

Chronic urticaria: do urticaria nonexperts implement treatment guidelines? A survey of adherence to published guidelines by nonexperts

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Summary

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Background Guidelines including level of evidence and grade of recommendation were recently published for chronic urticaria (CU).

Objectives To describe the therapeutic approach in patients with CU, and to depict how recent guidelines are implemented in the daily practice of management of CU.

Methods We performed a cross-sectional multicentre study through a questionnaire answered by 139 specialists. In total, 695 patients were evaluated, mean $\pm$ SD age 42.3 ± 15 years, 62.1% women. Of the patients, 168 were treated by an allergist, 473 by a dermatologist and in 54 cases the specialist was not stated. The drug prescribed was the main variable, and χ^2 and Fisher's tests were utilized for the statistical analysis.

Results Nonsedating anti-H1 antihistamines taken regularly were the most common drugs prescribed, followed by nonsedating anti-H1 antihistamines taken as needed, corticosteroids, sedating antihistamines taken regularly, sedating antihistamines taken as needed, anti-H2 antihistamines, leukotriene antagonists, ciclosporin and doxepin. Nonsedating antihistamines plus corticosteroids was the most frequent drug combination prescribed. When comparing between allergists and dermatologists we found a positive and significant correlation only between prescription of cetirizine, dexchlorfeniramine, leukotriene antagonists and anti-H2 antihistamines and being treated by an allergist. A positive correlation was found with desloratadine and being seen by a dermatologist. We did not find any difference in CU management in the rest of the treatments studied.

Conclusions It is surprising that a large amount of sedating antihistamines was prescribed. In many instances these were prescribed as needed. This fact could have a negative impact on urticaria control and patient satisfaction. It seems difficult for the nonexpert to differentiate between CU and any kind of physical urticaria.

Chronic urticaria (CU) can be defined as the occurrence of widespread daily or almost daily weals for at least 6 weeks which may be accompanied by angio-oedema.¹ While the weals are transient, the resolution of angio-oedema is slower than that of weals and could take up to 72 h. The natural

course of CU is usually self-limited, with spontaneous remissions and occasional relapses.²

Recently the European Academy of Allergology and Clinical Immunology (EAACI)³ and the British Society for Allergy and Clinical Allergology (BSACI)⁴ management guidelines were

published that included classification of urticaria and of level of evidence and grade of recommendation for different treatments. The EAACI guidelines recommend starting with non-sedating antihistamines, and if no response is achieved, using higher doses of antihistamines before considering alternative therapies. The BSACI guidelines also recommend nonsedating antihistamines as the first-line treatment for symptom control although they point out that this issue requires confirmation and comparative studies. However, the guidelines also state that it is becoming common practice to increase the dose above the normal recommendation in an attempt to achieve control. The British Association of Dermatologists has also published a guideline⁵ with similar recommendations. All three guidelines also agree on the need to avoid triggering factors such as the use of nonsteroidal anti-inflammatory drugs.

In the present study we wanted to describe the treatment that patients with urticaria actually receive. We also wanted to depict how these guidelines are implemented in daily practice in CU management. Finally, we also sought to explore if any differences in treatment exist depending on the specialist consulted.

Materials and methods

We performed a descriptive, cross-sectional multicentre study employing a structured questionnaire. One hundred and thirty-nine Spanish randomly selected specialists participated in the study. There were no urticaria experts. All Spanish geographical regions were represented. All physicians answered a questionnaire based on information from the first five patients with CU presenting in their practices. Patients were included if they were older than 18 years and had a diagnosis of CU. All patients signed a consent form.

Sample

Initially, 738 patients were recruited. We excluded 43 patients: 26 because of incomplete data, seven because they were younger than 18 years, four because a diagnosis of CU was ruled out, and six because the consent form was not signed. Therefore, 695 patients were evaluated. Mean $\pm$ SD age was 42.3 ± 15 years and 62.1% were women. Of the patients, 168 were treated by an allergist, 473 by a dermatologist and in 54 cases the specialist was not stated. The main variable was the drug prescribed.

Questionnaire

Doctors were asked to complete a questionnaire. Five patients already diagnosed with urticaria were included by each doctor. Physicians were requested to classify the type of urticaria and to report the drug or drugs that the patient was already taking at the time of the visit.

Other data collected included family history of urticaria, age at diagnosis, time with the disease, urticaria subtype and

triggers, site and extent of the urticaria, symptoms, presence of angio-oedema, and severity of the urticaria (presence and intensity of symptoms measured by the investigator on a scale of 0–3 for both weals and itching).

Statistical analysis

χ^2 and Fisher's tests were utilized for the statistical analysis in order to compare the drugs prescribed by both dermatologists and allergists and to compare the drugs used depending upon urticaria type.

Results

Table 1 shows the different types of urticaria identified.

Drugs prescribed

Of the patients with CU, 95.7% were receiving drug treatment. The drugs prescribed are summarized in Table 2.

When analysing the type and timing of antihistamines that were prescribed, nonsedating anti-H1 antihistamines taken regularly were the most frequently prescribed drugs, followed by nonsedating anti-H1 antihistamines taken as needed, sedating antihistamines taken regularly, and sedating anti-H1 antihistamines taken as needed.

Regarding the combination of two or more drugs, the most frequent association was systemic corticosteroids added to nonsedating antihistamines followed by a combination of anti-H1 with anti-H2 antihistamines. However, the combination of two or more anti-H1 antihistamines was not differentiated as a separate combination therapy. Table 2 lists the combinations of drugs used.

Antihistamine use

Antihistamines were the most frequently prescribed drugs for CU followed by corticosteroids.

Table 1 Type of urticaria (n = 695)

Spontaneous	475
Physical	423
Cold contact	24
Pressure	154
Heat contact	38
Solar	58
Dermographic	143
Vibratory	5
Other types of urticaria	235
Cholinergic	114
Exercise-induced	46
Aquagenic	40
Contact	35

A patient may have more than one type of urticaria.

Table 2 Drugs prescribed to patients with chronic urticaria

Drug	n (%)
Anti-H1 antihistamines	472 (67.9)
Anti-H1 antihistamines + corticosteroids	104 (15)
No treatment	30 (4.3)
Anti-H1 antihistamines + other	20 (2.9)
Anti-H1 antihistamines + anti-H2 antihistamines	14 (2)
Anti-H1 antihistamines + corticosteroids + other	11 (1.6)
Anti-H1 antihistamines + leukotriene antagonist	9 (1.3)
Anti-H1 antihistamines + corticosteroids + anti-H2 antihistamines	9 (1.3)
Anti-H1 antihistamines + doxepin	9 (1.3)
Corticosteroids	5 (0.7)
Anti-H1 antihistamines + ciclosporin	3 (0.4)
Ciclosporin	2 (0.3)
Other (not reported)	2 (0.3)
Anti-H1 antihistamines + corticosteroids + leukotriene antagonist	1 (0.1)

Table 3 Antihistamine prescribed

	Regularly	As needed
Levocetirizine	192	65
Hydroxyzine	85	61
Ebastine	66	59
Desloratadine	42	27
Cetirizine	34	20
Dexchlorfeniramine	18	26
Loratadine	13	21
Rupatadine	13	9
Fexofenadine	6	3
Ketotifen	2	2
Ciproheptadine	2	1
Clemastine	2	0
Mizolastine	2	0
Terfenadine	2	0
Diphenylhydramine	1	1
Mirtazapine	1	0

Table 3 shows in decreasing frequency the antihistamines prescribed. Levocetirizine ($n = 274$), hydroxyzine ($n = 160$), ebastine ($n = 134$), desloratadine ($n = 74$), cetirizine ($n = 57$) and dexchlorfeniramine ($n = 54$) were the most commonly prescribed antihistamines.

Antihistamines were prescribed regularly in 481 patients and as needed in 295 patients.

Taken regularly vs. as needed

When comparing the different antihistamines, only sedating antihistamines were prescribed more often on an as-needed rather than on a regular basis. This could be due to the fact that sedating antihistamines could be prescribed in addition to nonsedating antihistamines.

Table 4 Antihistamine dose prescribed

Antihistamine	Labelled dose (24 h), mg	Dose prescribed	
		Median	IQR
Cetirizine	10	10	10–10
Ciproheptadine	20	13	10–16
Clemastine	2	2	2–2
Desloratadine	5	5	5–8
Dexchlorfeniramine	Up to 12	6	5–6
Diphenhydramine	Up to 200	6	6–6
Ebastine	Up to 20	20	10–20
Fexofenadine	Up to 180	180	140–180
Hydroxyzine	Up to 300	25	25–50
Ketotifen	2–3	3	1–7.5
Levocetirizine	5	5	5–5
Loratadine	10	10	10–10
Mirtazapine	15–30	5	5–5
Mizolastine	10	NA	NA
Rupatadine	10	10	10–15
Terfenadine	Up to 120	150	120–180

IQR, interquartile range; NA, not applicable.

Antihistamine dose

Table 4 shows the antihistamine doses prescribed. We did not find for any antihistamine a median or mean dose which was above the labelled recommended dose. The tendency was to add a second drug instead of increasing the dose of antihistamines.

Comparison of drug depending on urticaria type

We compared the use of antihistamines and corticosteroids depending upon the urticaria classification. We found no significant differences in any type of urticaria when antihistamines were compared. We only found a significantly higher percentage of corticosteroids prescribed to patients classified as having contact urticaria as compared with the other urticaria types. We include these data in Table 5.

Comparison of drug prescribed between specialists

When comparing between allergists and dermatologists, a positive and significant correlation was found only between prescription of cetirizine ($P = 0.0042$), dexchlorfeniramine ($P = 0.0157$), leukotriene antagonists ($P < 0.0001$) and anti-H2 antihistamines ($P = 0.0029$) and treatment by an allergist. A positive correlation was found with desloratadine ($P = 0.0101$) and being treated by a dermatologist. We found no difference in CU management in the remaining treatments studied.

Urticaria features

In our study we included several data regarding the clinical features of the urticaria present. We found a family history of

Table 5 Drugs prescribed (%) depending on urticaria type

	Anti-H1	Corticosteroids
Exercise-induced	98.9	2.2
Dermographic	95.8	18.2
Cholinergic	94.7	14.1
Pressure	93.5	24.8
Cold contact	91.7	23.8
Solar	91.4	17.3
Contact	91.2	37.9*
Heat contact	89.5	12.1
Aquagenic	87.8	25.6
Vibratory	80	0

*P = 0.04.

urticaria in 15% of patients and a family background of atopy in 32% of the cases. The mean $\pm$ SD duration of CU was 4 ± 6 years. Eighty-five per cent of patients presented hives on the trunk. The mean $\pm$ SD total surface body area affected was $45 \pm 27\%$. Eighty per cent of patients with CU presented isolated hives whereas 20% of patients had both angio-oedema and hives.

Discussion

In a nationwide study⁶ urticaria was found to be the fourth most prevalent condition after rhinitis, asthma and drug allergy. Despite this morbidity and prevalence, it seems difficult for the nonexpert to differentiate between CU and any kind of physical urticaria. This fact is reflected in our study by a surprisingly high number of patients included in the pressure, aquagenic or heat contact urticaria group. The reason for this might also be that in a high percentage of patients CU is associated with pressure and it is difficult to separate both types. Likewise, aquagenic urticaria might correspond to cold urticaria, as no information was available regarding the tests which had been used to reach the final diagnosis.

Other data that support this issue are that when treatment was compared depending on urticaria type, there were no differences in the use of antihistamines or corticosteroids in any group except for contact urticaria. Thus, it seems that the subtype of urticaria does not dictate therapy and that all patients receive the same treatment approach. This is of special importance as antihistamines are known to be less effective in pressure urticaria and this might prompt the treating physician initially to choose a treatment different from a monotherapy with nonsedating antihistamines. The same could be applied to other physical urticarias with poor response to antihistamines.

We believe that despite efforts to disseminate a classification of different types of urticaria,^{5,7,8} this information does not reach the general dermatologist or allergist. It would thus seem that greater efforts need to be made to standardize feasible diagnostic tests for physical urticarias. A recently introduced electronic device for standardized testing of cold/heat

urticaria⁹ is an example of how such easy and feasible diagnostic procedures could be of benefit for diagnosis and efficient treatment.

Although guidelines are followed in general, the high number of sedating H1 antihistamines that were prescribed is surprising. In our study, hydroxyzine was the second most frequently prescribed drug, with no difference between dermatologists and allergists. It seems that the general perception of physicians is that patients with CU need a sedating drug in order to treat their urticaria as well as their anxiety. We believe that this therapeutic approach causes the opposite effect and has a negative impact on urticaria control and patient satisfaction. Moreover, in many instances these drugs are prescribed as needed instead of regularly. Furthermore, in all studies pruritus is the most disturbing urticaria symptom and itching control can be achieved with all nonsedating antihistamines.⁸

Another interesting observation is that antihistamines were not prescribed above the licensed dose. However, we should interpret this finding with caution as we did not differentiate between combining two different antihistamines and this could have happened in some cases. On the other hand, another possible reason could be that it may be hard for physicians to recognize that they are recommending a drug above the licensed dose. In this matter guidelines may not be very realistic. In addition, one study showed no benefit of such an approach.¹⁰ We believe that in order to make correct prescribing feasible, safety and efficacy studies with higher doses must be performed.

It is also surprising that combinations with an evidence-based medicine D grade of recommendation^{3,11} were used. In contrast, ciclosporin was seldom used, even though it received a grade B recommendation and several studies have reported its efficacy^{12,13} and *in vitro* ability to inhibit basophil degranulation.¹⁴

There were very slight differences in urticaria management depending on the specialist consulted. Allergists might have used more antileukotriene antagonists because they are more familiar with these drugs as they are used in the treatment of asthma.

Large multicentre double-blind randomized studies comparing side by side different antihistamines and other treatment options would facilitate the correct management of CU. To date, well-designed randomized controlled trials are lacking.³ This fact contributes a great deal to the lack of consistency between guidelines and poor compliance by physicians. It may also possibly explain why some physicians try drugs based merely on anecdotal reports.

There is a real need to expand and disseminate knowledge about the management of urticaria, which was recently dubbed by a leading expert as a 'Cinderella' disease.¹⁵ Another issue which remains to be resolved is accessible and accurate pathophysiology and treatment option information for patients with CU. However, until there is a treatment breakthrough for this disease, an important part of the treatment consists of counselling and explaining real treatment limitations. Practising medicine has a great deal to do with patient

education, and education has an even more critical role to play when no curative treatment is at hand.

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