CME review

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Pathophysiology of chronic urticaria
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**Objective:** To review the literature on the pathogenesis of chronic urticaria (excluding physical urticaria).

**Data Sources:** PubMed was searched using the keywords urticaria and either chronic or autoimmune or pathogenesis for articles published from January 1972 to June 2007. All searches were limited to the English language. References from review articles on chronic urticaria were also considered for inclusion in this review.

**Study Selection:** The authors selected relevant and current sources for inclusion in this review.

**Results:** No concise pathogenic mechanism has been identified for all cases of chronic urticaria, although evidence for a serologic mediator that may be autoimmune in nature has been identified in many cases. The activation of basophils and/or mast cells is a central feature in any theory proposed to explain this troubling disease.

**Conclusion:** Further research is needed to better define the mechanism or mechanism(s) responsible for the development of chronic urticaria. Such research will lead to more effective and possibly even curative treatments.


**Off-label disclosure:** Ms Brodell and Drs Beck and Saini have indicated that this article does not include the discussion of unapproved/investigative use of a commercial product/device.

**Financial disclosure:** Ms Brodell and Drs Beck and Saini have indicated that in the last 12 months they have not had any financial relationship, affiliation, or arrangement with any corporate sponsors or commercial entities that provide financial support, education grants, honoraria, or research support or involvement as a consultant, speaker’s bureau member, or major stock shareholder whose products are prominently featured either in this article or with the groups who provide general financial support for this CME program.

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**INTRODUCTION**

Histamine is an inflammatory mediator that induces pruritus, erythema, and edema, which are key signs and symptoms observed in urticaria. Although this is not the only mediator able to induce such effects, it is the one most clearly associated with this disease. As a consequence, much effort has focused on understanding the mechanism(s) responsible for histamine release in chronic urticaria (CU) and determining the source of this histamine. The 2 cells that are presumed to be the source are tissue resident mast cells or circulating and/or tissue-recruited basophils. Historically, physicians focused on the identification of physical causes or allergens to explain persistent hives or urticaria. The removal of these environmental factors was expected to clear or improve urticaria. Although many CU cases have a component of their disease that is triggered by physical agents (e.g., pressure, cold), this typically does not explain the initiation of all of the urticarial lesions or flares and suggests that there may be more than 1 trigger for most patients. Importantly, in most CU cases, no allergen or trigger can be found. These patients with CU are classified as having chronic idiopathic urticaria (CIU), and treatments have focused on symptom control. In the 1990s, scientists discovered a potential autoimmune mechanism for the pathogenesis of CU, which has been referred to as chronic autoimmune urticaria (CAU). Research into IgE and IgE receptor autoimmune responses has dominated the CU pathogenesis literature. We focus our review on the pathogenesis of CU and not physical or acute urticaria. CU has been defined as urticarial or angioedematous lesions that last longer than 6 weeks and have no obvious trigger.

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published from January 1972 to June 2007. All searches were limited to the English language. References from review articles on CU were also considered for inclusion in this review. We selected relevant and current sources for inclusion in this review. We highlight scientific milestones that have introduced the notion that CU may be induced by a serologic mediator such as an autoantibody or histamine-releasing factor (HRF) (which is not an immunoglobulin) and/or by alteration in the basophil or mast cells responsiveness to histamine-releasing agents. There is no widely accepted consensus on clinical criteria for the diagnosis of CAU, although as outlined herein many tests have been used to argue its existence. We hope the scientific community will develop such criteria that will be feasible to perform at both academic centers and in private practice settings, which would undoubtedly lead to better characterization of the differences between CAU and CIU.

STUDIES OF IgE RECEPTOR-MEDIATED HISTAMINE RELEASE

The most popular theory to explain the development of CU is referred to as the autoimmune hypothesis. This notion had its origins in 1924, when Lewis and Grant improved the technique of experimentally creating histamine wheals initially described by Eppinger in 1913. Lewis and Zotterman noted the similarity between the local response of histamine-mediated wheals to dermatographism observed commonly in patients with urticaria. Fifty years later, Ishizaka and Ishizaka concluded that IgE produced by antigen stimulation of B cells attaches to mast cells and basophils and can be cross-linked to cause histamine release. Soon thereafter, CIU patients’ blood basophils were noted by 2 groups in the 1970s to release decreased amounts of histamine after IgE receptor activation. This seemingly confusing result was hypothesized to be due to in vivo activation and is referred to as basophil hyporesponsiveness or hyporeleasability. Basophil hyporeleasability was believed to be due to a defect after IgE crosslinking but before histamine release (eg, a signaling defect). Other groups have noted an absence of skin mast cell IgE receptor hyporeleasability and found that CIU basophils display hyperreleasability to both normal and CIU serum. Vonakis et al recently reported their findings on blood basophil IgE receptor responsiveness in CIU patients. They found 2 basophil phenotypes, CIU responders and CIU nonresponders. CIU responder basophils have a dose response to IgE receptor activation similar to healthy individuals, whereas patients who are CIU nonresponders do not respond to ex vivo IgE receptor activation and have elevated levels of the IgE receptor regulating inhibitory phosphatases and SH2 domain–containing inositol 5-phosphatase types 1 and 2. These basophil functional phenotypes are stable in active disease and appear independent of the presence of autoimmunity factors. Whether these 2 distinctly different basophil phenotypes suggest 2 distinctly different CU mechanisms remains to be seen. Improvement in basophil hyporesponsiveness has been noted in patients who recover from CU. Collectively, this work suggests that basophil hyporesponsiveness is relevant to the pathogenesis of urticaria as either a primary or secondary effect.

SEROLOGIC STUDIES IN CIU: AUTOLOGOUS SERUM SKIN TEST, HISTAMINE RELEASE ASSAY, AND AUTOANTIBODIES

The suggestion that CU may have an autoimmune basis came from the recognition that thyroid autoantibodies and thyroid dysfunction were observed more commonly in patients with CU (Fig 1). The suggestion that a serologic factor is responsible for the pathogenesis of CU has been a dominant theme in the literature for more than 20 years (Fig 1). In 1986, a serologic mediator called HRF was identified in patients with CU using an in vivo skin test called the autologous serum skin test (ASST). Although the mediator in the serum that caused the wheal-and-flare reactions in CU patients could not be detected serologically, Grattan et al discovered that 7 of 12 patients (58%) develop wheal-and-flare reactions (within 30 minutes) at the site of intradermal injection of their own serum. In the 6 patients who were retested within 1 year, the ASST result was negative in patients whose disease had remitted, suggesting that this test result was only positive when the disease was active. In a 1988 study by Grattan et al, column chromatography of autologous serum from ASST-positive patients demonstrated that the predominant fraction responsible for the positive wheal-and-flare response resided in the 10- to 15-kD range. In 1990, Grattan et al realized that the skin pathologic findings of an ASST were similar histologically to an IgE-mediated late-phase reaction secondary to compound 48/80, suggesting that mast cells play a central role in urticaria. In fact, mast cell numbers were reduced histologically in both skin reactions, suggesting that mast cell
degranulation of CU may have occurred. Additionally, both have increased eosinophils and neutrophils within 30 minutes of injection followed by an influx of monocytes. However, evidence supports that numbers of skin mast cells in lesional and nonlesional skin in CU biopsy specimens is similar to healthy controls and consistent with the normal levels of serum tryptase levels seen in CU.

Claveau et al. expanded on this discovery a few years later when they noted that there was more histamine-releasing activity (HRA) (defined by in vitro basophil histamine release) in blister fluids obtained from lesional and nonlesional skin of patients with CU compared with control patients’ skin (10-fold increase of lesional CU skin compared with control skin and 7-fold increase in nonlesional CU skin vs control skin). More HRF was present in lesional vs nonlesional skin as well, but this finding was not statistically significant. Nonlesional skin of CU patients had a normal number of mast cells and histamine content. From this, it was suggested that HRF may act as a control factor for histamine release from skin mast cells. In parallel with the initial reports of serum-induced positive ASST results in CU patients, Gruber et al. reported the presence of human IgG antibodies targeting the Fc region of myeloma IgE in the serum of 3 of 6 patients with CU. This study also observed that there was a dose-dependent histamine release from peripheral blood basophils (of healthy adults) to CU sera. Early studies of serum fractions suggested that ability to induce a positive ASST result was found in the less than 20-kD range, whereas the CU serum fraction most commonly associated with inducing histamine release from normal basophils resided in the immunoglobulin size fractions. Grattan and colleagues followed up these findings and described a serum factor found in the fraction of more than 100 kD that was capable of inducing both a positive ASST and histamine release from donor basophils, which was later termed HRA. These studies culminated in the identification of anti-FceRIα IgG autoantibodies, which Hide et al. found to be the major HRF responsible for histamine release from normal basophils using serum from patients with CU. Interestingly, although all 26 CU patients had a positive ASST result, only 17 had detectable serum HRA that resided in the IgG fraction, providing support for a nonimmunoglobulin HRF. In a small subset of the study patients, more histamine was released when the donor basophils were stripped of IgE using lactic acid, implying that IgE is somehow necessary for release histamine from basophils (Fig 2). Approximately 30% of anti-FceRIα IgG autoantibodies are thought to bind to an epitope in common with IgE binding.

Characterization of the HRA found in the serum samples of patients with CU by Zweiman et al. confirmed previous findings that a factor in the IgG fraction of serum in 30% of CU patients induced histamine release from healthy donor basophils but not from donors with poor anti-IgE-mediated release (nonreleasing basophils). The study by Zweiman et al. also noted that IgE-stripped basophils released more histamine (11/13 patients) when incubated with HRA-positive sera compared with the normal, unstripped basophils (1/13 patients). Thus, in contrast to the study by Grattan et al. in 1991, it can be concluded that a component of the HRA-positive sera binds directly to the IgE receptor (FceRIα). It was also found that HRA levels decrease significantly when the disease remits as previously suggested by the earlier work of Grattan et al. Niimi et al. found that anti-FceRIα IgG autoantibodies stimulate histamine release from human foreskin mast cells (98/163 patients or 60%) as well. They estimated that the ratio of anti-FceRIα autoantibodies to anti-IgE autoantibodies is 4:1.

In the past 10 years, Tong et al. found that 40% of the patients had an autoimmune component to their CU based on human basophil testing. Collectively, studies have suggested that up to 45% of patients have autoimmune features with CU, leaving 55% of patients without an explanation for their CU. This latter group is now referred to as CIU. Soon thereafter, Fiebiger et al. developed a novel enzyme-linked immunosorbent assay (ELISA) to detect IgG anti-FceRIα. This ELISA was a significant advance because it provided a more standardized approach to diagnosis CAU than the ASST or in vitro HRA assay (Fig 3). Fiebiger et al. noted that IgG1 and IgG3 subtypes, which are known to fix complement, were the primary subtypes found in CAU, whereas IgG2 or IgG4, which do not fix complement, were the main IgG subtypes in other autoimmune diseases, such as pemphigus vulgaris, dermatomyositis, systemic lupus, and erythematous and bullous pemphigoid. Using a C5a blockade, Kikuchi et al. demonstrated that the histamine release observed from basophils is augmented by complement and confirmed the
Therefore, anti-FcRIα responsible for IgE binding and cause histamine release. Antibodies bind only unoccupied Fc receptors at the site donors basophils.32 Graphic by John Eckman and Sarbjit S. Saini.

original observation of Fiebiger et al.25 Most recently, IgG1, IgG3, and IgG4 subclasses were purified and found to also activate basophils to release histamine, expanding the potential antibody isotypes discovered by Fiebiger et al. that are able to cause histamine release and thus CAU.27 However, agreement was poor between results of functional HRA assay results and those obtained by immunoblot28 and ELISA.27 Horn et al29 proposed a hypothesis to explain why autoantibodies do not normally cause CAU, which he refers to as “conditional autoreactivity.” In his theory, anti-FcεRIα autoantibodies bind only unoccupied Fc receptors at the site responsible for IgE binding and cause histamine release. Therefore, anti-FcεRIα autoantibodies competitively inhibit IgE from binding to the Fc receptors. In CAU, they proposed that there is an imbalance in anti-FcεRIα vs serum IgE, resulting in greater binding of anti-FcεRIα to the receptor than IgE, leading to autoantibody-mediated basophil or mast cell histamine release.29 This theory would suggest that allergic individuals with high serum total IgE levels might be protected from anti–FcεRIα-mediated CAU, but there is no evidence to support or refute this notion.

CONTROVERSIES WITH THE AUTOIMMUNE HYPOTHESIS

Since the mid-1980s, most publications on the pathogenesis of CU have centered on an autoimmune mechanism, as noted in the timeline (Fig 1). The evidence in support of this theory is the high frequency of thyroid autoantibodies in this group, positive ASST results, the in vitro assays that demonstrate serum histamine release from healthy donors’ basophils (HRA), and/or the identification of IgG antibodies against IgE or FcεRIα in the serum samples of patients with CU that is related to HRA. However, several recent studies have noted that serum samples from patients without CU can also induce positive ASST results and in vitro histamine release from donor basophils.32

Surprisingly, few differences have been noted in clinical presentation,31 histology,33,34 or response to therapy between patients with CAU and CIU. Two studies have found that skin biopsy specimens of wheals from CIU patients with or without serum HRA show a similar pattern of infiltration with eosinophils, neutrophils, basophils, and lymphocytes.33,34 Although the skin infiltrate in CIU resembles that of allergen-induced late-phase reactions, the cytokine pattern in CIU (interleukin 4, interleukin 5, and interferon-γ) indicates a T₄10 response or a mixed T₄1/Th₂ response.34 Currently, the clinical utility of skin biopsy in CIU patients is to exclude alternate diagnoses, such as vasculitis, erythema multiforme, Sweet syndrome, tumid lupus, or urticarial-phase bullous pemphigoid. Some clinicians advocate biopsy to determine if the urticaria has a lymphocyte or neutrophil-predominant dermal infiltrate, given that dapsone is a therapy recognized for its antineutrophil effects.35

Patients with CAU have a greater association with autoimmune thyroiditis. A 2003 study by Bakos and Hillander36 found that 42% (11/26 patients) of CAU patients have antithyroid peroxidase antibodies vs 14% (3/22 patients) in the CIU group. A larger study of 288 CU patients found the frequency of thyroid antibodies to be 27% in CAU vs 11% in CIU patients.37 There are also mixed results with the use of thyroid replacement to treat CIU patients with evidence of thyroid autoimmune, but a direct pathogenic link has yet to be established.38 Although the studies cited in Figure 1 provide strong evidence of a CU mechanism involving anti-IgE and anti-FcεRIα antibodies, several concerns have emerged about this theory.

For example, evidence exists that autoantibodies of similar specificity to CAU (anti-FcεRIα and anti-IgE) can be found in healthy controls and non-CU disease states.25,29,32 The fact that the current assays (ASST, HRA, and ELISAs) are not specific for CAU have raised questions about the autoimmune basis of CAU. It is also unclear why such autoantibodies, if functional, do not lead to generalized anaphylaxis given their presence in circulation with both complement and blood basophils. In many of these studies, basophil release of histamine was studied by incubating basophils from healthy patients with sera of CU patients, which can vary from one basophil donor to the next. Basophils from patients with CU may, in fact, react differently.18,21,25 Fiebiger et al believed this result could be explained by an epitope to the autoimmune body that is hidden on the receptors of some healthy donors’ basophils.

CELLULAR ABNORMALITIES: BASOPHILS AND MAST CELLS

Over the decades a role for blood basophils in the development of CU has emerged. Besides the altered patterns of histamine release observed in CU basophils, Grattan et al39 noted that CU patients had peripheral blood basopenia, which correlated with the patients’ serum basophil HRA. They confirmed this reduction in basophils in a subsequent publication and suggested that this was explained by basophil...
Candida albicans

42 consecutive CU patients had case reports and case series is the notion that infectious agents theory frequently suggested in the literature in a number of most of these have little to no evidence to support them. One CU in addition to or instead of the theories mentioned herein, Although other mechanisms have been proposed to explain INFECTIOUS AGENTS occur independently of serologic or autoantibody mechanisms mentioned herein.

**INFECTIONOUS AGENTS**

Although other mechanisms have been proposed to explain CU in addition to or instead of the theories mentioned herein, most of these have little to no evidence to support them. One theory frequently suggested in the literature in a number of case reports and case series is the notion that infectious agents can trigger the development of urticaria. For example, half of 42 consecutive CU patients had Helicobacter pylori infection detected, and urticaria symptoms improved in 80% of CU patients treated for H pylori, leading to the hypothesis that H pylori may be a causative factor of CU.6 Yet other studies have found no association between the severity of CU and H pylori infection or effective treatment.44,45 A prospective, double-blind, placebo-controlled, crossover study by Schnyder et al50 that involved 46 patients found no relationship between CU and H pylori. In this study, patients had CU and active H pylori infection as determined by a positive carbon 13 urea breath test result. The study patients were divided into 2 arms, receiving either placebo or treatment (amoxicillin or lansoprazole) for 2 weeks. Two months later patients were tested for H pylori infection and treated for 2 more weeks with the reciprocal drug. A final evaluation of all patients was performed 2 months after the second treatment was initiated. This definitive study has led most clinicians to abandon the idea that H pylori induces or exacerbates CU.

Several articles have postulated a link between the yeast Candida albicans, but no double-blind, placebo-controlled study has been performed. In 1971, James and Warin47 found that 32% (32/100) of CU patients were infected with C albicans, which was similar to the percentage observed in the healthy population. Thirty-six percent of the CU patients had positive skin prick test results to C albicans. Unfortunately, this study did not evaluate skin prick test responses to C albicans in healthy controls. The CU subgroup with positive skin test results to C albicans were also more sensitive to traditional allergens. Hepatitis B has been associated primarily with acute urticaria but not CU. A few cases of hepatitis A associated with CU have been reported.48,49 In summary, the evidence that infections can trigger or exacerbate urticaria is largely circumstantial and is worthy of further study.

**CONCLUSION**

Although many studies have suggested an autoimmune mechanism for at least a subset of CU patients, this theory has some inconsistencies and at least half of the CU patients do not appear to have the autoimmune type and are therefore still best characterized as idiopathic. The current autoimmune tests mentioned herein lack specificity for CU. Although simple to perform, the ASST is not the best tool for diagnosing CU for a number of reasons. Namely, a positive ASST result persists even when urticaria remits.50 Additionally, within the group testing positive, the wheal redness and diameter vary widely, and interestingly this reaction peaks after 30 minutes rather than 15 minutes as is observed with classic type 1 allergen.51 One study that found that 58% of CU patients had a positive ASST result also noted that 45% of healthy controls reacted positively.30 In summary, the lack of a gold standard clinical test to define CAU has hampered the advancement of this field. Additionally, the reliance on basophils from healthy donors to define HRA introduces obvious variability and makes it impossible to correlate results across laboratories and to establish a standard. This test does not exclude the possibility that other factors found in serum (such as complement, chemokines, or cytokines) may be the actual trigger. This possibility is supported by the fact that IgG-depleted serum still leads to an active ASST.52 This, coupled with the 1988 study by Grattan et al that demonstrated that the predominant fraction able to produce a positive wheal-and-flare response is between the 10- and 15-kD molecular weight, which is substantially smaller than the molecular weight of immunoglobulins (150 to 190 kD), provides fairly strong evidence for another as yet unidentified HRF in CU serum.13

Finally, some investigators have evaluated CU patients using an autologous plasma skin test (APST) instead of the ASST.53 Asero et al53 found that CU patients more commonly have a positive APST result (86%) than a positive ASST result (53%). The hypothesis proposed to explain this difference is that there may be platelet-derived factors in the plasma (not serum), such as thrombin, bradykinin, and tryptase-like plasma proteases, that may also play a role in the wheal-and-flare skin reaction observed and ultimately in the urticaria itself.53 To date, no studies have compared the APST results of CU patients to healthy controls or patients with other autoimmune diseases, and therefore little can be said about the specificity of this test or in the evaluation of CU patients. Obviously, much more research is needed to determine the pathogenesis of CU so that the medical community can better diagnose, counsel, and treat these patients.

Identifying the pathogenic mechanism(s) for CU may someday lead to predictions about disease prognosis, individualized therapies, and an increased awareness of comorbid diseases. Although the last several decades have resulted in a
much greater understanding of autoimmune, serological, and even cellular factors that may be relevant for the manifestations of CU, this knowledge has not translated into clinical guidelines that help us counsel our patients on disease course or even their best treatment. Currently, the identification of autoimmune markers is not recommended or useful for general clinical practice but is certainly encouraged and commonly used in research studies. It has been suggested that CAU patients are most likely to respond to plasmapheresis or cyclosporine therapies based on theoretical notions but with no side-by-side comparisons of CIU vs CAU patients.54 Because these treatments are expensive, time-consuming, and associated with greater risk than most other CU therapies, they should not be used except in unusual circumstances. Based on current techniques to identify autoantibodies, approximately 30% to 50% of all CU patients would be considered nonautoimmune and therefore best categorized as having CIU. We have little understanding about what the causes are for this group, and we hope future research will pay more attention to this group. With the current pace of research in this area and the use of newer targeted biological agents (eg,omalizumab, rituximab, and/or tumor necrosis factor antagonists) to ferret out the relevance of specific biological pathways, we are hopeful that the next 20 years will provide greater guidance about workup and treatment that will be useful for both patients and clinicians.

REFERENCES


34. Ying S, Ikuchi Y, Meng Q, Kay AB, Kaplan AP. TH1/TH2 cytokines
a. CAU patients are at an increased risk for autoimmune thyroid disease.
b. CAU patients have better prognosis.
c. CAU patients respond better to biologics.
d. CAU patients are at an increased risk for bacterial and fungal infections.
e. CAU patients are at an increased risk for having children with CAU.

5. In 1986, Grattan et al noted that what percentage of CU patient have a positive ASST result?
   a. 12%
   b. 58%
   c. 75%
   d. 92%
   e. 100%

Answers on page 322.