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Review

Clinical phenotypes and biomarkers in chronic urticaria

Aray Batyrbayeva [a,b], Zhanat Ispayeva [b], Marat Pashimov [a], Jamilya Kaibullayeva [a], Madina Baidildayeva [a,*], Uldana Kapalbekova [a], Elmira Tokmurzayeva [a], Olga Plakhotina [a], Arailym Maldybayeva [a], Asem Salmanova [a], Leila Kuandykova [a], Kamila Turebekova [a]

[a] "Research Institute of Cardiology and Internal Diseases" JSC, Almaty, Kazakhstan
[b] Kazakh National Medical University named after S.D. Asfendiyarov, Almaty, Kazakhstan

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ABSTRACT

The medical field faces considerable challenges in treating chronic urticaria (CU), which includes both chronic spontaneous urticaria (CSU) and chronic inducible urticaria, owing to its varied nature. The complexity of this condition stems from multiple factors: varying disease mechanisms, different ways in which symptoms manifest, and inconsistent treatment outcomes. Although both forms of CU display hives that persist beyond six weeks, they have distinct causes and progression patterns. This study examines CSU specifically, exploring its various manifestations and associated biological indicators. Currently, there is a pressing need to identify reliable, accessible biomarkers for CSU to enhance diagnosis and develop targeted treatments. Better insights into how specific disease patterns are related to biological markers would significantly improve our understanding of CSU development and enhance patient treatment approaches.

1. Introduction

Chronic spontaneous urticaria (CSU) is a skin inflammation condition characterized by the unexpected occurrence of hives and/or angioedema persisting for 6 weeks or longer. Unlike chronic inducible urticaria (CIndU), which is triggered by specific factors such as temperature changes or urticarial vasculitis, a rare condition requiring biopsy confirmation, CSU occurs without clear external triggers. Various factors can worsen CSU symptoms, including psychological stress and the use of NSAID medications. Managing these triggers can help reduce symptom flare-ups [1,2]. The condition often occurs alongside other health issues, including thyroid disorders (affecting up to 57.4 % of patients), rheumatic conditions (up to 2.5 %), allergic conditions such as rhinitis (up to 18.8 %) and asthma (up to 10.6 %), and mental health issues such as depression and anxiety (up to 65 %), which often develop as a consequence of living with CSU. The condition affects between 0.02 % and 2.7 % of adults globally. Treatment typically begins with second-generation H1 antihistamines, but over half of patients do not achieve adequate symptom control. When symptoms persist, up to 75 % of patients experience limited or no relief even with increased dosing. Omalizumab, an anti-IgE antibody, is prescribed for antihistamine-resistant patients, although 12–34 % of patients do not respond to standard doses, and some patients show delayed responses in both clinical trials and real-world settings [3,4]. The underlying disease mechanisms of CSU are historically unclear. While mast cell and basophil activation are known to be central to this condition, other factors, such as autoantibodies, cellular infiltration, and activation of coagulation and complement systems, are thought to contribute, although their exact roles need further investigation. CSU patients can be categorized by their phenotypes (observable clinical characteristics) [5,6]. Understanding these distinct disease subtypes may help predict outcomes and, with new treatments in development, could enable more personalized therapeutic approaches in the future.

2. Chronic spontaneous urticaria phenotypes

The symptoms of chronic spontaneous urticaria (CSU) can manifest in different ways among patients. Approximately 30–50 % of individuals experience only hives, whereas 33–50 % suffer from both hives and deep tissue swelling (angioedema). A smaller group, approximately 10 % of patients, presented with angioedema as their sole symptom. A significant clinical pattern involves CSU occurring alongside chronic inducible urticaria (CIndU). Among the CIndU types, skin writing (dermatographia) and cholinergic urticaria are the most common, each affecting

* Corresponding author at: "Research Institute of Cardiology and Internal Diseases" JSC, Almaty, Kazakhstan.
E-mail address: madinabaidildaeva707@gmail.com (M. Baidildayeva).

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approximately 5 % of the general population [7,8]. Additional forms of CIndU include reactions triggered by cold exposure, sustained pressure, vibration, water contact, and sun exposure. Multiple elements influence how patients with CSU respond to treatment. Poor response to second-generation antihistamines is often linked to high initial UAS7 scores, the presence of concurrent CIndU, and prior steroid therapy. Patients who do not respond well to antihistamines are more likely to visit emergency rooms, have relatives with CSUs, and experience sleep problems. Additionally, individuals with severe symptoms and reduced quality of life typically show limited improvement with omalizumab treatment. Understanding these factors can guide treatment selection. The response to treatment varies on the basis of CSU subtype. Type I CSU patients generally respond well to omalizumab, whereas type IIb CSU patients typically have a poor response to both antihistamines and omalizumab [9,10]. In cases where patients have both type I and type IIb CSU, their response to omalizumab is often delayed. Patients who do not fit either type I or type IIb categories usually respond poorly to omalizumab and share certain immune characteristics, such as reduced IgE levels, with those who show delayed treatment response. Several factors indicate a longer disease course in CSU, including the simultaneous presence of CIndU, intense symptoms, swelling, and type IIb CSU. Research has shown that among CSU patients who initially achieved remission, those who experienced disease return (27 %) had significantly longer illness durations (96 months versus 36 months) than those without recurrence. Similarly, patients with concurrent angioedema (57 %) experienced longer disease periods (50 months versus 35 months) [11,12]. Type IIb CSU patients typically face both more severe symptoms and extended illness duration. Several indicators suggest a less favorable outlook, including repeated CSU episodes, development later in life, positive serum autoreactivity tests (ASST and CD63), and accompanying CIndU. A comparative study revealed that patients with concurrent CIndU were notably younger, developed symptoms earlier, had longer-lasting illness, and were more prone to type I CSU than were those without CIndU. Approximately 30 % of CSU patients show increased sensitivity to NSAIDs, known as NSAID-exacerbated cutaneous disease. However, when comparing severe CSU patients who do not respond to second-generation antihistamines, research has revealed similar proportions of type I and type IIb CSU patients among both NSAID-sensitive and NSAID-tolerant groups [13,14].

3. Classification of chronic urticaria

CSU manifests in diverse ways, resulting in several identifiable patterns of disease. Patients may show features of multiple patterns simultaneously, as these patterns often overlap. Disease classification typically considers several factors, such as the type of autoantibodies present, whether swelling occurs, associated health conditions, and how patients respond to different treatments. This discussion examines the main clinical patterns of CSUs and their associated biological markers [15,16].

A. Autoimmune chronic spontaneous urticaria

This form of CSU develops when the body produces antibodies that attack either the IgE receptor (FcεRI) or IgE molecules themselves. When these self-targeting antibodies activate mast cells, they release histamine and other substances that cause the characteristic skin to welcome and swell. Doctors often use the autologous serum skin test (ASST) to identify this type. During this test, injecting a patient's own serum under their skin may produce a welt, indicating the presence of these problematic antibodies. However, the ASST is not always reliable; some patients with immune-mediated CSU may test negative, so doctors need to consider other types of clinical evidence as well. Several biological markers help identify this form of CSU. Interestingly, these patients often have reduced total IgE levels, despite IgE playing a key role in the disease process. Scientists believe that antibodies targeting the IgE receptor may be more important than overall IgE levels in causing symptoms [17,18]. Many patients also present elevated levels of anti-thyroid peroxidase antibodies (anti-TPO), reflecting a common connection with thyroid autoimmune conditions. Another useful diagnostic tool is the basophil activation test (BAT), which measures how certain white blood cells respond to stimulation. A positive result revealed increased CD63 protein expression on basophils, suggesting the presence of activating autoantibodies. These patients typically have lower numbers of both basophils and eosinophils in their blood, indicating immune system disruption. Recent research has identified antibodies against tissue transglutaminase 2 (TG2) as potential markers in some cases. While this finding might represent a distinct subtype of immune-mediated CSU, more research is needed to understand its significance and relationship with other disease markers. Continued research into these various markers and the development of more accurate testing methods will help improve diagnosis and patient classification [19,20].

B. Nonautoimmune chronic spontaneous urticaria

Nonautoimmune CSU distinguishes itself from negative ASST results and lacks autoantibodies in diagnostic testing. Unlike its autoallergic counterpart, the mechanisms behind nonautoimmune CSU remain more elusive, encompassing multiple factors such as genetic components, external triggers, and disrupted inflammatory processes. While autoantibodies are absent, other immune-related mechanisms may still contribute to this condition, including shifts in cytokine patterns and immune cell activity. The identification of diagnostic markers for nonautoimmune CSU presents ongoing challenges, with fewer validated biomarkers than those for autoallergic CSU. Research has revealed heightened levels of general inflammatory indicators, including CRP. Studies have also reported increased D-dimer concentrations, suggesting the potential involvement of blood clotting processes, although the precise relationship requires further study [5,14]. Various cytokines likely play important roles as well. Recent studies have highlighted the potential significance of intestinal bacterial imbalance in nonautoimmune CSU development. Research has revealed alterations in gut bacterial populations, specifically increases in inflammation-promoting bacteria but decreases in beneficial anti-inflammatory species. These bacterial changes may enhance systemic inflammation and worsen urticaria symptoms, although researchers still need to establish a definitive causation. The current limitations in biomarker identification for nonautoimmune CSUs highlight the necessity for additional research. Future investigations should focus on discovering specific diagnostic indicators and understanding disease mechanisms. Advanced analytical approaches, such as metabolomics and other comprehensive molecular studies, may reveal new biomarkers that reflect the complex nature of the condition and could improve diagnosis and treatment selection [21,22].

C. Chronic spontaneous urticaria with angioedema

Swelling in deeper tissue layers, known as angioedema, often appears alongside the CSU. Although not considered a separate form of the condition, the occurrence of angioedema may indicate distinct clinical patterns and vary in therapeutic outcomes. Patients experiencing both conditions typically report more intense symptoms and decreased quality of life. Scientists have yet to fully grasp the exact mechanisms causing angioedema in CSU patients, although it might involve distinct inflammatory routes or cellular responses compared with cases without angioedema. Additional studies are needed to identify specific biological markers linked to angioedema in the CSU and determine whether its presence should influence treatment approaches [18,23].

D. Chronic spontaneous urticaria with comorbidities

CSU frequently manifests with other health conditions, including allergic disorders (such as asthma, hay fever, and eczema), autoimmune conditions, thyroid problems, and mental health challenges. These accompanying conditions can markedly affect disease progression, treatment success, and long-term outcomes. Each associated condition may show distinct biological markers; allergic conditions might show increased total IgE or serum sFcRI levels, whereas thyroid issues could present with modified anti-TPO measurements. Similarly, autoimmune

conditions often involve elevated levels of inflammatory markers. Mental health factors can influence symptom intensity and treatment effectiveness. A thorough understanding of these disease associations and their corresponding biological indicators is essential for developing personalized treatment plans [3,24].

E. Chronic spontaneous urticaria with H1-antihistamine resistance

Approximately half of CSU patients show limited improvement with regular H1-antihistamine treatment. This treatment resistance likely stems from complex inflammatory processes beyond histamine involvement. Research indicates that higher D-dimer levels and elevated neutrophil-to-lymphocyte ratios might predict a poor response to antihistamines, suggesting that both blood clotting processes and neutrophil-driven inflammation may contribute to treatment resistance. More investigations are needed to understand the underlying causes of antihistamine resistance and discover additional predictive markers [25,26].

F. chronic spontaneous urticaria with responses to specific therapies

Different CSU subtypes show varying degrees of success with specific treatments, such as omalizumab and cyclosporine. This treatment variability emphasizes the need to identify reliable biological indicators that can predict treatment outcomes. Research has shown that positive results from autologous serum skin testing (ASST), basophil activation testing (BAT), and increased basophil CD203c expression may indicate better responses to omalizumab. For cyclosporine, factors associated with better outcomes include longer disease duration, greater symptom severity, and elevated BAT and D-dimer levels. These findings suggest that different biological markers might predict responses to various treatments. Continued research to identify such predictive markers is crucial for developing more effective, personalized treatment approaches, particularly given the significant impact of CSUs on patients' daily lives [27,28].

4. Endotypes of chronic spontaneous urticaria

Chronic spontaneous urticaria manifests in several forms: Type I, Type IIb, combined Type I/IIb, and variants that do not fit either category. In type I (autoallergic) and type IIb (autoimmune) CSUs, mast cells are activated when IgE and IgG autoantibodies bind to and trigger FcεRI receptors. For type I CSU, the reaction occurs when autoallergens combine with IgE antibodies to stimulate FcεRI, triggering mast cell and basophil responses. Scientists have discovered over 200 proteins that can act as autoallergens in CSU patients, including IL-24, double-stranded DNA, tissue factor, thyroglobulin, and various other compounds. Research indicates that Type I CSU affects between 38 % and 58 % of patients. In type IIb CSU, the primary mechanism involves IgG autoantibodies targeting either FcεRI or IgE molecules already bound to FcεRI. When strict diagnostic criteria involving three positive tests are used, approximately 8 % of CSU patients show Type IIb characteristics, although less stringent criteria suggest that this percentage could be greater. Among the IgG subtypes, IgG1 and IgG3 are the main actors in complement activation and mast cell stimulation, with IgG4 playing a minor role. IgG2 shows no significant activity in this process [13,18]. While most patients exhibit either Type I or Type IIb CSU, approximately 7 % show characteristics of both types. Recent studies suggest that Type IIb patients frequently have concurrent Type I features, whereas the reverse is less common. Researchers hypothesize that type I CSU might evolve into type IIb CSU over time as patients develop additional autoantibodies, although more research is needed to confirm this pattern. A significant portion of CSU patients (approximately 41 % in one study) did not fit either the Type I or Type IIb classification. These cases may involve pathways independent of FcεRI receptor activation. Pathways independent of FcεRI may function either alongside established autoimmune mechanisms or operate independently. Blood Clotting and Complement System Involvement Approximately half of severe CSU patients show activated blood clotting factors. In the skin of CSU patients, eosinophils produce high levels of tissue factor, which triggers the formation of serine protease-active clotting factors. This process creates thrombin, which activates mast cells through protease-activated receptors [29,30]. The leakage of plasma containing these factors may also trigger skin mast cells and basophils. CSU patients present elevated IgE and IgG antibodies against tissue factor (1.4- and 1.6-fold higher than normal), suggesting connections between clotting and immune responses. By producing C5a and C3a complement components, active clotting factors and plasmin can stimulate mast cells and basophils. Compared with healthy individuals, CSU patients display higher blood levels of C5a. C5a production also occurs during fibrinolysis or when specific antibodies bind to mast cells and basophils. Scientists are still determining whether these processes directly cause CSU or are secondary effects of inflammation. The MRGPRX2 receptor enables non-IgE activation of various immune cells. It responds to neural peptides such as cortistatin and substance P [31]. Studies have shown that CSU patients have heightened skin sensitivity to MRGPRX2 triggers and increased receptor expression, particularly in severe cases. When the MRGPRX2 and IgE pathways are activated together, they can enhance mast cell responses and histamine release. Researchers have reported neutrophil accumulation in CSU skin lesions and increased neutrophil-to-lymphocyte ratios in patients. However, more biopsy studies are needed to confirm whether this represents a distinct disease subtype. Recent genetic studies have revealed that CSU-associated DNA regions are linked to autoimmune responses. Research has identified variations in immune system genes and other genetic markers that overlap with autoimmune conditions, although the clinical importance of these findings remains unclear [32].

5. Testing methods for chronic spontaneous urticaria pathophysiology

Various diagnostic methods are available for identifying different subgroups of chronic spontaneous urticaria (CSU), each offering unique insights into the underlying pathophysiology of this complex condition. Although not all these diagnostic tools are routinely employed in daily medical practice, they are instrumental in uncovering the diverse molecular and immunological mechanisms that drive CSU in different patient populations. By categorizing patients according to specific disease processes, such methods help refine treatment strategies and advance our understanding of CSU's heterogeneity. One well-established diagnostic method is the autologous serum skin test (ASST), which has been used for decades to assess autoreactivity in CSU patients. This test involves the intradermal injection of the patient's own serum, collected during an active phase of the disease, into their skin. The development of a reactive wheal at the injection site suggests the presence of functional factors, such as autoantibodies or other pro-inflammatory mediators, within the serum. By revealing autoreactivity, ASST contributes to distinguishing autoimmune subgroups of CSU. However, this method also comes with significant limitations. Though it demonstrates a strong ability to rule out certain conditions, the ASST is not highly specific for detecting functional autoantibodies, such as those targeting IgE or the high-affinity IgE receptor (FcεRI). Additionally, performing the ASST can be both technically challenging and time-intensive, potentially limiting its utility in routine clinical settings [16,33]. Moving beyond skin testing, advanced in vitro methods have been developed to explore the functional properties of patient sera in CSU, especially their impact on basophils—a major effector cell in allergic reactions and urticaria. Basophil activation can be triggered through multiple molecular pathways. In CSU, stimulation occurs either via direct allergen binding to FcεRI (the high-affinity IgE receptor) or indirectly through complement activation and signaling through chemokine receptors. Two widely recognized laboratory techniques assess serum-induced basophil activation by using basophils isolated from healthy donors as functional readouts. The basophil histamine release assay (BHRA) represents one of these approaches. This method quantifies the percentage of histamine released from donor basophils after exposure to patient sera. While the

BHRA has played an important role in understanding histamine-mediated urticaria mechanisms, its practical utility is hampered by variability in basophil reactivity among individual donors. Some individuals' basophils are inherently hypersensitive or hyporesponsive, contributing to inconsistent or ambiguous results. The assay's labor-intensive nature and dependence on fresh, functional basophil preparations further limit its widespread application [34]. The second key in vitro test, the basophil activation test (BAT), provides a more sophisticated, flow cytometry-based approach to studying basophil function. This method detects the upregulation of surface proteins—most notably CD63 and CD203c—on basophil membranes when they are activated. A positive BAT result is typically defined as the appearance of CD63 on more than 5 % of basophils in response to patient sera. Compared to the BHRA, the BAT offers greater reliability and precision, as it avoids the direct measurement of histamine levels and instead focuses on cell surface markers that are stabilized during activation. Moreover, the BAT can differentiate between distinct subgroups of CSU patients based on their patterns of basophil reactivity, offering novel insights into disease mechanisms [33,36]. Nevertheless, discrepancies occasionally arise between the BAT and BHRA results, prompting ongoing research to delineate the factors contributing to these differences. Hypotheses include variability in donor basophil receptor expression, patient autoantibody profiles, or differences in complement activation pathways, all of which warrant further investigation. In comparing the BHRA and BAT, researchers generally report similar overall trends in CSU patient cohorts, with both tests identifying subpopulations with autoantibody-mediated basophil activation. However, the BAT's enhanced sensitivity, ability to analyze multiple markers simultaneously, and adaptability to high-throughput settings have made it increasingly favored in clinical and research contexts. Additionally, flow cytometry-based methods like BAT are more amenable to standardization, potentially paving the way for wider adoption as a routine diagnostic tool in specialized CSU evaluations [35,36].

Biomarkers for chronic spontaneous urticaria

Validating biological markers is essential for better classification and recognition of CSU subtypes, which could lead to more individualized treatment approaches. This is particularly important given the connection between the autoimmune nature of CSU and varying treatment outcomes. When evaluating these markers, researchers must consider differences in testing methods, biological measurements, and detection thresholds, as current research lacks standardization. For type I CSU, routine identification remains challenging because of the multitude of known autoallergens and the limited availability of standardized tests. The frequency of type I autoantibodies in people without CSU remains undefined [18,37]. Currently, normal or elevated total blood IgE serves as the primary indicator for type I CSU, although the correlation between total IgE and autoallergen-specific IgE is modest and affected by various factors, including allergic conditions, sex, and patient age. Total IgE helps distinguish between Type I and Type IIb CSU, with Type I typically showing high ($\geq$100 IU/mL) or normal (>43 to < 100 IU/mL) levels, whereas Type IIb presents low levels ($\leq$43 IU/mL). However, there is debate about what constitutes low total IgE, with some researchers using 20 IU/mL as the threshold. While high IgE might suggest type I CSU, elevated levels are also common in allergic conditions and asthma, making this marker alone insufficient for definitive diagnosis [13,38]. Type IIb CSU is identified by three key characteristics: positive ASST results, positive basophil testing (BAT/BHRA), and the presence of specific IgG antibodies targeting IgE or FcεRI. While the ASST indicates circulating histamine-releasing factors, its specificity is limited, showing only 27 % positive predictive value for type IIb CSU. The ASST can detect various histamine-releasing factors in addition to autoantibodies and may even yield positive results in healthy individuals or those with other conditions. BAT measures how patient sera activate donor basophils by monitoring CD63 and CD203c protein expression. The PURIST study demonstrated that the BAT was 69 % accurate in identifying Type IIb CSUs, whereas the BHRA study was 88 % accurate. Researchers have concluded that either test alone approaches the accuracy of combining ASST, basophil tests, and IgG-anti-FcεRI antibody assessment. ELISA detection of IgG antibodies to FcεRI and/or IgE identified only 28 % of Type IIb CSU cases in PURIST [13,39]. This discrepancy between binding and functional tests may arise because most immunoassays do not differentiate between IgG subtypes; only IgG1 and IgG3 activate complement, whereas patients with IgG2 and IgG4 may have negative BAT/BHRA results despite having autoantibodies. Recent research has revealed that IgG antibody levels fluctuate over time, whereas activated basophil frequencies remain stable. Owing to limited test accessibility, these markers are not included in major international guidelines or routine clinical practice. Among CSU patients, approximately 50 % have positive ASSTs, but only half of these patients have positive BHRA results. Considering that approximately half of CSU patients have relevant IgG antibodies, only approximately 8 % can be definitively classified as type IIb CSU. The latest international guidelines (EAACI/GA2LEN/EuroGuiDerm/APAAACI) emphasize the importance of biomarker testing for understanding CSU prognosis and classification. Basic testing, including complete blood counts and inflammatory markers such as CRP and the erythrocyte sedimentation rate, is advised for all CSU patients, maintaining consistency with previous guidelines [29,40]. While the guidelines do not specify whether these tests should be conducted in primary or specialty care settings, the 2022 update introduces additional specialist-level assessments, including IgG-anti-TPO and total IgE measurements, particularly to help identify type IIb CSU cases. Research shows that patients exhibiting elevated anti-TPO (34 kU/L or higher) alongside reduced total IgE (below 40 IU/mL) more frequently have positive results in the ASST, BAT, and other autoimmune indicators characteristic of type IIb CSU. The guidelines highlight that the IgG-anti-TPO-to-total IgE ratio serves as the most reliable indicator for type IIb CSU, with the PURIST study establishing a threshold ratio of 2.88 or greater. Compared with type I CSU patients, type IIb CSU patients typically display distinct laboratory features when not taking steroids or immunosuppressants, including heightened CRP levels (5.0 mg/L or above, compared with normal levels of 3 mg/L), reduced basophil counts (below 0.01 × 109/L), low eosinophil counts (below 0.05 × 109/L), decreased total IgE, and increased IgG-anti-TPO. Reduced basophil counts and changes in basophil functional characteristics are key indicators of CSU activity [41,42]. Studies have shown that approximately half of CSU patients exhibit basophil deficiency, and many have basophils that show reduced responsiveness to anti-IgE stimulation. Interestingly, these basophils maintain their sensitivity to stimuli that do not involve the IgE-FcεRI pathway. These characteristics often indicate more severe disease and reduced treatment responsiveness. Clinical improvement typically correlates with increasing basophil numbers, whereas patients experiencing spontaneous remission show increased basophil histamine release. Positive results in basophil activation and histamine release tests often indicate increased disease activity, and positive responses to nonspecific IgE stimulation tests suggest increased disease duration. CSU patients also exhibit other immune system alterations. Low eosinophil counts typically indicate increased disease activity [35,43]. Various inflammatory markers, including IL-6 and tumor necrosis factor-α, are elevated and correlate with disease severity. The complement proteins C3 and C4 are expressed at higher levels in CSU patients than in healthy individuals, particularly in severe cases. Research has also revealed elevated CRP and D-dimer levels in CSU patients, with notably higher levels in severe cases. While our current understanding is still developing, these markers might help predict how patients respond to various treatments, including omalizumab, antihistamines, cyclosporin, and emerging therapies. Recent research has identified serum amyloid A (SAA-1) as a promising disease activity marker in CSU. Higher SAA-1 levels (approximately 11.7 mg/L) correlate with increased disease activity (UAS7 > 6), whereas patients with better disease control (UAS7 $\leq$ 6) have lower levels (approximately 1.7 mg/L). This correlation (Spearman's coefficient: 0.47, $P < 0.001$) suggests SAA-1′s potential as a disease control biomarker, although

additional validation studies are needed. Research has identified several biological markers that may predict the response of CSU patients to omalizumab treatment. Multiple studies, including a comprehensive *meta*-analysis, have demonstrated that higher baseline total serum IgE levels correlate with better and faster treatment response [44,45]. The *meta*-analysis revealed average total IgE levels of 163.2 IU/mL in complete responders, 179.9 IU/mL in partial responders, and 51.5 IU/mL in nonresponders. Early responders (complete response within 4 weeks) presented significantly higher IgE levels, averaging 56.5 IU/mL more than late responders did. Basophil FcεRI expression has also emerged as a potential predictor of omalizumab response. Research indicates that patients with normal or elevated IgE levels (>43 IU/mL) typically show at least a 100 % increase in IgE counts during the first 4 weeks of treatment, whereas only half of those with low IgE levels (≤43 IU/mL) achieve this increase. This pattern suggests that failure to double IgE levels by week 4 likely indicates nonresponse and type IIb disease. Higher total serum IgE correlates with increased disease activity, longer duration, and greater likelihood of type I endotype and omalizumab responsiveness [46,47]. Conversely, markers associated with the type IIb endotype, including an elevated IgG-anti-TPO-to-total IgE ratio, low baseline total IgE, reduced basophil FcεRI expression, basopenia, eosinopenia, and positive ASST and BHRA results, generally predict poor omalizumab response. BHRA positivity particularly indicates a poor response and high rates of angioedema and thyroid disease. While the underlying mechanisms are not fully understood, it is theorized that omalizumab reduces FcεRI and IgE density on basophils, affecting cell migration, which explains why patients with basopenia often have a reduced response. With respect to other CSU treatments, various predictive markers have been identified. High total serum IgE levels may indicate antihistamine resistance, whereas eosinopenia, elevated CRP, increased platelet volume, and increased serum platelet-activating factor levels suggest antihistamine resistance. For cyclosporine treatment, positive BHRA and ASST results, combined with low total IgE levels, typically predict favorable outcomes [46,47] (Table 1).

6. Overview of CSU treatment

The initial treatment approach for CSU consists of high-dose second-generation antihistamines, although more than half of patients do not achieve adequate symptom control with this treatment. While oral corticosteroids (OCSs) can be used for patients who do not respond to antihistamines and leukotriene blockers, they are typically prescribed

Table 1
Key biomarkers and their roles in CSU diagnosis, prognosis, and prediction of treatment outcomes.

Category	**Biomarker**	Description	Significance	Reference
Type I Biomarkers	Total IgE (normal/high)	High (≥100 IU/mL) or normal (>43 to < 100 IU/mL) total IgE levels are typically seen in Type I CSU. Elevated total IgE may indicate Type I CSU but is also influenced by atopy, sex, and age.	Helps distinguish Type I from Type IIb CSU but may not be specific due to overlap with other conditions.	[38,48–51]
Type IIb Biomarkers	Positive ASST	Indicates the presence of autoreactive circulating histamine-releasing factors. However, it has low specificity and can also be positive in healthy controls and other diseases.	Useful for identifying Type IIb CSU but lacks specificity and predictive value.	[48,52–54]
	Basophil Activation Test (BAT)	Detects the ability of serum from CSU patients to activate basophils from non-CSU donors. Highly specific and sensitive for identifying Type IIb CSU.	More reliable for identifying Type IIb CSU compared to ASST.	[48,52,55]
	Basophil Histamine Release Assay [34]	Measures histamine release by basophils. Predicted 88 % of Type IIb cases in the PURIST study.	Highly specific for diagnosing Type IIb CSU.	[48,52]
	IgG-anti-IgE and/or IgG-anti-FcεRI antibodies	Associated with Type IIb CSU but not always functional (some patients with these antibodies show negative BAT/BHRA results).	Indicates autoimmune mechanisms but lacks consistency across patients.	[48,52,56]
	IgG-anti-TPO/IgE ratio	A high ratio (≥2.88) is the best surrogate marker for Type IIb CSU. Typically, combined with low IgE levels and high anti-TPO levels.	Strong marker for Type IIb CSU and aids in distinguishing it from Type I CSU.	[42,56–58]
Other Diagnostic Biomarkers	Differential blood counts, CRP, ESR	Elevated CRP (≥5.0 mg/L), basopenia (<0.01 × 10^9/L), and eosinopenia (<0.05 × 10^9/L) are associated with Type IIb CSU and disease activity.	General markers for inflammation and disease severity.	[38,42,48–50,58,59]
	Serum Amyloid A (SAA-1)	Correlates with disease activity in CSU. High levels (median: 11.7 mg/L) associated with higher UAS7 scores compared to low levels (median: 1.7 mg/L).	May serve as a biomarker for disease control in CSU.	[60]
Predictors of Disease Severity	Basopenia	Approximately 50 % of CSU patients have basopenia, which is related to increased disease severity and slower treatment response.	Indicator of disease severity and progression in CSU.	[38,48–50,58,61–64]
	Eosinopenia	Associated with high disease activity.	Correlates with disease activity and severity.	[65]
	IL-6 and TNF-α	Upregulated in CSU and positively correlated with disease severity.	Inflammatory cytokines linked to severe disease manifestations.	[66]
	C3 and C4	Higher levels are associated with severe disease activity.	Complement proteins linked to immune activation and severity.	[67]
	CRP and D-dimer	Elevated in patients with severe CSU.	General markers of inflammation and coagulation in severe disease.	[68–71]
Predictors of Treatment Response	Total IgE	High baseline total IgE levels are associated with better and faster responses to omalizumab. Patients with levels > 43 IU/mL often respond; those ≤ 43 IU/mL may not.	Predicts responsiveness to omalizumab therapy.	[38,49,50,72–76]
	Low IgG-anti-TPO/IgE ratio	Predicts poor response to omalizumab.	Indicates limited efficacy of omalizumab in Type IIb patients.	[41,47,50,65,73–75,77,78]
	Positive BHRA, ASST	Associated with poor omalizumab response but better outcomes with cyclosporine.	May help guide selection of alternative treatments like cyclosporine.	[47,79,80]
	CRP, eosinopenia, platelet volume	Elevated CRP, eosinopenia, and increased platelet-activating factor levels are linked to antihistamine resistance.	Useful for identifying patients resistant to antihistamines.	[47,65,81,82]
	Basophil FcεRI expression	Predicts omalizumab response. Patients with low baseline FcεRI expression often have poor responses.	May serve as a future predictive test for omalizumab efficacy.	[74,75]

only for brief periods (approximately 10 days) owing to potential complications from extended use. Although some patients require repeated OCS courses since symptoms may return after stopping treatment, medical professionals advise against long-term OCS use because of possible systemic complications and associated healthcare expenses. For patients with difficult-to-treat CSU, several biological medications have emerged in recent years as alternative treatment options [28,83]. Omalizumab stands out as the pioneering biological therapy for CSU, receiving FDA approval in 2014. This humanized monoclonal antibody targets free IgE at its Fc region, preventing its interaction with FcεRI receptors on mast cells and basophils. While its complete mechanism of action is not fully understood, researchers believe that it works partly by blocking the effects of IgG autoantibodies targeting IgE or the alpha subunit of FcεRI, thereby reducing mast cell activation in the skin. The effectiveness of omalizumab has been demonstrated in patients both with and without autoantibodies through initial proof-of-concept and phase II clinical studies. Three major phase III trials (ASTERIA I, ASTERIA II, and GLACIAL) reported that, compared with placebo, omalizumab treatment led to significant improvements in both urticaria symptoms and quality of life. The benefits were dose dependent, with many patients achieving complete symptom resolution at the highest monthly dose of 300 mg given subcutaneously. Compared with the placebo, the ASTERIA II trial specifically revealed that both 150 mg and 300 mg doses significantly reduced weekly itch severity scores after 12 weeks. The treatment was effective regardless of patient characteristics or concurrent medications. On the basis of the results of clinical studies, regulatory bodies have approved omalizumab for CSU treatment, with the FDA permitting both 150 mg and 300 mg doses, whereas the EU specifically authorizes 300 mg subcutaneous injections every 4 weeks for patients 12 and above with antihistamine-resistant CSU, regardless of IgE levels or weight [84,85]. Research into 600 mg doses revealed no additional benefits over 300 mg treatments. Treatment protocols differ across regions. The American guidelines position omalizumab as a fourth-line treatment, following unsuccessful trials of standard and increased antihistamine doses, H2 blockers with leukotriene modifiers, and potent antihistamines such as hydroxyzine or doxepin. In contrast, European protocols introduce omalizumab earlier, as a third-line option after standard and elevated doses of unsedating antihistamines prove ineffective. The medication has a favorable safety profile, with primary side effects, including headaches (6.1 %), sinus inflammation (4.9 %), joint pain (2.9 %), and injection site reactions (2.7 %). No anaphylactic reactions occurred during phase III studies, and treatment was effective after 12 months. Several clinical questions remain unresolved, including understanding variable patient responses, optimal dosing adjustments, and treatment duration. Some partial responders have shown improvements with more frequent administration—every 2–3 weeks instead of monthly [86,87]. Nonresponders are typically identified after four monthly 300 mg doses, as response rates match placebo beyond this point. No standardized protocols exist for dose reduction or therapy duration once symptoms are controlled. The XTEND-CIU phase IV trial investigated extended treatment periods, comparing 24-week versus 48-week regimens. This randomized, double-blind study included patients aged 12–75 years with antihistamine-resistant CSU and specific urticaria activity scores. The results indicated sustained symptom control through 48 weeks of treatment. Interestingly, symptom recurrence patterns during the 12-week posttreatment period were similar between the 24-week and 48-week groups, suggesting potential advantages of longer treatment durations. IVIg therapy has demonstrated effectiveness in treating antihistamine-resistant CSU through its immunomodulatory properties. The treatment works by blocking Fc receptors, increasing the number of regulatory T cells, removing autoantibodies more efficiently, and increasing FcγRII expression. Several studies support its efficacy, with Pereira's research being particularly notable [88,89]. Their study revealed that monthly low-dose IVIg treatments (0.15 g/kg) helped 90 % of 29 participants, with complete symptom resolution in approximately 66 % of cases over 6–51 months. However, widespread adoption is hampered by high costs, time-consuming infusions, and limited efficacy data, making other biologics preferable unless IVIg is already indicated for other conditions. Research has revealed elevated TNF-α levels in both the affected and unaffected skin of CSU patients, leading to trials of TNF-α blockers (including etanercept, adalimumab, and infliximab). Initial success was documented with etanercept in treating concurrent delayed pressure urticaria and psoriasis. Subsequent studies revealed promising outcomes for various urticaria types. A retrospective analysis of 25 CSU patients treated with etanercept or adalimumab revealed that 60 % achieved complete symptom relief. While these drugs might benefit omalizumab-resistant patients, comparative studies are lacking. Safety concerns include increased infection risk and potential development of malignancies. This hybrid mouse-human antibody targeting CD20 depletes B cells, thereby reducing autoantibody production relevant to CSU. Although case reports indicate benefits for various urticaria types and hypocomplementemic urticarial vasculitis, the absence of comprehensive clinical trials has prevented FDA approval for CSU treatment [90,91]. IL-1 inhibitors were initially developed for CAPS, a group of inflammatory conditions that include familial cold syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease. These conditions involve NLRP3 gene mutations leading to excess IL-1β production and urticaria development. FDA-approved treatments include anakinra (IL-1Ra antagonist), canakinumab (IL-1β antibody), and rilonacept (IL-1β blocker). These medications have also shown promise in treating Schnitzler syndrome, which presents with urticaria and systemic symptoms. Current research, including a phase II trial of canakinumab, is exploring its potential in CSU management. Ligelizumab represents a new generation of humanized IgG1 monoclonal antibodies that, similar to omalizumab, demonstrate stronger IgE binding. Ongoing research includes comparative studies against omalizumab and placebo plus a year-long assessment of its CSU treatment efficacy. Another antibody, quilizumab, was engineered to target the membrane-bound IgE M1 prime segment, reducing the number of IgE-producing B cells and plasmablasts, with effects lasting up to six months posttreatment. Despite its initial promise, its development has been halted. Studies have revealed elevated spleen tyrosine kinase levels in certain CSU patients. This enzyme regulates inflammatory mediator production and release [83,92,93]. A topical Syk inhibitor, GSK2646264, is currently under evaluation for both CSU and cold urticaria treatment. This prostaglandin D2 receptor is expressed at increased levels on eosinophils in CSU patients. AZD1981, a PGD2R antagonist, is being studied as a potential anti-inflammatory treatment option. Bruton tyrosine kinase, which is crucial for B-cell development, represents another therapeutic target. Given the previous success of B-cell-targeting treatments such as rituximab, researchers are investigating the Btk inhibitor GDC-0853 for the treatment of antihistamine-resistant CSU. Interleukin-6 (IL-6) is important for CSU disease activity. While tocilizumab (an IL-6 blocker) has shown promise in treating related conditions such as urticarial vasculitis and Schnitzler's syndrome, formal CSU trials have not been conducted. Future research may explore the role of IL-6 in CSU pathogenesis and the potential of IL-6-targeted treatments. These developments suggest multiple promising pathways for expanding CSU treatment options, particularly for patients resistant to current therapies [94] (Table 2).

The treatment options for CSU are presently restricted to symptom management. The standard approved therapies outlined in international urticaria guidelines – antihistamines and omalizumab – work by blocking mast cell activation and its mediating effects. There is a pressing need for innovative therapeutic approaches that can alter the disease course of CSU rather than just managing symptoms. These new treatments should focus on pathways that precede mast cell activation, potentially preventing disease progression and associated conditions [83]. The key factors triggering skin mast cell activation are known to include autoantibodies, cytokines, and possibly changes in the gut microbiota, leading to compromised barrier function. While the concept of disease modification in CSU remains undefined, we have established

Table 2
The key aspects of treatments for chronic spontaneous urticaria.

Treatment Line	Therapeutic Options	Mechanism of Action	Efficacy/Clinical Evidence	Safety/ Monitoring	Future Directions & Considerations	References
First-Line	Second-generation H1-antihistamines (standard to 4x dose)	Block peripheral H1 receptors to mitigate histamine effects	– Variable response rates between different antihistamines – Mixed results comparing levocetirizine and bilastine – Higher doses may improve response in some patients	– Generally, well-tolerated – Some adverse effects at higher doses – Individual tolerability varies	– Need for individualized dosing strategies – Further research on optimal updosing approaches – Consideration of patient-specific factors	[27,28,95–100]
Second-Line	Omalizumab (Anti-IgE monoclonal antibody)	Binds free IgE and prevents interaction with FcεRI on mast cells and basophils	– Proven efficacy in multiple clinical trials (X-CUISITE, MYSTIQUE, ASTERIA I/II, GLACIAL) – Improves quality of life – Reduces urticaria activity scores and itching severity	– Favorable safety profile – Long-term safety established – Regular monitoring recommended	– Optimal dosing regimens under investigation – Cost-effectiveness considerations – Access barriers need addressing	[27,28,101–107]
Third-Line	Cyclosporine and other immunosuppressants	– Cyclosporine: Inhibits T-cell activation – Others: Various immune-modulating mechanisms	– Cyclosporine: Demonstrated efficacy in refractory cases – Limited evidence for other immunosuppressants – Case reports support use in selected patients	– Risk of nephrotoxicity – Requires monitoring of: • Renal function • Blood pressure • Liver enzymes	– Need for larger trials – Role of alternative immunosuppressants – Patient selection criteria	[27,28,95,108–112]
Emerging Therapies	– BTK inhibitors – Anti-IL-4/13 (Dupilumab) – Ligelizumab – Other targeted therapies	– Target specific pathogenic mechanisms: • BTK signaling •Cytokine pathways • High-affinity IgE binding	– Promising early results for BTK inhibitors – Mixed results for cytokine –targeted therapies – Ongoing clinical trials	– Safety profiles still under investigation – Long-term effects unknown – Need for careful patient monitoring	– Personalized treatment approaches – Biomarker development – Endotype-specific targeting	[14,28,113–118]

criteria for what constitutes a disease-modifying treatment (DMT) and how it differs from treatments that merely prevent symptoms [119] (Fig. 1).

7. Conclusion, future directions, and limitations

Chronic spontaneous urticaria emerges as a sophisticated immunological disorder characterized by remarkable clinical complexity and diagnostic intricacies. The condition's multifaceted nature demands a nuanced approach to understanding its underlying mechanisms and exploring potential therapeutic interventions. Diagnostic Landscape and Biomarker Challenges The quest for reliable diagnostic tools has led researchers to investigate various immunological markers and testing methodologies. Emerging diagnostic strategies include: Immunological Assessment Techniques: Total IgE measurements IgG anti-IgE autoantibody detection Specialized basophil-related investigations Autologous serum skin screening Despite promising initial insights, these approaches face significant limitations: Inconsistent standardization Restricted clinical accessibility High inter-individual variability Compromised diagnostic precision Immunological Complexity and Disease Mechanisms The intricate interplay between immune system components remains a critical research frontier. Key observations highlight: Substantial variations in innate and adaptive immune responses Differential basophil activation patterns Complex complement pathway interactions Evolving Therapeutic Strategies Targeted biological interventions have revolutionized treatment paradigms: Monoclonal antibodies targeting specific immune pathways Emerging therapies modulating cytokine interactions Personalized treatment approaches Persistent Challenges and Research Imperatives Critical areas demanding focused investigation include: Developing standardized diagnostic protocols Creating comprehensive testing methodologies Expanding research across diverse population cohorts Understanding disease phenotype evolution Technological Innovations and Future Directions Promising research trajectories encompass: Advanced omics technologies Machine learning predictive algorithms Molecular profiling techniques Comprehensive immunological characterization Strategic Research Recommendations: Enhance Biomarker Precision Validate Emerging Diagnostic Tools Develop Comprehensive Patient Classification Systems Create Predictive Treatment Models Investigate Treatment-Resistant Mechanisms Technological Approaches: Proteomics integration Transcriptomic analysis Metabolomic investigations Artificial intelligence-driven diagnostic models Conceptual Framework The CSU research landscape requires: Interdisciplinary collaboration Comprehensive longitudinal studies Flexible diagnostic frameworks Personalized therapeutic strategies Conclusion Chronic spontaneous urticaria represents a dynamic immunological challenge demanding sophisticated, multifaceted research approaches. Bridging molecular insights with clinical applications remains the ultimate goal, promising improved patient outcomes and enhanced understanding of this complex disorder. The path forward necessitates: Continuous scientific innovation Collaborative research efforts Holistic patient-centered approaches Technological integration By maintaining a comprehensive, adaptable research perspective, the scientific community can progressively unravel the intricate mechanisms underlying chronic spontaneous urticaria.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

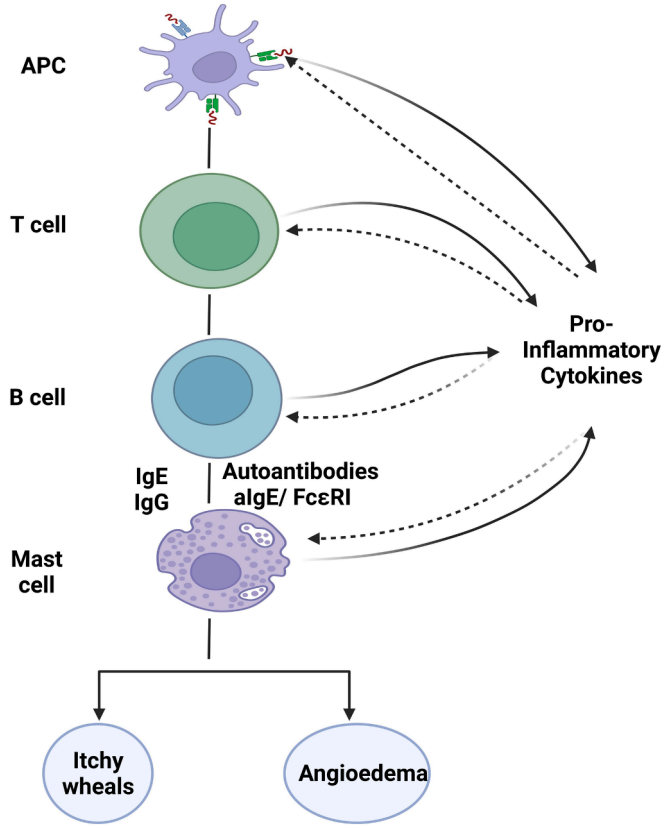

Fig. 1. Factors that exacerbate chronic spontaneous urticaria include mechanisms of mast cell activation, such as IgE and IgG autoantibodies, proinflammatory cytokines, and autoimmune disorders. These elements contribute to increased inflammation and mast cell activity, leading to the persistence of CSU symptoms.

Authors' contributions

All the authors contributed to the study conception, design, data collection, and writing of the manuscript. All the authors read and approved the final manuscript.

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Aray Batyrbayeva: Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation. **Zhanat Ispayeva:** Methodology, Investigation, Funding acquisition, Formal analysis. **Marat Pashimov:** Writing – original draft, Data curation. **Jamilya Kaibullayeva:** Methodology, Investigation, Funding acquisition, Formal analysis. **Madina Baididayeva:** Writing – review & editing, Project administration, Conceptualization. **Uldana Kapalbekova:** Methodology, Investigation, Funding acquisition. **Elmira Tokmurzayeva:** Methodology, Investigation. **Olga Plakhotina:** Writing – review & editing, Data curation. **Arailym Maldybayeva:** Methodology, Data curation. **Asem Salmanova:** Methodology, Investigation. **Leila Kuandykova:** Methodology, Investigation. **Kamila Turebekova:** Writing – review & editing, Methodology.

Data availability

Data will be made available on request.

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