

# Utility of routine laboratory testing in management of chronic urticaria/angioedema

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**Background:** Laboratory tests are routinely ordered to identify or rule out a cause in patients with chronic urticaria/angioedema (CUA). The results of these tests are usually within normal limits or unremarkable.

**Objective:** To investigate the proportion of abnormal test results in patients with CUA leading to a change in management and in outcomes of care.

**Methods:** Retrospective analysis of a random sample of adult patients with CUA from 2001–2009.

**Results:** Cases totaled 356: 166 with urticaria and angioedema (AE), 187 with urticaria, and 3 with only AE. Patients were predominately women (69.1%) and white (75.6%), with a mean age of  $48 \pm 15$  years. Abnormalities were commonly seen in complete blood counts (34%) and in complete metabolic panels (9.4%). Among the 1,872 tests that were ordered, results of 319 (17%) were abnormal. Of 356 patients, 30 underwent further testing because of abnormalities in laboratory work. This represented 30 of 1,872 tests (1.60%). Only 1 patient benefited from a subsequent change in management.

**Conclusions:** Laboratory testing in CUA patients referred for an Allergy and Immunology evaluation rarely lead to changes in management resulting in improved outcomes of care.

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## INTRODUCTION

Chronic urticaria/angioedema (CUA) is defined as occurrence of urticaria or angioedema for 6 weeks or longer. The rate of CUA has been estimated to be 0.5 to 1% of the general population.<sup>1</sup> In most cases, no exogenous cause is identified, despite extensive laboratory testing.

The appropriate laboratory evaluation for patients with CUA is an area of controversy about which recommendations differ. Practice Parameters released by the Joint Task Force on Practice Parameters in 2000 endorsed limited laboratory testing: complete blood count (CBC) with differential, urinalysis, erythrocyte sedimentation rate (ESR), thyroid stimulating hormone (TSH), and liver function tests. Thyroid autoantibodies also could merit consideration in selected cases,<sup>2</sup> because thyroid autoimmunity is more frequent in patients with CUA than the general population.<sup>3</sup>

More recent recommendations have advocated ordering fewer laboratory studies for patients with CUA.<sup>4–8</sup> A systematic review of 6,642 patients found that underlying causes for CUA were identified in only 1.6% of cases.<sup>8</sup> Another study by the same authors concluded that, unless the history indicates otherwise, the only useful tests are an ESR and a CBC

with differential to exclude serious underlying illnesses.<sup>8–10</sup> The European Academy of Allergology and Clinical Immunology guidelines also recommend a CBC and ESR or C-reactive protein (CRP) in evaluating chronic spontaneous urticaria. These guidelines strongly advise against costly general screening programs.<sup>11</sup>

We carried out this study to investigate the utility of routine laboratory tests performed in the assessment of patients with CUA. We investigated the rate of abnormal laboratory tests in patients undergoing evaluation for CUA at a tertiary referral center. We hypothesized that few abnormal laboratory test findings would lead to a change in management or clinical benefit.

## METHODS

### Study population

Cases of CUA were chosen using the Cleveland Clinic electronic medical record, Epic (Epic Systems Corp, Verona, Wisconsin). Patients who were assigned ICD-9 codes 708.1, 708.9, or 995.1 for visits at the internal medicine Allergy and Immunology clinics at the Cleveland Clinic main campus and regional medical practices from 2001 to 2009 were selected. This study was approved by the Cleveland Clinic Institutional Review Board.

### Patient selection

Patients were included if they had a diagnosis of CUA with a duration greater than 6 weeks. Patients who had undergone laboratory testing and skin biopsy for CUA at an outside facility were excluded. Patients with acute urticaria (<6 weeks), contact urticaria, or C1 inhibitor deficiency and who were younger than 21 years of age were also excluded.

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### Analysis

Data were extracted from medical records, including demographic characteristics, clinical history, duration of CUA, social history, family history, laboratory tests, and imaging studies, and were entered into Microsoft Excel 2003 (Microsoft Corp, Redmond, Washington). Statistical analysis was performed using JMP version 8.0 (SAS Institute Inc, Cary, North Carolina). Data are reported as mean (standard deviation) and interquartile range (IQR) unless otherwise indicated.

## RESULTS

### Demographic characteristics

A total of 1,072 charts were reviewed: 356 patients fulfilled criteria for inclusion and comprised 166 (46.6%) with both urticaria and angioedema (AE), 187 with urticaria alone, and 3 with only AE. Demographic data are shown in Table 1. Patients were predominately women (69.1%) and white (75.6%). The average age at the time of visit for women was  $47 \pm 15$  years, with symptoms originating at  $43 \pm 17$  years with a mean duration of 12 months (4.00–48.0). Men were slightly older at the time of visit,  $50 \pm 15$  years with symptoms starting at  $48 \pm 16$  years, with a shorter mean duration of 7 months (3.00–43.5).

### Medications

Most patients were taking antihistamines, 324/356 (91.0%) at initial presentation; 66% were second-generation agents, and 39% were first-generation H1 antihistamines. Sixty-seven (18.8%) patients were taking concomitant H2 antihistamines, and 4% were taking doxepin. Sixty (16.9%) were taking oral corticosteroids, 20 (5.62%) were taking an anti-leukotriene, 1 was on topical corticosteroids, and 1 was taking dapsone.

### Laboratory Testing

Results of diagnostic tests obtained are displayed in Figure 1. Abnormalities were commonly seen in complete blood screens (34%) and also in complete metabolic panels (CMPs) (9.4%). Most abnormal CBCs had a slightly elevated or

reduced neutrophil count or a mildly elevated eosinophil count, for which no further workup was pursued. Most aberrant CMPs involved slightly abnormal transaminases or liver function, for which further workup was not pursued. Sedimentation rate was elevated in 17.4% (37/213) of cases. The CRP was abnormal in 2 of 18 (11.1%) patients. Thyroid-stimulating hormone was lower than the normal reference range in 10, elevated above the normal reference range in 12, and normal in 240 of 262 (91.6 %) patients. Among women, 7 were classified as hyperthyroid, 10 as hypothyroid, and 164 as euthyroid. Three men were hyperthyroid, 2 hypothyroid, and 78 euthyroid, corresponding with our overall sex distribution. Antithyroid antibodies were abnormal in 21.6% (77/356) of cases, with this more often observed in women.

Serum-specific immunoglobulin E (IgE) was obtained in 15 patients and was elevated in 4 cases. Immediate hypersensitivity skin testing was performed on 21 patients for CUA, with 14 (66.7%) having negative tests. Three patients underwent skin biopsies with histopathology not consistent with leukocytoclastic vasculitis.

A small number of tests were obtained with unremarkable findings including but not limited to: rheumatoid factor, hepatitis panel (hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibody), peripheral smear, C2, C3, C4, and chest x-ray.

As shown in Table 2, a mean of 6.00 (3.00–7.50) tests were obtained, with 1.00 (0.00–2.00) being abnormal. Forty-three patients had no laboratory tests ordered. Of the 1,872 tests that were ordered, 319 (17%) were abnormal—more commonly in women (244/1312, 18.6%) than men (75/560, 13.4%).

### Outcomes of patients with abnormal tests results that led to a change in management

Of 356 patients, 4 had an abnormal CBC that required further management (Fig 2). One patient had a leukocytosis with a white blood cell count of 12.6 (4.0–11.0 k/ $\mu$ L) and an increased neutrophil count of 73.7 (40–70%) that was attributed to an upper respiratory infection. A repeat white blood cell count was in normal range 3 months later. A second patient had an elevated platelet count of 521 (150–400 K/uL) and was referred to Hematology, where she was diagnosed with essential thrombocytosis. These 2 patients were well controlled on doxepin and a second-generation H1 antihistamine, respectively. The remaining 2 patients had an elevated eosinophil count and monocytosis, respectively, and did not return for follow-up appointments or laboratory work.

Two patients had abnormalities in their complete metabolic panels involving elevated transaminase values: One patient had an alanine aminotransferase of 55 (0–45 U/L), and the other had an alanine aminotransferase of 75 and aspartate aminotransferase of 65 (7–40 U/L). Both were subsequently seen in Gastroenterology and diagnosed with fatty liver disease. Their urticaria symptoms were well controlled on a 2<sup>nd</sup>-generation H1 antihistamine. A third patient had a high

Table 1. Demographic Characteristics of Patient Population

|                                                                  | Total            |
|------------------------------------------------------------------|------------------|
| Number of patients (%)                                           | 356              |
| White                                                            | 269 (75.6)       |
| Age at time of visits (years)                                    | $48 \pm 15$      |
| Age of onset of diagnosis (years)                                | $44 \pm 17$      |
| Duration of CUA (months)                                         | 9.00 (4.00–48.0) |
| Urticaria and angioedema                                         | 166 (46.6)       |
| Urticaria only                                                   | 187 (52.5)       |
| Angioedema only                                                  | 3 (0.84)         |
| Physical urticaria/angioedema syndrome excluding dermatographism | 67 (18.8)        |
| Dermatographism                                                  | 45 (12.6)        |
| History of hyperthyroidism                                       | 5 (1.40)         |
| History of hypothyroidism                                        | 45 (12.6)        |

Abbreviation: CUA, chronic urticaria/angioedema.  
Data reported as mean  $\pm$  SD or median and IQR.

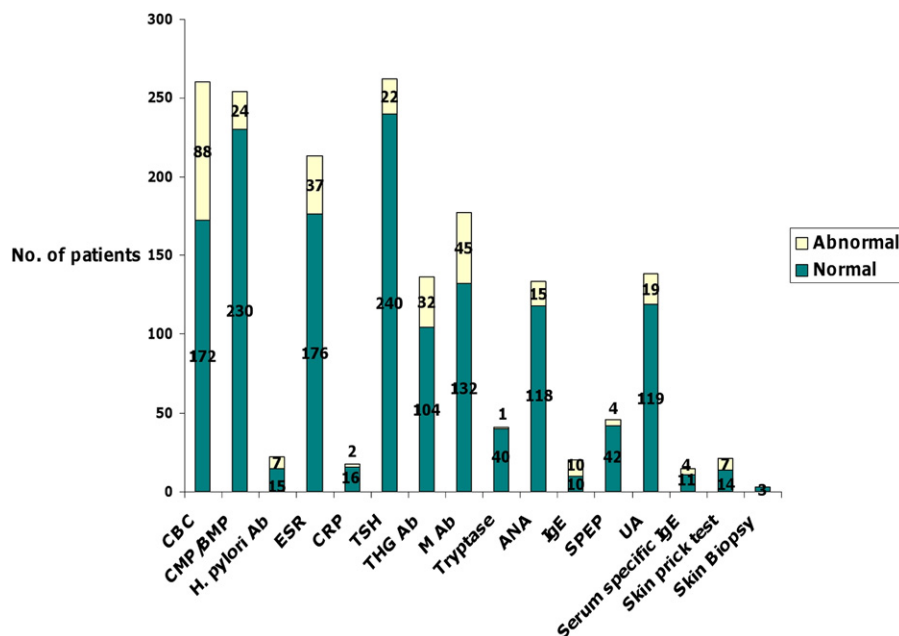


Figure 1. Diagnostic studies ordered in 356 patients with CUA are displayed according to abnormal or normal test results. Overall, 17% of tests ordered were abnormal. Definitions of abbreviations: CUA, chronic urticaria/angioedema; CBC, cell blood count; CMP/BMP, complete/basic metabolic panel; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; THG, thyroglobulin; M, microsomal; ANA, anti-nuclear antibody; IgE, immunoglobulin E; SPEP, serum protein electrophoresis; UA, urinalysis.

serum calcium, 10.7 (8.5–10.5 mg/dL); a follow-up ionized calcium was normal.

In the 22 patients tested for *H. pylori*, 7 (32%) were abnormal. Five received triple or quadruple therapy. Three continued to have urticaria despite this treatment. One patient did not follow-up after therapy. A fifth patient was well controlled before initiating treatment. Among the 2 patients who were not treated for *Helicobacter pylori*, 1 patient was only seen once and was lost to follow-up. The other patient never underwent treatment for *H. pylori*, but her urticaria was well controlled with antihistamines.

Table 2. Summary of Tests

|                                                                                | Total            |
|--------------------------------------------------------------------------------|------------------|
| Total median number of tests done                                              | 6.00 (3.00–7.50) |
| Total median number of tests which were abnormal                               | 1.00 (0.00–2.00) |
| Ratio of abnormal tests/total tests (%)                                        | 319/1,872 (17.0) |
| Ratio of patients with abnormal tests (% all patients)                         | 187/356 (52.5)   |
| Abnormal tests which changed management/total tests (%)                        | 30/1,872 (1.60)  |
| Patients who improved by change in management (% all patients)                 | 1/356 (0.28)     |
| Unknown whether a patient improved after change in management (% all patients) | 6/356 (1.69)     |

Data reported as median and IQR.

One in 37 patients underwent further testing for an elevated ESR of 34 (age adjusted: 0–28 mm/Hr) because of persistent symptoms of urticaria and angioedema despite treatment with cetirizine and ranitidine twice daily and cyproheptadine as needed. A repeat ESR was 24, and results of serum protein electrophoresis, thyroglobulin, and microsomal antibodies were unremarkable.

Thyroid-stimulating hormone was abnormal in 6 of 22 patients. None of these patients had a documented history of thyroid disease. Four patients were minimally hyperthyroid, with TSH values ranging from 0.179 to 0.369 (0.400–5.500 uU/mL); repeat TSH results were normal. A patient with a TSH of 0.287 was only seen once and was lost to follow-up. Another patient with a TSH of 28.7 experienced well-controlled urticaria on a 2<sup>nd</sup>-generation H1 antihistamine before thyroid hormone supplementation was started.

Eight euthyroid patients underwent further workup for elevated levels of thyroglobulin and/or microsomal antibodies ( $n = 12$ ). Six were referred for Endocrinology consultation. A patient with a history of hypothyroidism with a normal TSH but elevated microsomal antibody improved with an increase in dose of levothyroxine from 88  $\mu$ g to 150  $\mu$ g. Previously, her chronic urticaria was well controlled on 175  $\mu$ g of levothyroxine. Three months before her evaluation, she had a myocardial infarction, and her levothyroxine was reduced from 175 to 88  $\mu$ g because of a TSH of 0.103  $\mu$ U/mL, which was similar to previous results. Her urticaria resumed and persisted despite antihistamine blockade. After

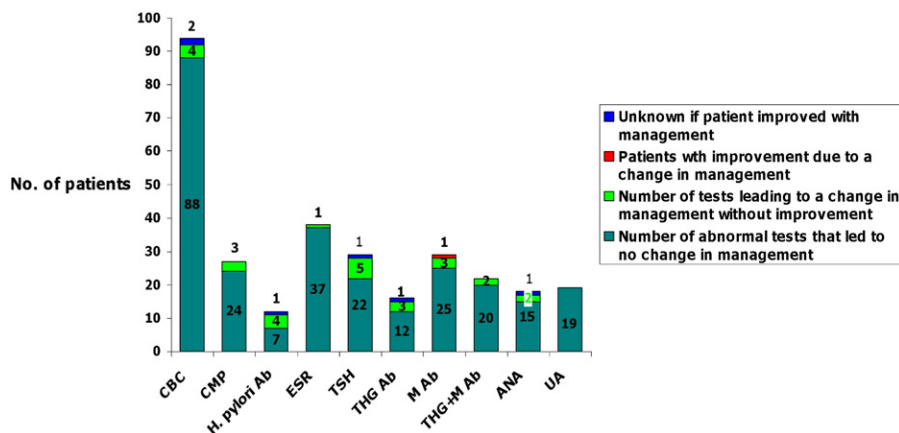


Figure 2. Management outcome of 187 patients with abnormal test results during evaluation of CUA. CRP, serum tryptase, total IgE; SPEP, serum-specific IgE; immediate hypersensitivity skin testing was performed in a small number of patients ( $n < 11$ ), and results were unremarkable (data not shown). Definitions of abbreviations: CUA, chronic idiopathic urticaria or angioedema; CBC, complete blood count; CMP, complete metabolic panel; ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; THG, thyroglobulin; M, microsomal; ANA, antinuclear antibody; UA, urinalysis.

titration of her levothyroxine, her urticaria resolved, and she was able to taper off antihistamines. Three others were told to return for annual examination. Endocrinology consultants did not recommend pursuing further tests for 1 patient, whereas another patient never followed up for consultation. Regarding the 2 patients not seen by Endocrinology, 1 was placed on levothyroxine 150  $\mu\text{g}$  for 2 months with no change in his condition, and the other followed-up with a primary care physician who obtained no further laboratory tests. Except for the patient who improved after levothyroxine was increased, the remaining 7 eventually were well controlled on 2<sup>nd</sup>-generation antihistamine therapy with 1<sup>st</sup>-generation antihistamines as needed.

Two patients had positive antinuclear antibodies (ANAs). The first patient, with an ANA level of 4.7 ( $<1.5$  optical density ratio) and indeterminate antihistones and anticentromeres antibodies, was sent for rheumatology consultation. The patient was reassured and advised to follow-up if needed. The other patient, with an ANA of 2.3 and ESR of 27 (age adjusted: 0–29 mm/hr), was advised to have these monitored in the future. Another patient was diagnosed with monoclonal gammopathy of undetermined significance based on results of serum protein electrophoresis, and was referred to a hematology consultant who labeled these findings as “nonspecific.” These patients achieved well-controlled urticaria with antihistamines taken daily. One patient was found to have an elevated tryptase of 26.7 (1.9–13.5  $\mu\text{g/L}$ ); 6 repeat tryptase determinations were between 15 and 17, leading to no change in therapy.

Changes in management based on abnormal laboratory values leading to consultation or other treatment occurred in 1.60% (30/1872) of tests ordered. Among the 356 patients, only 1 (0.28%)—with a history of hypothyroidism—improved after additional changes in management based on laboratory findings obtained.

## DISCUSSION

We have described the diagnostic evaluation of 356 patients with CUA. In the evaluation of these patients, 1,872 laboratory tests were obtained. Although 17% were abnormal, rarely did such findings lead to a remarkable change in management or clinical improvement. In only 1 case were outcomes of care improved based on results of a laboratory test that was ordered. Our findings support recent recommendations<sup>6–8,11</sup> to limit laboratory evaluation in patients with CUA, so the diagnostic evaluation can serve to rule out an underlying cause for CUA in a cost-effective manner, thereby providing “reassurance value.” More extensive evaluation is not warranted in the absence of features detected by the patient’s history or physical examination that would direct further inquiry.<sup>6, 9,12</sup> Our experience also suggests dose advancement of antihistamines (eg, prescribing 4 times the conventional dose of a 2<sup>nd</sup>-generation agent for at least 4 weeks<sup>13</sup>) may be a reasonable strategy before pursuing more extensive diagnostic evaluation.

Although CBC ( $n = 260$ ), CMP, or basic metabolic panel (BMP) ( $n = 254$ ), ESR ( $n = 213$ ), and TSH ( $n = 262$ ) were the most frequently ordered tests in our study, none resulted in an improvement in patient outcome. Only 1.5% of CBCs, 1.2% of CMP/BMPs, 0.47% of ESRs, and 1.9% of TSHs prompted additional investigation. None of these patients provided a history or had physical examination findings, other than CUA, that would have encouraged ordering these laboratory tests.

Thyroid autoantibodies were found in 21.6% of our patients, which is similar to rates reported by others.<sup>5,14,15</sup> Only 1 patient with a history of hypothyroidism improved while being placed on thyroid replacement therapy, whereas a euthyroid patient with increased microsomal antibodies showed no change in symptoms. Although 17.4% (37/213) of our

patients had abnormal ESRs, only 1 patient underwent additional testing, which did not result in improved outcomes. Four of our patients were diagnosed with *H pylori* and received standard treatment. In none of these cases did the course of CUA improve with therapy.

Among the 30 patients who required additional workup for laboratory abnormalities, 29 achieved control of symptoms on a regimen of H1 and H2 antihistamines and in select cases with the addition of doxepin. Only 1 of these 30 patients benefited from subsequent evaluation. These results reinforce the importance of optimizing medical therapy before performing extensive laboratory investigation. Even if the 6 patients who underwent secondary testing at an outside institution (which was unobtainable for review) were incorporated with the 1 patient whose management led to a better outcome, only 1.97% (7/356) of our patients would have benefited.

Several limitations of our study merit mention. The number of laboratory tests and physician evaluation for CUA were not standardized. Two hundred eighty-nine of 319 tests were not further evaluated; thus, we cannot exclude the possibility that some underlying systemic conditions were missed. Most of these tests were in the abnormal range, but to only a modest or minimal degree; for this reason, they may have been regarded as clinically insignificant. We report a population seen at an academic medical center; for this reason, these findings may not be generalizable to a community practice. However, one would expect our patient population to have more complicated disease, and for this reason the low rate of abnormalities on laboratory studies observed may actually overestimate the rate in community allergy/immunology practice. Our chart review included ICD-9 codes for idiopathic, unspecified urticaria, and angioneurotic edema not elsewhere classified. Only 3 patients had isolated angioedema, which was less than expected<sup>7</sup>; the reasons for this are unclear. A number of patients being seen for angioedema without urticaria have had this related to antihypertensive therapy (eg, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker) and would have been classified as having acute angioedema and for this reason would have been excluded. We also excluded patients whose laboratory testing was performed before being seen for consultation at a referral center. This may have introduced bias by eliminating patients more likely to have had abnormal laboratory tests leading to identification of an underlying etiology. Patients with C1 inhibitor deficiency syndromes were also excluded. None of our patients underwent laboratory tests for basophil histamine release activity or autologous serum skin testing, and we cannot comment on the utility of such testing in the diagnostic evaluation of patients with CUA. Future studies consisting of a prospective, large population cohort would be helpful in addressing these limitations.

Our findings imply that performance of routine laboratory testing in patients with CUA is unlikely to uncover an underlying cause for this condition. The cost and burden of this

testing must be balanced against the low rate of remarkable findings resulting in a change in treatment leading to improved outcomes of care, and the reassurance value of providing patients with the knowledge that CUA is unrelated to an underlying condition.

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