

## Assessment of Chronic Spontaneous Urticaria from Medical Microbiology Background: Review Article

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### ABSTRACT

**Background:** Urticaria is characterized by pruritic, well-circumscribed, variable-sized, erythematous wheals that can appear anywhere on the body. After a few hours, it typically disappears. Wheals, pruritus, and/or angioedema that last for more than six weeks characterise the common skin illness known as chronic urticaria (CU). Between 0.1% and 0.6% of the population suffers with urticaria associated with CU.

**Objective:** Review of literature about chronic spontaneous urticaria from Medical Microbiology Background.

**Methods:** We searched PubMed, Google Scholar, and Science Direct for relevant articles on chronic spontaneous urticaria. However, only the most recent or thorough study was taken into account between February 2013 and February 2022. The authors also evaluated the value of resources culled from other works in the same genre. Therefore, documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

**Conclusion:** Despite chronic spontaneous urticaria (CSU)'s low mortality rate, the disease's abrupt onset of varying symptoms over time and its chronic nature has a major negative effect on patients' health-related quality of life. Fatigue, soreness, disrupted sleep, and lack of focus are also typical symptoms, which are often linked to the persistent itching that comes with urticaria. Urticaria is an allergic reaction characterized by the development of angioedema, wheals (hives), or both. The severity of the illness must be noted in the patient's history, angioedema, dermatographism, and other systemic symptoms how often they occur (abdominal discomfort, joint pain, and fever), in addition to the duration of the illness.

**Keywords:** Chronic spontaneous urticarial, Medical microbiology.

### INTRODUCTION

Common symptoms of chronic urticaria (CU) include wheals, pruritus, with or without angioedema, and a duration of at least six weeks. A quarter of all occurrences of urticaria can be attributed to CU, with an incidence of 0.1% to 0.6% <sup>(1)</sup>. When treating acute urticaria (AU), a thorough patient history is generally used to pinpoint potential triggering variables like food or drugs. By avoiding the aggravating variables, AU's course can be controlled, and it is characterized by quick reactions to symptomatic relief. However, in around 80% of CU patients, neither the underlying cause nor the pathophysiology of the condition are known. Chronic spontaneous urticaria is the diagnosis for those people whose urticaria manifests as without clear external stressors <sup>(2)</sup>.

In chronic spontaneous urticaria (CSU), itchy wheals and/or angio-oedema develop suddenly and without provocation. Wheals are temporary, varyingly sized, and irritating or burning bumps on the skin's surface. Wheals show up at the same time as localized skin responses and go away by themselves (often over the course of several hours). Rapid, severe, deeper, and sometimes painful swellings of the subcutis and lower dermis are known as angio-oedemas. They are slower to resolve than wheals and can linger anywhere from a few hours to a few days <sup>(3)</sup>.

#### Aetiopathogenesis of CSU:

##### a) *Type IIb autoimmunity:*

CSU patients who test positive for ASST have a greater rate of positivity than the general population.

Anti-IgE or anti-high-affinity FcRI antibodies are found in the blood of about 40% of CSU patients. It's more likely that people will have anti-Fc RI antibodies than the other kind. Autoantibodies to the FcRI receptor on dermal mast cells and basophils can produce IgE-independent, sustained activation and degranulation of both cell types. However, IgG-anti IgE antibodies attaching to and crosslinking IgE attached to receptors on mast cells and basophils may activate and degranulate these cells <sup>(4)</sup>.

When bound to free FcRI, IgE specific for high-affinity IgE receptors can either induce cross-linking of the receptor with its antigen-binding fragment or cause mast cell degranulation when linked to the receptor by the Fc domain <sup>(5)</sup>.

The prevalence of several other autoimmune illnesses is higher among CSU patients. These include rheumatoid arthritis, diabetes, hypothyroidism, hyperthyroidism, and Sjogren's syndrome among others. Patients with CSU frequently have IgG anti-thyroid antibodies <sup>(6)</sup>. TPO-specific IgE antibodies have also been detected, though <sup>(6)</sup>, anti-IgE medication may benefit CSU patients <sup>(7)</sup>.

Several autoimmune disorders (AIDs) have been linked to CSU, these diseases tend to be chronically inflammatory in nature, involve a wide variety of cells and mediators, manifest in a wide variety of tissues, and result in substantial morbidity and mortality, especially in women between the ages of 40 and 50 <sup>(6)</sup>.

If an autoimmune aetiology were to be hypothesised, the T helper cytokine profile associated

with Th17 would seem to be the most likely one to be implicated. Maintaining, sustaining, and activating Th17 cells all require IL-23. In addition to producing TNF-alpha, IL-17, IL-6, IL-8, IL-22, and IL-23, Th17 cells also secrete a plethora of additional cytokines<sup>(8)</sup>. Patients' blood and skin biopsies contained much higher levels of IL-6 than any other cytokine examined at CSU. The synthesis of IL-6 involves multiple types of immune cells, including B cells, Th17 cells, eosinophils, and innate immune cells<sup>(9)</sup>.

In the acute phase of inflammation, hepatocytes and IL-6 combine to generate CRP and fibrinogen. Chemotaxis and a more reactive phenotype in MCs are two additional effects of IL-6, which also promotes MC proliferation<sup>(10)</sup>.

#### **b) Type I autoimmunity (autoallergy):**

Hypersensitivity of type I, IgE-mediated, to selfantigens is known as "autoimmunity," and it can provoke the degranulation of basophils and mast cells. IgE antithyroid peroxidase (anti-TPO) antibody levels are elevated in patients with CSU compared to healthy individuals. Several skin conditions, such as atopic dermatitis and bullous pemphigoid, have been associated to autoallergic activation of mast cells<sup>(4)</sup>. One possible cause of these conditions is the activation of cutaneous mast cells by IgE bound to homologous antigens present on the skin. However, TPO can be released from the thyroid and circulate in the body, where it can bind to cells via the FcR1 receptor. Because thyroid peroxidase (TPO) has extracutaneous manifestations, unlike many other autoimmune skin illnesses, CSU's symptoms are not just limited to the skin. Basophil degranulation in the presence of TPO antigen in vitro has been shown to be triggered by anti-IgE TPO antibodies, suggesting that these antibodies have a role in CSU pathogenesis<sup>(11)</sup>.

#### **Clinical features of CSU:**

Wheals (hives) and angioedema, or both are symptoms of urticaria, a condition characterized by the occurrence of any or all of these symptoms<sup>(12)</sup>.

#### **• The wheal in urticaria patients often has three characteristics:**

1. A variable-sized centre swelling that is virtually always surrounded.
2. An itchy or occasionally burning feeling.
3. Brief normal skin appearance should return in 30 minutes to 24 hours at the outside<sup>(12)</sup>.

#### **• Two characteristics of angioedema in urticaria patients include:**

1. Reddening and swelling of the lower dermis, subcutis, or mucous membranes that occurs suddenly and is easily observable.
2. Occasionally pain instead of itch.
3. Inflammation and reddening of the subcutaneous tissue or mucous membranes that develops suddenly and is quite noticeable<sup>(12)</sup>.

#### **Urticarial activity score:**

The urticarial activity score (UAS) is a likert-type symptom intensity scale that combines three measures of urticarial illness severity (itch, presence, and amount of wheals) into a single daily score between 0 and 6. (From 0 to 3). Top dermatologists, allergy doctors, and asthma specialists in Europe all recommend it<sup>(13)</sup>. The UAS has been applied to routine clinical practice and numerous controlled clinical investigations. It was particularly approved for use in tracking and monitoring chronic urticarial activity<sup>(14)</sup>.

#### **Diagnostic workup:**

##### **1-Proper history taking:**

It is important to get a complete medical history that includes details like how long the illness has lasted, how often attacks with angioedema, dermatographism, or systemic symptoms have occurred, and how severe they have been<sup>(15)</sup>.

##### **2-Total serum IgE Level:**

According to recent studies, CSU patients have higher total IgE levels than healthy people. However, compared to individuals with allergies or atopic illnesses, those with CSU have lower total IgE levels<sup>(16)</sup>. According to **Schoepke et al.**<sup>(17)</sup> autoimmune CSU had significantly lower levels of total IgE serum level than non-autoimmune CSU<sup>(18)</sup>.

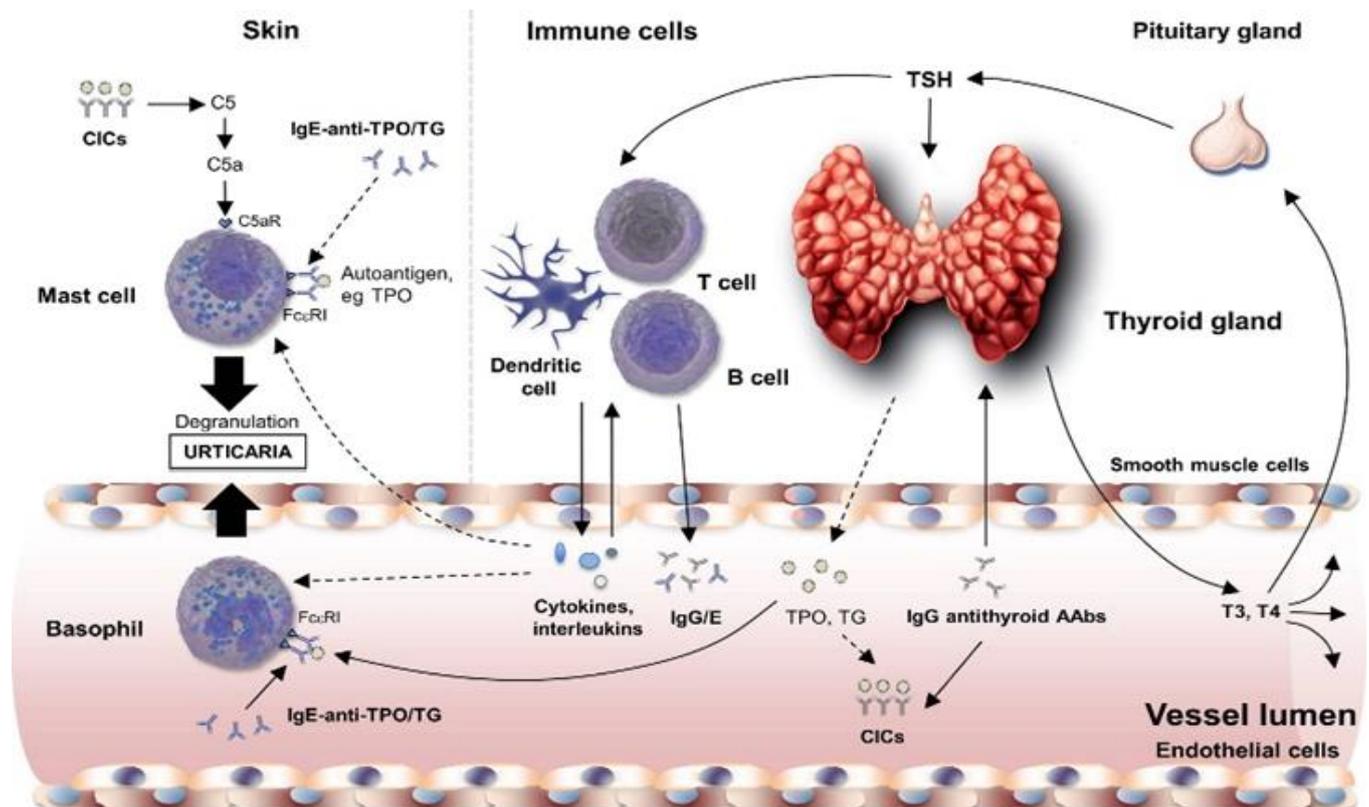
##### **3-Differential Blood Count, CRP, and ESR:**

In the absence of a clear cause for the urticaria symptoms, a differential blood count and CRP or ESR are all that should be performed<sup>(19)</sup>.

C-reactive protein (CRP) was found to be elevated in patients with CSU, especially those with positive ASST, and to have a strong correlation with other inflammatory markers including blood leukocyte/neutrophil counts, erythrocyte sedimentation rate (ESR), serum levels of IL-6, and disease activity in a number of clinical trials<sup>(20)</sup>. Blood levels of CRP were also found to be significantly related to CSU activity or severity in the majority of trials. Most studies have linked C-reactive protein to additional markers of CSU activity including as D-dimer, MMP-9, and IL-6. Therefore, CRP could be utilized as a diagnostic to monitor individuals with CSU and CRP levels may be an indicator of CSU activity<sup>(21)</sup>.

##### **4-Thyroid function tests and thyroid autoantibodies:**

Antithyroid IgG AAbs raise the threshold at which MCs become activated. Rumblyrt and others claim that when MCs experience inflammation in the thyroid, it leads to a systemic inflammatory response and lowers their stimulus tolerance. IgG antithyroid AAb synthesis may be triggered by TSH via stimulation of cytokine production<sup>(6)</sup>.



**Figure (1):** Possible shared etiology between autoimmune thyroid disorders and chronic spontaneous urticaria <sup>(6)</sup>.

### 5- Skin prick test (SPT):

Allergy rhinitis, atopic eczema, acute urticaria, and food allergies are all examples of IgE-mediated type I allergic reactions, and the skin prick test (SPT) is the gold standard for detecting these conditions. Allergy sensitivity can be evaluated with SPTs, and immunotherapy plans can be developed based on the results <sup>(22)</sup>. The SPT is an effective method for diagnosing urticaria since many patients feel relief after avoiding the allergen for which a positive result is obtained <sup>(23)</sup>.

### SPT approach recommended:

Patients are instructed to refrain from using antihistamines three days previous to the test and from using corticosteroids fourteen days prior to the test. One week before to the test, the patient is instructed to stop using any tricyclic antidepressants or mast cell stabilisers. Patients are advised to discontinue the use of any topical steroid or immunomodulatory creams on the testing region one week prior to the test. The test is performed on a small sample of healthy skin. The volar aspect of the forearms is where the test is typically administered. To begin, both a negative control (buffer saline in glycerol) and a positive control (histamine phosphate, 10 mg/mL) are utilized. After that, allergens are applied to the forearm of each subject <sup>(23)</sup>.

Aeroallergen positive SPT is frequently found in CSU participants, but not all CSU subjects have sensitization. H1 antihistamines can suppress skin reactivity and prevent SPT responses for up to 5 days,

producing false-negative test findings. Consequently, it's probable that the rate of positive SPTs is larger than what has been reported <sup>(24)</sup>.

### 6-Autologous serum skin test (ASST):

The most reliable human clinical test for determining in vitro basophil histamine-releasing activity is the autologous serum skin test (ASST). It looks for the presence of FcεRI and/or IgE autoantibodies in the bloodstream and measures their functionality. Both the sensitivity and specificity of ASST are quite high, at 70%. Serum FcεRI autoantibody levels are highly linked with urticaria disease activity <sup>(15)</sup>.

### Technique for autologous serum skin testing:

After drawing 5 mL of blood from a vein, the blood is placed in sterile vacutainers and left to coagulate at room temperature for 30 minutes. This process does not involve the use of a clotting accelerator. A medical lab receives the serum and spins it in a centrifuge for 15 minutes at 2,000 revolutions per minute. It is important to provide a space of at least three centimeters between the injection sites of 0.05 mL of autologous serum and 0.9% sterile normal saline when performing the procedure on the unaffected volar aspect of the forearm. After thirty minutes, we will examine the wheals that have formed at each injection point. If the serum-induced wheal at 30 minutes was 1.5 mm or more than the saline-induced response, then the ASST was considered to have produced a favourable result <sup>(15)</sup>.

### 7-Novel biomarkers:

Heat shock proteins (Hsp) have recently received attention for their complicated involvement in inflammation and immunity, owing to their potential to increase cytokine production and adhesion molecule expression, as well as function as regulators of cell-mediated and humoral immune responses and complement activation. Patients with CSU had higher levels of Hsp70 in their blood and tested positive for anti-Hsp70 antibodies<sup>(25)</sup>.

Hsp70 appears to perform a dual protective and pro-inflammatory role by stimulating the NF-kappaB pathway and the IL-6 signaling system. While, also aiding in anti-inflammatory immunoregulatory T-cell responses. Anti-Hsp70 antibodies may trigger pro-inflammatory pathways, and it has been hypothesized that Hsp70 functions as an autoantigen in CSU, evoking cell-mediated and humoral immune responses. Patients with moderate to severe CSU had higher levels of anti-Hsp70 antibodies and plasma Hsp70 concentration<sup>(20)</sup>.

### Advanced oxidation protein products (AOPPs):

Additionally, it has been suggested that oxidative stress influences enzyme activity and triggers the production of pro-inflammatory cytokines, which both contribute to CSU pathophysiology. Their consequences appear to be caused by insufficient antioxidant defences against reactive oxygen species<sup>(20)</sup>.

AOPPs have recently been studied as potential new oxidative stress indicators in CSU. According to **Nettis et al.**<sup>(26)</sup>, CSU patients have significantly greater levels of AOPPs<sup>(26)</sup>.

### 8- Basophil activation test (BAT):

Single-cell analysis of the basophil population before, during, and after stimulation with allergens or controls is made possible by BAT, thanks to flow cytometry. Whole blood is frequently used for performing BAT. Basophil activation can be identified by the overexpression of specific surface proteins, with CD63 being the most often utilised activation marker<sup>(27)</sup>.

IL-39 has the ability to upregulate CD203c, which is expressed on resting cells and is elevated a little earlier than CD63. While, CD164 and CD13 colocalize with CD203c in vesicles different from these, CD107a and CD107b colocalize with CD63 in secretory lysosomes. Additionally, CD45 and CD18/CD11b1 upregulation can be seen, but they are not nearly as dichotomous as the upregulation of CD63<sup>(28)</sup>.

CD63 is a tetraspanin found in the secretory lysosome membrane of basophil granulocytes and mast cells. It's a 4-transmembrane protein implicated in the generation of exosomes and the rearrangement of cell membranes. It is especially useful as a biomarker of basophil activation, albeit the precise nature of its role in these

processes is yet unclear. Histamine secretion into the cell supernatant is strongly and directly correlated with basophil CD63 surface expression<sup>(29)</sup>.

### CONCLUSION

Despite CSU's low mortality rate, the disease's abrupt onset of varying symptoms over time and its chronic nature has a major negative effect on patients' health-related quality of life. Fatigue, soreness, disrupted sleep, and lack of focus are also typical symptoms, which are often linked to the persistent itching that comes with urticaria. Urticaria is an allergic reaction characterized by the development of angioedema and wheals (hives), or both. The severity of the illness must be noted in the patient's history, angioedema, dermographism, and other systemic symptoms how often they occur (abdominal discomfort, joint pain, and fever), in addition to the duration of the illness.

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