

# Chronic Urticaria/Angioedema (CUA): Which Diagnostics, if any, Inform Etiology and Response to Treatment?



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In addition to migratory pruritic urticaria (hives or welts), sometimes associated with angioedema and often dermatographia, systemic symptoms including arthralgia and even frank arthritis<sup>1,2</sup> may be present in patients with chronic urticaria/angioedema (CUA). CUA that is persistent, inducible, or spontaneous for at least 6 weeks is defined as chronic.

Patients and health care providers are often frustrated in their attempt to identify an environmental cause that is responsible for the condition. Certain inducible exposures such as to cold, heat, pressure, water, vibration, ultraviolet light (physical urticarias), stress, seasonal pollen contact with wet skin, medications (especially nonsteroidal anti-inflammatory drugs), and rarely certain foods, all termed chronic inducible urticaria, sometimes may be confirmed with a provocative challenge, for example, ice cube test for cold urticaria, and controlled by avoidance of precipitating exposures. Specific laboratory or skin testing adds little to inform prognosis that is usually excellent.<sup>3</sup> Autoimmunity (presence of autoantibodies to IgE and/or IgE receptor alpha subunit [anti-Fc-epsilon-R1- $\alpha$ ] on mast cells and basophils) may be operative in some cases, generally determined clinically with the finding of a positive autologous serum skin test result and/or *in vitro* basophil activation test. Specificity of both tests appears to be low. However, the description of IgE class of autoantibodies present in CUA is intriguing.<sup>4</sup> There are rare case reports of CUA responding to anti-B-cell therapy in the form of rituximab, though the interpretation of evidence for an autoimmune pathogenesis for CUA is controversial and begs the question—Does autoantibody testing, or any other testing, inform treatment or prognosis?

At least at this time, a growing body of evidence over the past decade supports an answer of “no,” unless there are associated, atypical clinical features such as fever, lesions lasting more than 48 hours, bruising, pain instead of itch, anaphylaxis, and high peripheral blood eosinophil count (above 1500/ $\mu$ L), which may suggest other possibilities in the differential diagnosis including autoinflammatory diseases, connective tissue diseases such as lupus, serum sickness, mast cell disorders including mastocytosis and mast cell activation syndromes, hypocomplementemic

urticarial vasculitis, cryoglobulinemia, hypereosinophilic syndrome, and Schnitzler syndrome.

Once the clinical diagnosis of CUA has been made, treatment begins with a second-generation H1 antihistamine, often cetirizine, the major active metabolite of hydroxyzine, in standard and up to 4 to 6 times standard dose depending on response, tolerability, and patient size. As an alternative, fexofenadine in standard and up to 4 times standard dose can be used. Owing to their soporific effects, the antihistamine doxepin, and cyproheptadine, an old medication with combined antihistamine/antiserotonin effects, dosed at bedtime can be considered if urticaria is disturbing sleep. Failing adequate dosing of H1 blockers, omalizumab (monoclonal anti-IgE R1- $\alpha$ ) is now more commonly added. These 2 interventions effectively manage most patients. Anti-cysteinyl leukotrienes, H2 blockers, and combination of 2 or more H1 blockers provide little, if any, added benefit and only complicate the regimen and increase cost. In those uncommon patients in whom H1 blockers and omalizumab fail to provide adequate control, a trial of any one of various disease-modifying antirheumatic drugs beginning with cyclosporine, for which the evidence is strongest, may be considered. Adrenocorticoids are best avoided because of long-term side effects but can be used with severe exacerbations or severe, persistent disease. Other disease-modifying antirheumatic drugs with only minimal or low-grade clinical evidence to support efficacy include methotrexate, sulfasalazine, mycophenolate, dapsone, and hydroxychloroquine, to name those more commonly used. Off-label use of other biologic agents such as rituximab, TNF inhibitors, intravenous immune globulin, and plasma exchange has been described,<sup>5</sup> but reproducible evidence for efficacy is not compelling. Consistent with current guidelines,<sup>3</sup> we have not found any testing to be predictive of response to specific treatments nor informative about prognosis, which is usually good for CUA.

In this issue, Carrillo-Martin et al<sup>6</sup> expand the evidence by presenting their findings of a retrospective analysis of 725 electronic medical records of patients identified by *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision* codes who were evaluated for CUA between 2010 and 2018 at their tertiary care center, the Mayo Clinic in Jacksonville, Fla. Analyses were made to evaluate changes in outcome for patients in whom at least 1 test was performed to evaluate CUA, the costs generated by these tests, and the tendencies to order specific tests.

Of these, 543 patients had at least 1 test performed. More than 5000 tests were performed in the evaluation of these patients, most of which were within normal range; except for 5 cases (0.9%), tests with abnormal results did not lead to

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changes in management or outcome. They conclude that their data reinforce current recommendations to minimize testing.

The 2017 guidelines<sup>3</sup> recommend limited laboratory evaluation with complete blood cell count and inflammatory markers erythrocyte sedimentation rate and C-reactive protein. The findings of Carrillo-Martin et al suggest that even these most basic tests add little to the evaluation and management of patients with CUA.

Their data add additional support for the notion that a careful history, including patients' cell phone pictures of stages of their skin eruption, and physical examination are still far more informative than screening laboratory tests to make the diagnosis of CUA and, on occasion, raise the possibility of other differential diagnoses requiring further diagnostic inquiry. For the future, our rapidly expanding knowledge of mast cell pathophysiology including understanding of relevant genetics, epigenetics, biome, and immune regulatory networks may lead to the dream of personalized medicine. The goal then would be to use clinical and next-generation *in vitro* analytics, both to confirm diagnostic endotype and to determine reliable, individualized, safe, and effective treatment for CUA and other diseases. For

now, physicians and other health care providers can counsel patients with classic CUA and save money and time by eschewing further laboratory studies.

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