

“Chronic Urticaria”: Recommendations From an Allergist and Immunologist

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On November 3, 2017, Dr Luz Fonacier discussed her perspective as an allergist and immunologist on the current literature and recommendations on chronic urticaria (CU) at the American Contact Dermatitis Society midyear meeting, the Frontiers in Dermatitis conference. Dr Fonacier started by defining CU and differentiating chronic spontaneous urticaria (CSU) from chronic inducible urticaria by the ability to identify a trigger in the latter entity. Notably, she identified the growing understanding that 50% of CSU cases have autoantibodies directed against the subunit of its high-affinity receptor of immunoglobulin (Ig) E or to IgE itself, leading to mast cell or basophil degranulation.

She went on to highlight the prevalence of CU in the general population, which ranges from 0.5% to 5%, including features of either angioedema or urticaria alone or a combination of urticaria, angioedema, systemic complaints, and/or aspirin intolerance.^{1–4} She noted that the duration of CU varies greatly; however, physical urticarias (eg, dermatographism, cholinergic urticaria, cold urticaria, solar urticaria, vibratory angioedema, and aquagenic urticaria) tend to be the longest, with persistence for many years. Angioedema, in particular, was also identified as being associated with prolonged duration, increased disease severity, and reduced quality of life in CSU. Interestingly, the true prevalence of physical urticaria is difficult to precisely determine. Yet, estimates include cholinergic urticaria, accounting for 5% of physical urticarias associated with CSU and 30% of all cases of physical urticaria, dermatographism in 2% to 5% of the general population, and rare observation of aquagenic urticaria and vibratory angioedema. Up to 40% of patients with chronic inducible urticaria have concomitant physical urticaria and thus may be less responsive to conventional pharmacotherapy. Description, challenge procedures, and treatments for physical urticaria/angioedema are summarized in Table 1.

For evaluation of CSU, Dr Fonacier recommended that history and physical examination to assess disease activity were essential.

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However, she sighted that the role of basophil testing in diagnosis and management remains controversial. Several tools were also identified for evaluation of disease activity (eg, Urticaria Activity Score 7 [<https://www.itchingforanswers.ca/docs/UAS7-Questionnaire.pdf>] or Angioedema Activity Score [http://moxie-gmbh.de/media/pdf/aas_scoringtemplate_moxie.pdf]), as well as the impact on quality of life and control of urticaria (eg, Chronic Urticaria Quality of Life Questionnaire [<https://www.itchingforanswers.ca/docs/CU-Q2OL-Questionnaire.pdf>] or Angioedema Quality of Life Questionnaires [http://moxie-gmbh.de/media/pdf/ae-qol_scoringssystem_moxie.pdf]). The basophil activation test (eg, BÜHLMANN Flow-CAST) can coassess disease activity by measuring CD63 up-regulation, whereas the indirect basophil activation test is currently used as a tool for indirectly diagnosing autoimmune urticaria. For predicting response to treatment, the basophil histamine release assay (BHRA) serves as a marker for responsiveness to cyclosporine A and omalizumab. In particular, CSU patients with a positive BHRA are more likely to respond clinically to cyclosporine and to have a slow response to omalizumab compared with patients with a negative BHRA.^{5,6} Hence, a BHRA test may be useful in choice of therapy for CSU patients who are unresponsive to H₁ antihistamines.

In evaluating CU, Dr Fonacier also suggested that limited laboratory testing may be justified for patient reassurance. Extensive autoantibody testing is not favorable from a cost-benefit standpoint and does not improve patient care outcomes. She also reviewed consensus recommendations from the Practice Parameters Task Force, which also favor the following limited routine tests to confirm or rule out underlying conditions: complete blood count with differential, erythrocyte sedimentation rate, liver function tests, and thyroid-stimulating hormone.⁷

For treatment of CU, Dr Fonacier reviewed current targets including modulation of inflammation and blockade of histamine release and the effects of histamine on blood vessels. First-line therapy for CU was identified with treatment by second-generation H₁ antihistamines, as first-generation H₁ antihistamines have adverse effects of sedation and anticholinergic effects. However, 5% to 50% of CU patients do not have a satisfactory response. If patients do not respond to the recommended dosage of H₁ antihistamines, she suggested a second-line therapy with up to 4 times the recommended dose of second-generation H₁ antihistamines.⁸ For CSU unresponsive to therapy with higher doses of H₁ antihistamines, omalizumab was recommended at 150 or 300 mg every 4 weeks as a third-line therapy suitable for long-term treatment and effectively

TABLE 1. Overview and Treatment for Physical Urticaria/Angioedema Syndromes⁷

Type	Manifestations	Prevalence	Challenge Procedure	First-Line Treatment (Response Rate)	Other Treatments
Dermatographism	Rapid-onset wheal/flare after skin pressure	2%–5%	Stroke skin with tongue blade	H ₁ antihistamines (95.8% respond)	—
Delayed pressure urticaria	Onset of wheal/flare 4–6 h after application of pressure	2%	15 lb hung on shoulder for 10–15 min	H ₁ antihistamines (very poor)	Steroids, sulfasalazine, danazol, dapsone, nonsteroidal anti-inflammatory drugs
Cold urticaria	Pruritus/swelling confined to cold-exposed areas +/- systemic symptoms	0.05%	Ice cube test on forearm for 5 min	Cyproheptadine, doxepin	B ₂ sympathomimetics, aminophylline, induction of tolerance, epinephrine (epi) self-injector
Cholinergic urticaria	Pinpoint (1–3 mm) hives surrounded by large flares +/- systemic symptoms	0.2%	Methacholine intradermal or partial immersion in 42°	Cetirizine, ketotifen, hydroxyzine	Danazol, induction of tolerance (or epi self-injector if severe)
Solar urticaria	Pruritus/swelling confined to sun-exposed areas	0.4%	Exposure to specific wavelengths	Chlorpheniramine, hydroxyzine (poor response)	Induction of tolerance, photochemotherapy (eg, PUVA, highly effective), chloroquine
Aquagenic urticaria	Rapid-onset pinhead-sized wheals after water exposure	Rare	Water compress 35°C for 30 min	H ₁ antihistamines	Barrier cream, selective serotonin reuptake inhibitors, phototherapy
Vibratory angioedema	Local erythematous and edematous lesions following local stimuli of a vibratory or fractional nature	Rare	Vortex on forearm	Hydroxyzine, fexofenadine	Induction of tolerance
Exercise-induced urticaria	Onset wheal/flare during exercise	—	Treadmill (and food identification if relevant)	Avoidance	Epinephrine self-injector

treats relapse after discontinuation.^{9,10} Dr Fonacier highlighted that rapid onset of clinical improvement with omalizumab treatment has been reported within 1 week of therapy.¹⁰ She also stated that although IgE levels before initiation of omalizumab are not recommended, there has been demonstration that IgE levels greater than 100 IU/mL are predictive of faster relapse after discontinuation.¹¹ Lastly, she closed by suggesting cyclosporine and other immunomodulatory therapies (such as dapsone, sulfasalazine, or hydroxychloroquine) as alternative treatments for recalcitrant CU.

Overall, Dr Fonacier provided an exciting and enlightening review of evidence in the pathophysiology of CU and treatment recommendations. Given that CU is a common entity in the field of dermatology, it was refreshing to gain the allergist and immunologist perspective on this topic. We look forward to future lectures from Dr Fonacier at upcoming meetings with the American Contact Dermatitis Society.

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