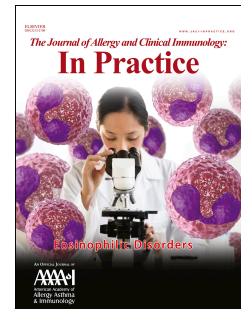


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Management of urticaria by French specialists compared to international guideline recommendations

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Clinical implications box: There are some discrepancies between published guidelines and real-life practice of French physicians.

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To the Editors,

The urticaria group (GUS) of the French Society of Dermatology participated in and endorsed the international guidelines for urticaria (1). Since the first international guidelines were published in 2009, the care of patients with chronic urticaria has clearly improved (2). However, there are some discrepancies between the published guidelines and real-life practice, as outlined by Wood (3). We therefore decided to perform an online survey among the GUS physicians to evaluate their clinical practices regarding some specific points of the guidelines.

Thirty-nine out of 51 (76%) of the active members of the GUS, including 4 urticaria experts and 7 members from departments with UCARE certification from the GA₂LEN group, replied to the questionnaire. Most of the GUS members were dermatologists, other allergists, internal medicine physicians and/or immunologists. This survey (Online Repository) outlined some specificities of the French physicians. It appears that the French approach more closely mirrors the US guidelines (4) (Table 1).

Two-thirds of the GUS members do not (or only as an exception) prescribe an elimination diet.

Almost half of the GUS members never recommend an elimination diet, whereas the remaining recommend this diet sometimes or as an exception; most recommend a well-balanced diet rather than an elimination diet.

Most GUS members do not use combinations of antihistamines.

Whereas the international guidelines recommend increasing doses of H1-antihistamines, and not H1-antihistamines combinations, in cases of insufficient efficacy at the labeled dose, the French consensus on chronic urticaria in 2003 recommended combining first and second generation H1-antihistamines (5). To date, no publication has compared the effect of H1-antihistamines at higher than licensed doses with the combination of several molecules. Almost two-thirds of the survey participants do not combine first and second generation H1-antihistamines. More than half do not combine second generation H1-antihistamines. This is mainly done in cases of insufficient efficacy, poor tolerance of an increased dose or before

increasing the dose. Furthermore, the association of H1- and H2-antihistamines is infrequently used.

A minority of GUS members had been confronted with the situation of omalizumab prescription during pregnancy thus far.

The use of omalizumab during pregnancy is only recommended in cases of absolute necessity; 69% of the survey participants had never been confronted with the need to decide whether to prescribe omalizumab during pregnancy. In cases of pregnancy occurring during omalizumab treatment, 10% continued it while 13% interrupted it, and the remaining survey participants had not yet been confronted with this situation.

Most GUS members use alternative treatments before omalizumab.

According to the international guidelines, no alternative treatment except omalizumab is recommended for CU that is unresponsive to H1-antihistamines at a 4-fold dose (step 3). Almost one-third of the participants prescribe omalizumab, whereas the others prescribe montelukast (59%), methotrexate (10%), dipyridamole (10%), colchicine (5%), doxepin (5%), hydroxychloroquine (5%), or tranexamic acid (2.5%); 13% prescribe other therapies, such as phototherapy, cyclosporin A, and alprazolam, before omalizumab.

Most GUS members perform validated provocation tests for chronic inducible urticaria.

Approximately 69% of the participants perform relevant provocation tests in variable accordance with the ClndU subset. The ice cube test, warmed wet compress test, and pressure test are the more often performed tests. Only 22% of the participants reported that they are able to determine trigger thresholds.

Most GUS members promote a patient's quality of life rather than the absence of hives.

Ninety-seven percent of GUS members do prescribe treatment escalation to decrease urticaria activity and improve the patients' quality of life, but only 2.5% aim to obtain complete resolution of symptoms. It has not yet been shown that complete remission during treatment decreases CU total duration or the risk of subsequent relapses after treatment disruption.

The use of UAS7=0 to define complete remission is a stringent criterion. A recent publication recommended the use of the UAS7 and UCT documented at 4 weekly intervals after the introduction of therapy in both clinical trials and real-life studies (6). The assessment of complete remission was based on different scores according to GUS members; in decreasing order, the assessment was based on a combination of UAS7=0 and UCT=16, UAS7=0, DLQI=0 or UCT=16.

A majority of GUS members, mostly dermatologists, use methotrexate as step 4.

Cyclosporin A is the fourth step of the therapeutic algorithm. In cases of omalizumab failure, 44% of the survey participants reported that they prescribe cyclosporin A, and 59% prescribe methotrexate. Methotrexate is not labeled for CU, but dermatologists are familiar with its prescription, and this strategic preference is possibly explained by their participation in the French randomized controlled MUCIS study (7). It is foreseeable that the lack of recently published methotrexate results could modify this prescription in the future (7). Seventy-five percent of those who prescribe cyclosporin A use it as fourth-line therapy, as recommended.

Most GUS members use a longer lapse of time between the different treatment steps.

According to the recently published algorithm of treatment, H1-antihistamines should be taken for 4 to 8 weeks (single- and 4-fold dose) before determining a treatment failure and proceeding to the subsequent prescription of omalizumab. Sixty-nine percent of the GUS members considered these time lapses too short. Except for in patients with very severe CU, treatment was re-evaluated after 4 weeks by only one-third, while 20.5 and 36% of the physicians waited 2 and 3 months, respectively.

Most GUS members do not prescribe oral corticosteroids.

Sixty-nine percent of the survey participants never prescribe corticosteroids and 23% prescribe them only as an exception. If prescribed, corticosteroid doses varied from 1 to 10 mg/kg/day, and the duration was less than 7 days in 75%.

There are still unmet needs in the management of chronic urticaria, such as determining the time point at which to consider H1-antihistamine failure or intolerance, assessing the usefulness of switching molecules at least once, evaluating whether the early use of omalizumab has an impact on the duration of CU, validating sets of clinical and/or biological

117 markers predictive of omalizumab efficacy and establishing an algorithm for the use of
118 omalizumab in terms of the duration, doses and disruption.

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146 **Table and Online Repository Legends:**

147 **Table 1:** Comparison of the international guidelines, the North American guidelines and the
148 French position in the therapeutic management of chronic urticaria.

149 **Online Repository Legend:** Survey: questions and responses.

150

Therapeutic habits in chronic urticaria					
	As an exception	Often	Sometimes	Always	Never
Do you recommend low-histamine diets for patients with chronic urticaria? N (%)	9 (23%)	0 (0%)	11 (28%)	1 (3%)	18 (46%)
Do you combine first generation H1-antihistamines with second generation H1-antihistamines? N (%)	13 (33%)	1 (3%)	10 (26%)	0 (0%)	15 (38.5%)
Do you combine H1-antihistamines with H2-antihistamines? N (%)	13 (33%)	2 (5%)	4 (10%)	0 (0%)	20 (51%)
Do you combine different second generation H1-antihistamines? N (%)	7 (18)	6 (15%)	10 (26%)	0 (0%)	16 (41%)
	In which situation? - Before trying to increase the dose of one second generation H1-antihistamine up to 4-fold: 4 (17%) - In cases of insufficient results after increasing the dose of a molecule up to 4-fold: 12 (52%) - In cases of poor tolerance to a 4-fold increased dose of H1-antihistamines: 11 (48%) - Other reasons: 5 (22%)				
Do you prescribe doxepin for chronic urticaria? N (%)	10 (26%)	1 (3%)	1 (3%)	0 (0%)	27 (69%)
Do you prescribe a leukotriene receptor antagonist for chronic urticaria? N (%)	8 (20.5%)	10 (26%)	16 (41%)	0 (0%)	5 (13%)
Cyclosporin A					
Do you prescribe cyclosporin A for chronic urticaria? N (%)	16 (41%)	0 (0%)	8 (20.5%)	0 (0%)	15 (38.5%)
If yes, what is the usual dose?	<3 mg/kg/d: 3 (12.5%) 3 mg/kg/d: 16 (67%) >3 mg/kg/d: 5 (21%)				
If yes, when do you prescribe cyclosporin A?	Prior to omalizumab: 4 (17%) In cases of omalizumab failure: 18 (75%) Other : 1				
Systemic corticosteroids					
	As an exception	Often	Sometimes	Always	Never
Do you prescribe systemic corticosteroids in chronic urticaria? 12/39 N (%)	9 (23%)	0	3 (7%)	-	27 (69%)

If yes, what is the usual dose? N (%)	10 mg/d: 1 (8%) 0.5 mg/kg/d: 3 (25%) 1 mg/kg/d: 4 (33%) Other: 4 (33%)
If yes, what is the usual duration? N (%)	<3 days : 5 (42%) 3-7 days : 4 (33%) Other: 3 (25%)
Pregnancy	
Do you prescribe omalizumab in pregnant patients? N (%)	Yes: 3 (8%) No: 9 (23%) Not yet confronted: 27 (69%)
In case of pregnancy during omalizumab treatment, what is your attitude? N (%)	Stop: 5 (13%) Continue: 4 (10%) Not yet confronted: 30 (77%)
Inducible chronic urticaria (IndCu)	
Do you perform provocation tests for suspected IndCu? N (%)	Yes: 27 (69%) No: 12 (31%)
Which tests could you perform? N (%)	Ice cube: 25 (93%) TempTest®: 5 (18.5%) Pressure test: 21 (78%) Fric Test: 7 (26) Heat test: 13 (48%) Wet compress: 23 (85%) Effort test: 13 (48%) Photo tests: 9 (33%)
For IndCu, are you able to determine the trigger thresholds? N (%)	Yes: 6 (22%) No: 21 (78%)
Are the following devices available in your practice?	TempTest®: 4/6 Vortex: 2/6 Bicycle: 0
Therapy failure	
In cases of failure or inadequate response to a 4-fold dose increase of H1-antihistamines, which alternative treatments do you use before omalizumab? N (%)	Montelukast: 23 (59%) None: 12 (31%) Methotrexate: 4 (10%) Dipyridamole: 4 (10%) Doxepin: 2 (5%)

	Hydroxychloroquine: 2 (5%) Colchicine: 2 (5%) Other: 5 (13%) Tranexamic acid: 1 (3%) Disulone: 0 (0%)
In cases of failure of omalizumab, which other treatment(s) do you prescribe? N (%)	Methotrexate: 23 (59%) Cyclosporin A: 17 (44%) Other: 7 (18%)
Miscellaneous	
What is your main objective when considering therapy escalation? N (%)	Complete remission: 1 (3%) Clinical improvement and improvement of the quality of life assessed by the patient: 38 (97%)
How do you define complete remission? N (%)	UAS7=0: 16 (41%) UCT=16: 10 (26%) DLQI=0: 11(28%) Combination of UAS7=0 and UCT=16: 17 (43%)
Except in severe cases of chronic urticaria, how long do you wait before escalating the treatment?	1 month: 13 (33%) 2 months: 8 (21%) 3 months: 14 (36%) Other : 4 (10%)
What is your opinion about the proposed duration of each step in the international guidelines? N (%)	Relevant: 10 (26%) Too short: 27 (69%) Other: 2 (5%)

	EAACI/GA ₂ LEN/EDF/WAO 2018 guidelines	US 2014 guidelines	French survey on real-life practice
Step 1	Monotherapy with sgAH	Monotherapy with sgAH	Monotherapy with sgAH
Step 2	Increase dose sgAH (up to 4x)	One or more of the following: -Add another sgAH -Add H2-antihistamines, LTRA, fgAH at bedtime	One or more of the following: -Switch another sgAH -Add another sgAH -Association sgAH to fgAH -Increase dose sgAH (up to 4x)
Step 3	Add on to sgAH omalizumab	Dose advancement of potent antihistamine as tolerated (e.g hydroxyzine or doxepin)	-69% add on to alternative treatments including LTRA (<i>see Appendix</i>) -30% prescribe omalizumab
Step 4	Add on to sgAH cyclosporin A	Add an alternative agent: Omalizumab or cyclosporin A Other anti-inflammatory agents, immunosuppressants, or biologics	-omalizumab* -59% use rather methotrexate than cyclosporin A as step 4
Escalation therapy	If inadequate control: after 2-4 weeks or earlier, if symptoms are intolerable	Assess for patient's tolerance and efficacy	Assess for patient's tolerance, quality of life and efficacy after 4 weeks or later 90% except in severe cases

sgAH: second-generation H1-antihistamine, fgAH: first-generation H1-antihistamine, LTRA: leukotriene receptor antagonist

*if not used at step 3