria the updosage of non-sedative antihistamines for 4x, if necessary (1,2,4).

Corticosteroids are not recommended for long-term use, only for short time.

Ciclosporin has a moderate direct effect on mast cell mediator release and is the only agent of this type to inhibit basophyle histamine release.

There are some studies in which Ciclosporin was associated with non-sedative antihistamines with good results in acute refractory urticaria to antihistamines, but with adverse reactions, the risk/benefit ratio being greater than in corticotherapy.

Phototherapy reduces the numbers of mast cells in the upper dermis and it is used in mastocytosis and is helpful in treatment-resistant patients with this condition. For the treatment of chronic spontaneous urticaria and symptomatic dermographism, UV-A and UV-B treatment for 1–3 months can be added to antihistamine treatment.

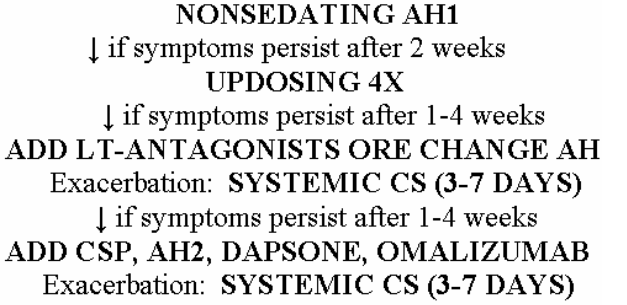
Omalizumab (anti-IgE monoclonal antibodies) has now been shown to be effective in selected patients with cholinergic urticaria, cold urticaria and solar urticaria.

Antagonists of tumor necrosis factor and iv Ig are recommended as last option and we have to wait for 1-4 weeks with high dose administration of antihistamines. Severity of urticaria may fluctuate, and since spontaneous remission may occur at any time, it is recommended to re-evaluate the treatment every 3–6 months.

We can administrate tranexamic acid and sodium cromoglycate in chronic spontaneous urticaria, nifedipine in symptomatic dermographism and colchicine and indomethacin in delayed pressure urticaria.

There are double-blind placebo controlled studies of great trials with non-sedating AH1. It's possible, that these are insufficiently, needing alternative therapies. Other studies are necessary to recommand or to refuse these alternative therapies (1,5).

Figure no. 1. Treatment algorithm for urticaria



In the treatment of children we use second generation non-sedating H1-antihistamines as first choice, for childrens over six months. First generation antihistamines have a lower safety profile. Therefore a strong recommendation was made to discourage the use of first generation antihistamines and up-dosing (weight adjusted) of second generation AH1 is recommended as in adults.

In pregnant and lactating women it is recommanded to avoide systemic treatments in the first trimester, but the effects of increasing doses were not studied. No fetal modifications were reported after using of second generation AH1. In present there are enrolled but not finalized studies with cetirizine and loratadine. These, because not needing prescription, were taken by women before confirmation of a pregnancy. Loratadine and desloratadine are suggested.

There are also some limitations of these guidelines (1,6):

- the lack of a more detailed assessment of the quality criteria for individual studies;
- greater importance on avoiding confusion that would have resulted from using different systems of evaluation of samples quality;
- to assess the quality of evidence and security profile.

In conclusion, the quality of life in urticaria patients is severely affected and it is important a cooperation between patient and physician. The aim of treatment is to achieve the absence of and complete protection from symptoms, triggering factors should be identified and avoided as far as possible and any associated diseases should be treated.

The indicate medication is second generation antihistamines up to four-fold higher, corticosteroids and ciclosporin. First generation sedating antihistamines should no

longer be used. We should reevaluated the treatment every 3–6 months, using the most inoffensive and efficient one. It is also very important information, education and cooperation with the patient.

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