

Evidence-based diagnosis and treatment of chronic urticaria/angioedema

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ABSTRACT

Chronic urticaria/angioedema (CUA) continues to be a vexing condition for both patients and health care providers. Despite progress made in recent years to improve our understanding of the pathogenesis of CUA and its treatment, many patients continue to experience ongoing symptoms and impaired quality of life. In the overwhelming majority of cases, a definite etiology is not identified. Laboratory testing may be justified based on its "reassurance value"; however, extensive routine testing is not favorable from a cost-benefit standpoint and does not lead to improved patient care outcomes. The target for effective management is to control CUA with a combination of avoidance measures, lifestyle changes, and regular administration of medication. A step-care approach to pharmacologic management that is favorable from the standpoint of balancing the potential for benefit with the potential for harm can lead to substantial improvement in quality of life. This article will focus on achieving improved outcomes for patients with CUA based on evidence-directed recommendations for diagnosis and management.

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In a review article published in the *Journal of Allergy* in 1954,¹ Sheldon, Mathews, and Lovell stated,

The long range management of some of the more refractory cases of urticaria continues to present a difficult problem for even the most expert in the field.

More recently, a review article² began with this statement,

Despite many advances, management of chronic urticaria remains a formidable challenge for both clinicians and patients.

The more than a half century that elapsed between the publication of these two review articles was a period during which major progress in our understanding of the causes of leading chronic diseases—including cardiovascular disease and many types of cancer—was achieved, and the role of behaviors and the importance of social, economic, and environmental influences as risk factors for leading chronic diseases was established. This improved understanding has led to development of effective interventions in both clinical and community settings, including progress in primary prevention.^{3,4}

However, these two review articles^{1,2} on chronic urticaria/angioedema (CUA) basically relay the same message. CUA continues to be a vexing condition for both patients and physicians and continues to be associated with substantial impairment in quality of life.⁵

This article is intended to highlight diagnostic strategies and therapeutic options for CUA, with the hope and belief that recent evidence can guide us in realizing the potential that exists for improving outcomes in patients with CUA.

EVIDENCE-BASED DIAGNOSIS

Most CUA Cases Are Idiopathic

In their classic series published in 1969, Champion *et al.*⁶ described 554 patients with CUA seen from 1956 to 1967. This article is still widely cited for its description of the proportions of cases with both urticaria and angioedema (65%), urticaria alone (15%), or angioedema alone (20%). However, the article is also notable for another reason: an etiology for CUA was "unknown" in 79% of their cases. In many review articles and book chapters,^{7–9} CUA is described as being "idiopathic" in 80% of cases. Although a citation is not provided for this estimate (at least that this author is able to find), one may assume that this article from 1969 is the source for this estimate.

Table 1 from this article⁶ appears as Table 1 here also. In considering the diagnoses of patients who comprised the 21% for whom an etiology was ostensibly identified, one can appreciate that this is an overestimate: 81% of this subgroup were so classified based on presence of a physical urticaria/angioedema syndrome, most of these based on dermatographia. Another 15% had "allergic urticaria"; in some cases this

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Table 1 Etiologies for chronic urticaria/angioedema in 554 patients

	No. of Cases	Urticaria Patients (%)
Ordinary urticaria and/or angioedema of unknown etiology	438	79.1
Allergic urticaria	17	3.1
Cholinergic urticaria	28	5.1
Dermographism	47	8.5
Other physical urticarias	19	3.4
Cold	14	
Light	3	
Pressure	2	
Pregnancy urticaria	3	0.5
Hereditary angioneurotic edema	2	0.4
Totals	554	100.1

Source: Ref. 6.

was attributed to foods (cheese, fish, shellfish, grapes, nuts, and plums) and in other cases to ingestion of trace amounts of penicillin in "penicillin-sensitive" individuals. Even if we accept the patients in the "allergic urticaria" category as having had a valid cause identified for their CUA, they comprise only 3% of the total number of patients in this series. Other estimates in the literature also imply that a definite etiology is found in only 5% or less of patients with CUA.^{10,11}

Given that in the overwhelming majority of cases CUA is not associated with an underlying etiology that we can identify, routine performance of laboratory testing or immediate hypersensitivity skin testing may be more likely to reveal abnormal findings that are of no clinical relevance and are incidental in nature.

Positive predictive value is the likelihood that a diagnostic test will be "positive" in someone with the condition we are aiming to diagnose. In the case of IgE-mediated allergy to a food, the estimated positive predictive value of skin testing for foods is only 50%.¹² Moreover, the predictive value of a test will vary according to the prevalence of disease in the population undergoing testing.¹³ The prevalence of true food allergy in a population of patients with CUA is less compared with a population of patients being evaluated for suspected food allergy. Routine performance of immediate hypersensitivity skin testing for foods is apt to falsely label a substantial proportion of patients with CUA as having "food allergy." There is a potential harm in doing this. Patients in our care are vulnerable, and they experience an impact from receiving a diagnosis. A new diagnosis may be something one needs to worry about. Patients who are given restric-

tive diets experience the burden of scrutinizing labels and engaging servers in restaurants concerning contents of their menu selections. There are other areas of medicine in which the harms associated with "overdiagnosis" have been more precisely characterized, such as screening mammography for women between the ages of 40 and 50 years. According to a Cochrane review,¹⁴ to prevent 1 death from breast cancer, screening mammography would need to be performed in 2000 women annually from age 40 to 50 years; however, 10 otherwise healthy women would be "overdiagnosed" and labeled as having breast cancer. This would result in six lumpectomies and four mastectomies. In addition, 200 women would be told of an abnormal mammogram and may experience psychological or emotional harm from anxiety associated with the need for further investigation and greater scrutiny of their screening mammography studies in the future.

Finding a Brown M&M

Van Halen was a popular touring rock band in the 1980s. Their concerts featured major stage productions (Fig. 1). The band was notorious for its outrageous backstage antics and partying habits. They also had a reputation for including very detailed specifications in lengthy contracts for their concerts. These details pertained to technical arrangements for the concert, so as to safeguard against possible injuries to band members. Some of the demands made in the contracts seemed rather frivolous. The contracts included a stipulation that bowls of M&Ms be available backstage, with an additional clause that stated: "There will be no brown M&M's in the backstage area, upon pain of forfeiture of the show, with full compensation." This sentence appeared in the contract within a description of myriad technical specifications pertaining to the stage performance. When David Lee Roth, Van Halen's lead singer, would arrive at a new venue, he immediately would seek out the M&M bowls backstage. If he found a brown M&M, he would conclude that the contract had likely not been reviewed in full detail and that appropriate preparations for the stage show had not been made. He would immediately request a comprehensive check of all preparations required for the concert.¹⁵ For David Lee Roth, a brown M&M served as a warning sign.

Because the condition of CUA is idiopathic in the overwhelming majority of cases, evaluation proceeds with the understanding that finding a "brown M&M" serves as a warning sign that an underlying condition may be present. A comprehensive history and physical examination should be performed, directed to identify potential underlying etiologies. The relationship of pruritus and urticaria/angioedema episodes to medications, food items, time of day, menstrual cycle, phys-



Figure 1. Van Halen on stage.

ical stimuli, exertion, occupational exposures, stress, or other factors should be determined. The appearance and characteristics of urticaria/angioedema lesions should also be discerned. Lesions that leave residual bruising or span >24 hours raise the suspicion that a vasculitis is present. When the history or physical examination suggests an underlying cause is present (e.g., fatigue, constipation, and heat/cold intolerance combined with thyromegaly), appropriate testing (e.g., thyroid stimulating hormone [TSH]) should be obtained.

When there is no “brown M&M” found in the course of a comprehensive history and assiduous physical examination, what is appropriate for *routine* testing? A recent study¹⁶ assessed the usefulness of diagnostic testing in CUA patients, in terms of whether it leads to improved outcomes. A retrospective analysis was performed to identify patients in whom laboratory abnormalities were uncovered that subsequently led to a change in management associated with improved outcomes. In this series of 356 patients with CUA, 1872 tests were performed, a mean of 6 tests per patient. Seventeen percent of these tests were abnormal; 8.4% of patients subsequently underwent additional testing based on these findings. Only one patient had a change in management leading to improvement in CUA based on findings from laboratory testing performed at initial evaluation. Previously, CUA had been well controlled while she was being treated for hypothyroidism with 175 μg of levothyroxine daily. Three months before her evaluation, she had a myocardial infarction and her daily dose of levothyroxine was reduced from 175 to 88 μg . Her CUA worsened and persisted despite regular antihistamines. She had elevated TSH and antithyroid antibodies. After upward titration of her levothyroxine dose, CUA improved.

These data support the interpretation that for patients with CUA whose history and physical exam lacks atypical features, routine laboratory testing rarely yields clinically significant findings. Consistent with the aforementioned data, recent guidelines^{17,18} recommend limited laboratory evaluation in patients with CUA, so that diagnostic evaluation can serve to rule out an underlying cause for CUA in a cost-effective manner, while in most cases providing “reassurance value” for the patient and his/her family.

There is an honest difference of opinion as to the appropriate diagnostic testing that should be ordered on a routine basis for patients in whom a thorough history and physical examination is otherwise unremarkable. Some maintain that limited or no testing is warranted, whereas others would obtain more extensive testing—striving to rule out presence of an underlying etiology with greater certainty.

A survey of members of the Joint Council of Allergy/Immunology Practice Parameters Task Force¹⁹ led to a consensus for ordering the following tests in CUA patients without an atypical history or finding on physical examination:

- Complete blood count with differential
- Erythrocyte sedimentation rate
- Liver enzymes
- TSH

It should be noted that the diagnostic usefulness of obtaining the aforementioned tests routinely in patients with CUA has not been established.

EVIDENCE-BASED TREATMENT

There is high-quality evidence from multiple randomized controlled trials, which have established an-

tihistamines as first-line therapy for patients with CUA.¹⁹ Based on their safety advantage compared with first-generation antihistamines,²⁰ monotherapy with a second-generation antihistamine should be prescribed for initial management.

Because monotherapy with a second-generation antihistamine may not control CUA adequately in many cases, the clinician has several options for advancing therapy. These include (a) adding an H₂-antihistamine; (b) adding an antileukotriene; (c) adding an H₁-antihistamine, either a first-generation agent at bedtime or a different second-generation agent.¹⁹ One, more than one, or all of these options can be prescribed. Studies assessing the relative efficacy of these options for controlling CUA have not been reported.

When the aforementioned therapy is not associated with adequate control of CUA, a two- to fourfold increase in the Food and Drug Administration–approved dose of a second-generation antihistamine can be entertained. In a study of 80 subjects with refractory CUA,²¹ 72% of whom had previously received oral corticosteroids, 75% responded to higher than conventional doses of either levocetirizine or desloratadine. Moreover, higher doses of these agents were well tolerated.

Individuals with more moderate–severe CUA who are not well controlled on agents that lack significant risk for untoward effects become candidates for agents that may entail burden and/or pose risk for harm. Relative to other therapeutic options (see later in text), the intervention that is most favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden is dose advancement of a potent first-generation antihistamine.¹⁹

Doxepin is 775 times more potent than diphenhydramine on a molar basis.²² In a randomized, double-blind, crossover study in which 50 subjects with CUA were randomized to doxepin at 10 mg t.i.d. and to diphenhydramine at 25 mg t.i.d., doxepin was associated with superior outcomes.²³ Greater proportions of subjects had total or partial control of pruritus and urticaria (74% versus 10%; $p < 0.001$) and total clearing of pruritus and urticaria (43% versus 5%; $p < 0.001$) while taking doxepin than diphenhydramine. Surprisingly, diphenhydramine was also associated with statistically significantly higher rate of sedation than doxepin (46% versus 22%; $p < 0.05$). These data provide indirect evidence supporting antihistamine dose advancement for patients with CUA unresponsive to combination therapy described previously. Dose advancement of other potent first-generation antihistamines, such as hydroxyzine, may also be associated with greater efficacy than conventional dosing.²⁴

More than one-half of patients may not achieve satisfactory control of CUA with antihistamine treatment.²⁵ CUA patients who do not respond to combi-

Table 2 Agents reported to be efficacious in patients with refractory CUA

Sulfasalazine
Dapsone
Hydroxychloroquine
Stanozolol
Colchicine
Methotrexate
Intravenous γ globulin
Mycophenolate mofetil
Cyclosporine
Tacrolimus
Sirolimus
Cyclophosphamide
Warfarin
Nifedipine
Chrysotherapy
Antitumor necrosis factor
Others

Source: Refs. 2 and 30.
CUA = chronic urticaria/angioedema.

nation antihistamine therapy, with or without an antileukotriene, including dose advancement of a potent H₁-antihistamine as tolerated, may be categorized as having “antihistamine-resistant,” or refractory, CUA.¹⁹ Sulfasalazine, dapsone, methotrexate, colchicine, and a number of other therapeutic agents (shown in Table 2) have been reported to have efficacy in patients with refractory CUA in case reports or case series.^{2,26–28} However, such studies may be subject to bias and do not provide high-quality evidence. Randomized controlled trials tend to be rated as high quality; however, the quality of evidence can be lowered based on methodological issues and other factors.²⁹ The reader is referred to recently published reviews for a detailed description of these therapeutic options, including mechanism of action and appropriate dosing and precautions for prescribing each agent.^{2,30}

Four of the agents listed in Table 2 have been studied in randomized controlled trials.

Hydroxychloroquine

In a double-blind study in which 21 subjects with CUA were enrolled, those randomized to hydroxychloroquine exhibited statistically significant improvement in quality of life, as assessed by global symptom severity score and quality of life, compared with placebo. A trend for improvement in urticaria activity scores and medication reliance was also reported.³¹ A larger study is required to more convincingly establish the therapeutic usefulness of hydroxychloroquine. Hydroxychloroquine was well tolerated in this study. Although

rare, there is a risk of retinopathy from hydroxychloroquine.³² Virtually all cases have been observed in individuals with a treatment duration that exceeded 5 years and/or exposure to a dose of >6.5 mg/kg per day. A baseline ocular examination is recommended in the 1st year of hydroxychloroquine therapy, with regular annual screening after 5 years—sooner for individuals (*e.g.*, older age, preexisting retinopathy, and presence of renal or hepatic insufficiency) at elevated risk.

Stanozolol

Fifty-eight subjects with CUA “not responding to conventional treatment” were randomly assigned to receive stanozolol at 2 mg twice daily along with cetirizine at 10 mg daily, or cetirizine at 10 mg daily and placebo tablets twice daily.³³ After 12 weeks, more subjects randomized to stanozolol showed marked to complete resolution of urticaria compared with placebo (chi-square, $p < 0.01$; intention to treat analysis, $p < 0.007$). There was also a statistically significant decline in mean severity score at 12 weeks ($p < 0.001$).

Two subjects taking stanozolol in this study exhibited elevation in liver enzymes; otherwise, stanozolol was well tolerated. In patients with C1-inhibitor deficiency syndromes treated with stanozolol or other 17 α -alkylated androgens, common adverse effects included but were not limited to acne, masculinization in women, mood alteration, weight gain, and hypertension.³⁴ The 17 α -alkylated androgens also have been associated with risk for hepatic adenoma and hepatic carcinoma.³⁵ Use of stanozolol is relatively contraindicated in children; in patients with hepatic insufficiency, breast, or prostate cancer; or who are pregnant.

Although this randomized controlled trial provides evidence in support of the efficacy of stanozolol, in view of its potential for serious untoward effects, this agent should be reserved for patients with refractory CUA who have failed other therapeutic agents that may be better tolerated or associated with less potential for harm.

Cyclosporine

Several randomized, double-blind, controlled trials have investigated the therapeutic usefulness of cyclosporine compared with placebo in CUA.^{36–38}

One study randomized subjects with CUA to either cyclosporine or cetirizine at 10 mg/day.³⁶ Only 2 weeks after randomization, 80% of subjects randomized to cetirizine developed “daily severe relapses requiring systemic steroid treatment” and were “crossed over” to open cyclosporine treatment.

In two other studies in which subjects were randomized to cyclosporine or cetirizine, “refractory” was defined as poor control of CUA despite a daily dose of

cetirizine at 10³⁷ or 20 mg.³⁸ The therapeutic benefit of cyclosporine can be assessed using the data from these two studies, by combining the primary outcomes—urticaria activity score and urticaria severity score—compared with subjects randomized to treatment with cetirizine, subjects randomized to cyclosporine were almost four times (risk ratio = 3.57; 95% CI = 1.45–8.81) times more likely to experience benefit in symptom scores.¹⁹ This provides evidence supporting the therapeutic usefulness of cyclosporine for patients with CUA.

Adverse effects of cyclosporine include hypertension, acute and chronic nephrotoxicity, hyperlipidemia, gingival hyperplasia, hyperkalemia, neurotoxicity, hypomagnesemia, hyperuricemia, and thrombotic microangiopathy.³⁹

In the 2013 update of the Urticaria/Angioedema Practice Parameter,¹⁹ a critical appraisal of the literature supporting the therapeutic usefulness of cyclosporine judged this evidence to be of low quality, based on a number of methodological shortcomings in the aforementioned studies, leading to a weak recommendation for use of cyclosporine for refractory CUA. The weak recommendation does not imply that cyclosporine may not be of benefit in properly selected patients with refractory CUA. Rather, it signifies the need for clinicians to carefully consider whether administration of cyclosporine is favorable from the standpoint of balancing the potential for benefit with the potential for harm and discuss this openly with patients to determine that proceeding with a trial of cyclosporine is consistent with their values and preferences.

Omalizumab

Omalizumab has become the best-studied agent for treatment of refractory CUA and the agent for which the data in support of its efficacy are most methodologically sound. The efficacy and safety of omalizumab have been investigated in several randomized controlled trials.

Ninety subjects were enrolled in a double-blind, placebo-controlled study⁴⁰ in which a single dose of 75, 300, or 600 mg of omalizumab or placebo was administered. Subjects in this study had CUA that was poorly controlled despite treatment with H₁-antihistamines. Subjects who received either 300 or 600 mg of omalizumab exhibited statistically significant improvement in urticaria activity scores compared with placebo.

A second double-blind placebo-controlled study enrolled 49 subjects with CUA and IgE autoantibodies to thyroperoxidase.⁴¹ After 24 weeks, those randomized to omalizumab showed statistically significantly greater reduction in urticaria activity scores; 59% of those randomized to omalizumab were symptom free compared with 14% receiving placebo.

In a third study of CUA subjects poorly controlled on H₁-antihistamines, 323 subjects were randomized to three

subcutaneous injections of omalizumab at 4-week intervals: 75, 150, or 300 mg or placebo, followed by a 16-week observation period.⁴² The primary end point, itch severity score, and other prespecified secondary end points, were significantly improved ($p < 0.001$) after 12 weeks in subjects randomized to 150- and 300-mg doses compared with placebo. Only 10% of subjects randomized to placebo were “hive free” at week 12, compared with 23 and 53%, respectively, who received 150 and 300 mg of omalizumab. However, the rate of serious adverse events was higher in subjects randomized to 300 mg (6%) compared with 150 (1%) or 75 mg (1%) or placebo (3%).

In a fourth randomized, controlled study, 336 of 480 subjects screened for participation, whose CUA remained poorly controlled despite advancement of H₁-antihistamines to four times the conventional dose in combination with H₂-antihistamines and/or an antileukotriene,⁴³ received six injections of omalizumab at 300 mg or placebo on a monthly basis. Subjects maintained their prerandomization regimens of high-dose H₁-antihistamine, H₂-antihistamine, and/or antileukotriene during the treatment period of the study. The primary objective of the study was to assess safety. Efficacy was assessed at 12 and 24 weeks. Statistically significant differences were observed in subjects randomized to omalizumab compared with placebo for itch severity score at 12 weeks ($p < 0.001$) and for other outcome measures at 12 and 24 weeks. No remarkable differences in adverse or severe adverse events were reported for omalizumab compared with placebo.

Although the primary outcome of this fourth study was not an efficacy measure, subjects who were enrolled had poorly controlled CUA despite combination pharmacotherapy and maintained this treatment during study participation. This is an important feature of the design of this study. Subjects enrolled in some of the studies described previously “had remained symptomatic despite the use of approved doses of H-1 antihistamines,”⁴¹ or were categorized as “refractory” based on “persistence of symptoms...despite treatment with cetirizine.”³⁷ The external validity of the findings from these studies can be questioned based on the lack of a protocol for systematic escalation of antihistamine treatment to eliminate those whose condition was not truly antihistamine resistant. In the three randomized trials of cyclosporine cited previously,^{36–38} the comparator treatment was cetirizine at a daily dose of either 10 or 20 mg. This is an important point, because inadequate dose titration of an efficacious comparator treatment can lead to a potentially misleading claim of effectiveness.²⁹ This methodological shortcoming, known as “indirectness,” is one of the reasons the practice parameter on urticaria/angioedema¹⁹ determined that cyclosporine merits a weak recommendation for patients with refractory CUA.

Several key observations emerge from the randomized controlled trials of omalizumab for CUA. Compared with the experience with omalizumab for moderate-severe persistent asthma,⁴⁴ efficacy of omalizumab was observed in study designs that entailed a “one size fits all” approach,^{40,42,43} rather than incremental dosing based on total serum IgE level and body weight. Also, in contrast to the experience in asthma,⁴⁴ many with CUA who benefited with omalizumab did so promptly: within 1–2 weeks.^{40–43} Similar to the experience with asthma, however, there are no validated biomarkers or clinical features that can predict salutary response, and subjects experienced recrudescence of symptoms after stopping omalizumab in association with study termination.

Omalizumab should not be regarded as a first-line agent for management of CUA, similar to its role in patients with asthma, and should be reserved for patients who are antihistamine resistant.¹⁹ Omalizumab is costly⁴⁴ and may be difficult to obtain based on lack of insurance coverage for an agent that is currently approved by the U.S. Food and Drug Administration only for intractable asthma. Omalizumab is associated with less potential for harm compared with other therapeutic alternatives (*e.g.*, cyclosporine) for refractory CUA, but its administration entails the burden of receiving injections on a monthly basis in a medical setting. Many questions—including optimal patient selection and treatment duration—remain concerning omalizumab.

CONCLUSION

In the overwhelming majority of CUA patients, an etiology is not identified and management entails realistic expectations and regular use of medications. Diagnostic evaluation should entail a comprehensive history and physical examination. If no “brown M&M” is found, routine performance of extensive testing is not warranted. Treatment may be prescribed using a “step care” approach,¹⁹ relying on H₁-antihistamines without or with H₂-antihistamines and/or antileukotrienes, as required to achieve control of CUA. When CUA can not be controlled with combination therapy including H₁-antihistamine dose advancement as tolerated, a number of therapeutic options may be considered. The evidence is more methodologically sound with omalizumab than with all other alternative agents shown in Table 2. Omalizumab carries the potential to dramatically improve outcomes in patients with refractory CUA, as well as the means to remedy the somber view of CUA routinely described in review articles^{1,2} for more than the past half-century.

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