

Urticaria and Angioedema: Understanding Complex Pathomechanisms to Facilitate Patient Communication, Disease Management, and Future Treatment



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Chronic spontaneous urticaria (CSU) is primarily a T2-dominant disease with a complex genetic background. Skin mast cell activation can be induced not only via the IgE-FcεRI axis but also from several other distinct mechanisms, molecules, and receptors involved in CSU onset, persistence, and exacerbation. These include autoallergy, autoimmunity, central or peripheral neuroimmune dysregulation, activation of both extrinsic and intrinsic coagulation pathways, and microbial infections. Besides mast cells, recent reports suggest the active and direct involvement of basophils and eosinophils. Several biological characteristics or biomarkers have been linked with CSU's known endotypes and may help forecast therapeutic responses. The introduction of biologic therapy for CSU has been a major advance in the last 10 years. The cornerstone of angioedema (AE) pathogenesis is increased vascular permeability and plasma leakage into the deeper dermis and subcutis, either mediated by histamine or bradykinin (BK). C1-inhibitor deficiency, hereditary or acquired, is the primary cause of BK-mediated AE due to increased plasma BK concentration. Other complex conditions have been identified, with some likely involving contact system dysregulation and other putative mechanisms related to vascular endothelial dysfunction. The approval of multiple hereditary-AE-specific therapies for both prevention and acute attacks has revolutionized treatment of this disease. Any new knowledge of the pathogenesis of CSU and AE offers the opportunity to improve patient information, physician-

patient communication, prediction of therapeutic responses, selection of precise tailor-made treatment for each patient, and exploration of novel treatment options for those who do not achieve disease control with current medications. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:94-106)

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Urticaria is a frequent inflammatory condition characterized by the sudden and unpredictable onset of transient pruritic wheals that usually last less than 24 hours.¹ Many patients with urticaria also have angioedema, and in some patients with urticaria, angioedema is the predominant or only manifestation.

Angioedema is a clinical condition defined by intermittent, localized, and self-limiting swelling of the subcutaneous and/or submucosal tissue due to a temporary increase in vascular permeability. Angioedema can be painful or burning, it can come with pruritus or be asymptomatic,² may persist for up to 72 hours before spontaneous resolution, and usually affects the face, extremities, and genitalia.³ Wheals, in patients with urticaria, are mediated by mast cells and histamine. Angioedema is mast cell

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Abbreviations used

<i>aaCSU</i> - Autoallergic CSU
<i>ACEIs</i> - Angiotensin-converting enzyme inhibitors
<i>AE</i> - Angioedema
<i>aiCSU</i> - Autoimmune CSU
<i>ASST</i> - Autologous serum skin test
<i>AU</i> - Acute urticaria
<i>BAT</i> - Basophil activation test
<i>BK</i> - Bradykinin
<i>C1-INH</i> - C1-inhibitor
<i>CIndU</i> - Chronic inducible urticaria
<i>CSU</i> - Chronic spontaneous urticaria
<i>CU</i> - Chronic urticaria
<i>dsDNA</i> - Double-stranded DNA
<i>HαT</i> - Hereditary alpha-tryptasemia
<i>HAE</i> - Hereditary angioedema
<i>HP</i> - <i>Helicobacter pylori</i>
<i>Hsp</i> - Heat shock proteins
<i>MRGPRX2</i> - Mas-related G-protein coupled receptor X2
<i>PAF</i> - Platelet activation factor
<i>PTPN22</i> - Phosphatase-22
<i>SEB</i> - Staphylococcal enterotoxin B
<i>SP</i> - Substance P
<i>TF</i> - Tissue factor
<i>TPO</i> - Thyroid peroxidase

mediated, in patients with urticaria, or bradykinin (BK) mediated, in patients with hereditary angioedema (HAE).

The current classification of urticaria is based on both the duration of the disease and the relevance of triggers of signs and symptoms. Based on how long urticaria persists, there are 2 types: acute and chronic, characterized by wheals and/or angioedema that occur for up to 6 weeks and longer than 6 weeks, respectively. Chronic urticaria (CU) is further subdivided into 2 subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). In CSU, signs and symptoms appear spontaneously. In CIndUs, they develop in response to specific and definite triggers, including physical stimuli (symptomatic dermatographism/urticaria factitia, cold- and heat-induced urticarias, delayed pressure urticaria, solar urticaria, and vibratory angioedema) and nonphysical triggers (cholinergic urticaria, contact urticaria, and aquagenic urticaria).²

Acute urticaria (AU) is a common disorder affecting almost 15% of the population at least once in their life. CU is less common, with a point-prevalence estimation of approximately 1%. In the past few years, the prevalence of AU and CU has risen in both adults and children.⁴⁻⁸ CSU accounts for approximately 80% of all cases of CU, thus making it the most prevalent type of CU.⁹ Approximately 60% of patients with CSU report angioedema episodes at least once in their lifetime. In contrast, in 10% to 20% of cases, angioedema is the first or only manifestation of CSU (known as isolated angioedema without wheals).¹⁰ HAE and other diseases that manifest with BK-mediated recurrent angioedema without wheals, such as angioedema due to acquired C1-inhibitor (C1-INH) deficiency, are much less common. BK-mediated types of angioedema, including HAE, are discussed below and shown in Table I.³

Despite the rising prevalence of CU over the years, several unmet needs exist regarding our understanding of the disease and inadequate response to existing therapeutic options. Recent reports have described newer pathogenetic aspects of CU. This knowledge

is being used for better patient information and counseling, assessment of disease characteristics, predicting therapeutic responses, and exploring novel treatment options for those who do not achieve disease control with current medications. The current review highlights some essential novel insights on the pathogenesis of urticaria and angioedema and their role in improving patient communication, disease management, and future treatment.

NOVEL INSIGHTS ON THE PATHOGENESIS OF URTICARIA

Virtually all recent discoveries related to the pathogenesis of urticaria come from studies from patients with CSU. As of now, little is known about the pathogenic drivers in acute urticaria and CIndU. Whether or not the pathogenic mechanisms identified in CSU are also relevant in acute urticaria or CIndU needs to be investigated in future studies. What is clear for all types of urticaria is that the degranulation of skin mast cells plays a central role in the pathogenesis, and it can be induced by many distinct mechanisms resulting in the release of several preformed and newly synthesized mediators such as histamine, cytokines, and chemokines, including TNF- α , IL-1, IL-4, IL-5, IL-6, IL-8, IL-16, CCL-2, CCL-3, transglutaminase 2, and regulated on activation, normal T cell expressed and secreted (RANTES), and arachidonic acid metabolites including prostaglandin D₂, leukotriene E₄, and platelet activation factor (PAF).¹¹ These mediators induce vasodilatation, increase vascular permeability, stimulate sensory nerves, and act as chemoattractants for inflammatory cells such as neutrophils, eosinophils, basophils, and lymphocytes, cumulatively generating clinical signs and symptoms. Activated cutaneous sensory nerves and infiltrating cells contribute to the inflammatory response initiated by skin mast cell degranulation and are of clinical relevance in urticaria.¹²

In CSU, 2 distinct triggers for skin mast cell activation and degranulation have been identified (autoimmune and autoallergic), and several others are currently being explored. Below, we briefly discuss some novel insights on the pathogenesis of CSU.

Emerging endotypic classification of CSU

An “endotype” represents a subtype of a disease defined by a distinct functional or pathophysiological mechanism. It differs from “phenotype,” which indicates any observable characteristic or trait of a disease without necessarily any mechanistic implication.

Over the years, chronic autoimmune spontaneous urticaria,¹³ now called type IIb autoimmune CSU (aiCSU),¹⁴ has been defined and characterized as a distinct subset of CSU. This classification is based on the modified original one by Gell and Coombs to distinguish an antibody-mediated cell-stimulating reaction designated as type IIb (eg, stimulation of basophils and mast cells by autoantibodies), rather than an antibody-mediated cytotoxic reaction involving complement activation classified as type IIa.¹⁵

Biomarkers and clinical characteristics of this subset have also been studied,¹⁶ and prevalent autoimmune comorbidity has been recognized.¹⁷ More recently, autoallergic pathways have been implicated in stimulating mast cell degranulation in CSU, called autoallergic CSU (aaCSU), also sometimes called type I aiCSU.^{14,18}

In aaCSU, IgE antibodies are generated against several autoantigens such as thyroid peroxidase (TPO), thyroglobulin, tissue factor (TF), double-stranded DNA (dsDNA), and IL-24.^{19,20} Although anti-dsDNA IgE antibodies have been demonstrated, no evidence of anti-dsDNA IgG has been documented in these patients.²¹ The IgE autoantibodies cross-link high-affinity Fc ϵ R1

TABLE I. Angioedema without urticaria

Type	Subtype	Pathology	Mechanism	Diagnostic clues
Hereditary	C1-INH deficiency—type 1	Quantitative deficiency of C1-INH	C1-INH is a serine protease inhibitor, which primarily regulates the contact system by inhibiting various enzymes from the contact, coagulation, and fibrinolytic pathways	• Low plasma C1-INH (<50%) • Low C1-INH function • Low plasma C4 (<50%)
	C1-INH deficiency—type 2	Dysfunctional C1-INH	Qualitative or quantitative defect of this enzyme results in loss of its inhibitory action and unregulated activation of the contact system to release more BK and cause angioedema	• Normal/raised plasma C1-INH • Low C1-INH function • Low plasma C4 (<50%)
	Normal C1-INH	Currently 7 subtypes exist: 1. Mutations in gene coding the coagulation factor XII (HAE-f12) 2. Mutations affecting the plasminogen gene (HAE-PLG) 3. Mutations involving the angiopoietin gene (HAE-ANGPT1) 4. Kininogen gene mutation (HAE-KNG1) 5. Myoferlin gene mutation (HAE-MYOF) 6. Heparan sulfate 3-O-sulfotransferase 6 mutation (HAE-HS3ST6) 7. Genetic cause still unknown (HAE-U)	Increased activation/activity of factor XII further activates plasma kallikrein to release more BK from HMWK Possibly, increased conversion of plasminogen to plasmin, which enhances the activation of the contact system, as plasmin also acts as an activator of factor XII ANGPT1 regulates the integrity of the endothelial barrier. In these patients, endothelial barrier dysfunction may lead to plasma leakage Possibly affects the N-terminal cleavage site of kininogen, facilitating breakdown into BK form with longer half-life and higher than normal activity Gain-of-function mutation may increase localization of VEGFR2 to plasma membrane, increasing vascular permeability Hypothesized to decrease HMWK chaperoning into the cell resulting in more HMWK available for cleavage producing increased bradykinin levels Further investigations are warranted to identify newer mutations and involved pathomechanisms	• Normal plasma C1-INH • Normal C1-INH function • Normal plasma C4
Acquired	Pharmacologically induced (ACEIs, ARBs and gliptins)	Inhibition of ACE prevents degradation of BK, leading to its increased levels	Reduced breakdown of BK results in increased plasma concentration of BK and angioedema	• Positive relevant medication history
	C1-INH deficiency	Production anti-C1-INH antibodies and/or lymphoproliferative diseases such as monoclonal gammopathy of undetermined significance, splenic marginal zone lymphoma, and non-Hodgkin lymphoma (excess consumption)	Degradation of C1-INH by antibodies or excess consumption results in C1-INH deficiency and angioedema (similar mechanism to HAE-C1-INH)	• Low plasma C1-INH • Low C1-INH function • Low plasma C4 • Low plasma C1q (differentiating point from HAE)
	Idiopathic mast cell—mediated (formerly also called histaminergic)	Diagnosis of exclusion, patients respond to antihistamines or other mast cell—targeted therapies such as omalizumab	Exact mechanism is unclear	—
	Idiopathic non—mast cell mediated (formerly also called nonhistaminergic)	Diagnosis of exclusion, patients do not respond to antihistamines or other mast cell—targeted therapies	Exact mechanism is unclear	—

ACEIs, Angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BK, bradykinin; C1-INH, C1-inhibitor; HAE, hereditary angioedema; HMWK, high molecular weight kininogen.

receptors on mast cells and basophils, resulting in their degranulation. Notably, the serum concentration of anti-IL-24 IgE antibodies in patients with CSU correlated with disease activity and was reduced by autologous serum therapy in a subset.²² Interestingly, in CSU patients with high IgE levels, most of the IgE was directed against autoallergens/autoantigens, contrasting to those without CSU.²³

In contrast, aiCSU is typified by the presence of IgG (complement-fixing IgG1 and IgG3 subtypes) or IgM autoantibodies against the FcεR1 receptor or IgE. Binding of these antibodies to their target induces mast cell activation and degranulation. Recent studies have demonstrated anti-FcεR1 IgG antibodies in 25% to 52% of patients with CSU. This subset of patients is also frequently associated with other autoimmune comorbidities such as Hashimoto's thyroiditis and connective tissue disorders,²⁴ whereas it demonstrates positive autologous serum skin test (ASST), autologous plasma skin test, and basophil activation test (BAT). Altrichter et al²⁵ have recently demonstrated IgM and IgA autoantibodies to FcεR1, in addition to IgG.

The recent PURIST study characterized patients with CSU positive for all 3 markers of type IIb aiCSU, that is, presence of anti-FcεR1-IgE IgG antibodies, positive BAT, and positive ASST, and found only 8% of patients to be triple positive. These patients also showed higher IgG-anti-TPO levels and low total serum IgE compared with triple negatives. Thus, the IgG-anti-TPO/IgE ratio has been recommended to be a suitable marker of aiCSU in routine clinical practice.¹⁶

Role of cells other than mast cells in CU

Mast cells are the initial and key drivers of the development of signs and symptoms in CSU, but recent reports suggest the involvement of 2 other cells, basophils and eosinophils.

Role of basophils. A subset of patients with CSU shows peripheral basopenia and functional impairment of basophils, thus suggesting their possible role in CSU. According to the ability of basophils to be activated from FcεR1 stimulation, patients with CU can be classified as reactive and nonreactive. Among the nonreactive subset, there was a subgroup that demonstrated marked basopenia, reduced expression of IgE receptors, increased serum reactivity, and autoantibodies against TPO, possibly hinting toward an autoimmune background. This subgroup had the most impaired quality of life.²⁶

Other indicators of basophil involvement in CSU include reduced expression of basophil chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) receptors compared with healthy controls, increased serum levels of the pruritogenic and Th2-promoting cytokine IL-31 secreted by basophils, and increased expression of CD63 by CSU basophils correlating with serum autoreactivity.²⁷

Role of eosinophils. Eosinophils appear to also play an important role in CSU, as in other chronic inflammatory disorders like asthma.²⁸ Their involvement is reflected by their presence in lesional and nonlesional skin. As with basopenia, eosinopenia in patients with CSU is also associated with high disease activity.²⁹ There is evidence that some patients with CU exhibit autoantibodies against the low-affinity IgE receptor (FcεRII/CD23) expressed on eosinophils. The agonistic effect of these autoantibodies is able to activate eosinophils to secrete the eosinophil mediators, major basic protein, and eosinophilic

peroxidase that are able to stimulate mast cells to release histamine.³⁰

Another mode of involvement is the activation of the coagulation system by TF released from eosinophils.³¹

Role of the coagulation system

Recent studies have highlighted the activation of both extrinsic and intrinsic coagulation pathways in CSU.³² TF expressed by eosinophils acts as the possible trigger for activating the coagulation cascade on endothelial cells. This activation results in thrombin generation, which may induce mast cell degranulation,³³ resulting in vascular leakage of serum in patients with CU.³⁴

Role of cytokines

CSU is primarily a Th2-dominant disease involving type 2 cytokines such as IL-4, IL-5, and IL-13.³⁵ Kay et al³⁵ have further demonstrated the upregulation of alarmins IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in lesional CSU skin, which play a critical role in Th2 skewing of the immune system. However, CSU has been considered by others to be a mixed Th2/Th1 immune disorder due to the involvement of type 1 cytokines such as IFN-γ and TNF-α.³⁶

IL-35, a suppressor of Th1 and Th17 cells, has been shown to be involved in CSU pathogenesis. The investigators demonstrated that Asian patients with CU had significantly lower levels of IL-35 compared with atopics and healthy controls. In addition, IL-35 concentration increased after antihistamine therapy.³⁷

Another cytokine that appears to be a relevant driver of CSU disease activity in a subset of patients is IL-17.^{38,39} Interestingly, in patients with severe CSU, unresponsive to H1 antihistamine and omalizumab, disease activity was significantly reduced after treatment with secukinumab, an anti-IL-17A antibody.³⁹

Mediators beyond histamine

It has long been speculated that several mast cell mediators are involved in CSU pathogenesis, in addition to histamine, as not all patients are controlled with antihistamines. One such mediator is PAF, which has been shown to induce wheal and flare reactions independent of histamine.⁴⁰ Over the years, several other mediators have been found to be elevated in the serum of patients with CSU, such as vascular endothelial growth factor,⁴¹ IL-6,⁴² and matrix metalloproteinase-9.⁴³

Recently, Kasperska-Zajac et al⁴⁴ have proposed that heat shock proteins (Hsp), which are produced and released by mast cells, may be involved in the pathogenesis of CSU, as in multiple autoimmune disorders. They detected higher levels of circulating Hsp-70 and anti-Hsp-70 antibodies in patients with CSU compared with healthy controls. However, the exact role of Hsp in CSU is unclear, and further studies are needed to evaluate it.

Triggers of mast cell activation

Activation of skin mast cells via IgE and/or its high-affinity receptor appears to be a relevant pathogenic mechanism in many patients with CSU, and this is supported by the efficacy of anti-IgE treatment, which results in a rapid neutralization of free IgE and, consequently and slowly, the reduction of FcεRI expression. However, a substantial rate of patients with CSU does not benefit from anti-IgE treatment, suggesting that other pathways of skin mast cell activation and degranulation are relevant in this subgroup of patients. Several other molecules and receptors have been identified, which activate skin mast cells independent of the IgE-FcεRI axis.

The most important among these newer identified mast-cell receptors is mas-related G-protein coupled receptor X2 (MRGPRX2). MRGPRX2 is preferentially expressed by skin mast cells and is upregulated in patients with severe CSU.⁴⁵ This distribution pattern possibly explains the isolated involvement of skin in CSU, sparing other mast cell-rich areas like the lungs and gut. Its ligands include eosinophilic major basic protein, eosinophil peroxidase, and substance P (SP).⁴⁶

Apart from urticaria, MRGPRX2 agonists also mediate mast cell hypersensitivity reactions causing type 2 inflammation, drug-induced hypersensitivity reactions and anaphylaxis, non-histaminergic itch, and neuroinflammation (eg, postoperative pain). Recent studies have highlighted a variety of ligands stimulating this receptor and resulting in mast cell degranulation such as basic secretagogues, neurokinin peptides, host defence antimicrobial peptides, and small molecule compounds (eg, neuromuscular blocking agents).⁴⁷ Thus, this receptor has become a potential therapeutic target for reducing mast cell degranulation to ameliorate such disease conditions.

In particular, SP, a neuropeptide released from skin nociceptor nerve endings, has been shown to contribute to local neuroinflammation causing vasodilation by direct action to endothelial cells. But it is now evident that SP can directly activate mast cells via the MRGPRX2 receptor contributing to a neuroinflammation process that can explain non-FcεRI CU-related pathomechanisms. Notably, SP could be the possible link between CSU exacerbations related to emotional stress.¹²

The complement factor 5 receptor C5aR (CD88) is the receptor for C5, a crucial step in IgG-mediated mast cell degranulation (type IIb aiCSU). Interestingly, C5aR is commonly expressed by skin mast cells in inflamed skin and synovial mast cells in rheumatoid arthritis, but not by lung mast cells, gastrointestinal tract mast cells, or synovial mast cells in patients with osteoarthritis,^{48–50} providing another possible explanation of the isolated skin involvement in most patients with CSU.

Role of infections

Viral infections are linked to the onset of acute spontaneous urticaria in some patients⁶ and can cause exacerbation of CSU. A recent study has demonstrated an association between CSU and human herpesvirus-6 infection, but further large-scale studies are needed to prove a causal relation.⁵¹ Also, the molecular mechanisms of the effects of viral infections on CSU remain to be identified and characterized. A recent review has highlighted urticaria to be the second most common cutaneous manifestation of COVID-19 infection.⁵² A recent study performed by the global network of urticaria centers of reference and excellence⁵³ demonstrated that COVID-19 results in CU exacerbation in 1 of 3 patients, with higher rates in patients with severe COVID-19.⁵⁴ Interestingly, COVID-19 vaccination has also been associated with acute urticaria or angioedema episodes with a pooled estimated incidence of less than 5%^{55,56} as well as exacerbation of CSU.⁵⁷

As for bacterial infections, the potential role of *Helicobacter pylori* (HP) in CSU has been widely discussed without any consensus. A recent systematic review and meta-analysis showed that HP may be associated with the occurrence and persistence of CSU. HP eradication may be beneficial in reducing symptoms in some HP-positive patients with CSU,⁵⁸ but this may be unrelated to HP eradication, and antimicrobial therapy is not a generally recommended therapy.

Altrichter et al⁵⁹ have recently documented higher levels of IgE against staphylococcal enterotoxin B (SEB) in patients with CSU compared with healthy controls, but the difference was not significant. However, SEB IgE antibodies from patients with CSU can induce basophil histamine release, and their levels are significantly correlated with CSU activity. Thus, SEB IgE may play a pathogenetic role in a subgroup of patients with CSU, but further studies are needed to validate this claim.

Another systematic review has documented that parasitic infestation and sensitization is more likely in patients with CSU compared with healthy controls, particularly *Blastocystis hominis*, *Toxocara*, and *Anisakis simplex*.⁶⁰

Role of the genetic background in urticaria

Recent data suggest that genetic background may play a role in the pathogenesis of urticaria in a subset of patients, most notably certain human leukocyte antigens (HLA) class II molecules. Researchers have documented an increased prevalence of HLA-DR4 and HLA-DQ8 alleles in patients with CU compared with healthy controls. In addition, HLA-DR4 and DQB1*0301/4 have been strongly linked with positive basophil histamine release assay (BHRA) and positive ASST, compared with “double negative” CU patients.¹³

Furthermore, a presumably strong link has been demonstrated between protein tyrosine phosphatase-22 (PTPN22) polymorphism and autoimmune (ASST+) CSU susceptibility.⁶¹ These genetic associations may be one of the possible explanations for CSU and underlying autoimmune diseases, as both HLA class II alleles and PTPN22 are strongly linked with autoimmunity. Notably, a recent study from China identified an association between single nucleotide polymorphisms of CACNA1C gene (encoding a calcium voltage-gated channel) with either a susceptibility to develop CSU, or response to treatment with desloratadine.⁶²

Another interesting observation is the sporadic association of hereditary alpha-tryptasemia (HαT) with a special variant of urticaria/angioedema called vibratory urticaria/angioedema,⁶³ including a severe form of familial vibratory urticaria.⁶⁴ HαT is an autosomal dominant genetic condition occurring due to tandem duplications or triplications of the alpha-tryptase encoding *TPSAB1* gene, resulting in elevated serum basal tryptase levels.⁶⁵ These patients may present with symptoms suggestive of systemic mastocytosis and are more prone to develop anaphylaxis, especially when exposed to hymenoptera venom.^{66,67} Recent recommendations suggest ruling out HαT in patients presenting with symptoms of mast cell activation, including urticarial exanthem, and serum tryptase level greater than 6.2 ng/mL.⁶⁶

Thus, to summarize, CU may be speculated to be a complex genetic disorder with variable penetrance. However, most studies concerning genetics in CU are sporadic with inconclusive results. Thus, more large-scale studies are necessary to validate the role of genetics in CU.

NOVEL INSIGHTS ON THE PATHOGENESIS OF BRADYKININ-MEDIATED ANGIOEDEMA

Mast cell-mediated recurrent angioedema in patients with urticaria can resemble, in its clinical presentation, BK-mediated angioedema, for example, in patients with HAE. However,

TABLE II. Demographic factors and potential biomarkers in CSU to predict disease characteristics and improve physician-patient communication

Disease characteristic	Name of demographic factor/biomarker	Remarks
CSU severity or activity	Clinical • Age at onset • Sex • Disease duration • Angioedema, concomitant inducible urticaria, NSAID hypersensitivity • Response to antihistamines	Increased CSU severity/activity associated with: • Older⁷⁶ • Female⁷⁷ • Longer^{76,77} • Presence^{78,79} • Low⁸⁰
	Serological/hematological • Autologous serum skin test (ASST) • C-reactive protein • Basophil count, eosinophil count • Mean platelet volume • D-dimer, prothrombin fragment 1+2 • Vitamin D • Antithyroid peroxidase (TPO) antibodies • IL-6, IL-18, IL-17 • Basophil activation test (CD63, CD203 expression)	• Positive^{78,81,82} • Elevated^{81,83,84} • Low⁸⁵ • Elevated^{86,87} • Elevated⁸⁸⁻⁹⁰ • Low⁹¹⁻⁹³ • Elevated⁷⁹ • Elevated^{42,94,95} • Positive⁹⁶
Disease course	• Antithyroid antibodies • CD63 expression • C-reactive protein	• Elevated levels are associated with a longer disease course^{79,97} • Positive and higher values are associated with a longer course, and earlier spontaneous resolution in pediatric CSU⁹⁸ • Elevated levels are associated with shorter disease duration⁸⁴

CSU, Chronic spontaneous urticaria; NSAID, nonsteroidal anti-inflammatory drug.

there are several differences in clinical presentation and response to treatment.⁶⁸ BK-mediated angioedema tends to follow a slower “trajectory” with a slower progression to maximal severity (12-24 hours) and longer duration of angioedema episodes (3-5 days) if untreated. Urticaria patients with angioedema benefit from the treatment with antihistamines, omalizumab, and glucocorticoids, although the latter are not used for the routine treatment of patients with CU. These treatments do not work in patients with BK-mediated angioedema.⁶⁹ Thus, it is crucial to distinguish between mast cell-mediated and BK-mediated types of angioedema.⁷⁰

The cornerstone of angioedema pathogenesis is increased vascular permeability and plasma leakage into the deeper dermis and subcutis, either mediated by histamine or BK. BK-mediated angioedema occurs due to enhanced activation of the contact system and factor XII, resulting in increased production of BK (activated factor XII breaks down plasma kallikrein to release BK by hydrolysis of high molecular weight kininogen [HMWK]). BK subsequently acts on endothelial B2 receptors to increase vascular permeability and plasma leakage. C1-INH, a serine-protease inhibitor, is the main regulator of this contact system, thereby regulating BK production.³ Thus, C1-INH deficiency, hereditary or acquired, is the primary cause of BK-mediated angioedema due to increased plasma BK concentration.

HAE, due to C1-INH deficiency, is a rare autosomal dominant genetic condition characterized by recurrent attacks of angioedema that most of the time are attributed to mutations in SERPING1, the gene coding C1-INH. As a result, there is either quantitative deficiency of C1-INH (type 1), or functionally defective C1-INH (type 2). Over 500 types of mutations have

been identified in the SERPING1 gene; however, in 5% to 10% of cases of HAE-C1-INH, no mutation has yet been identified. The frequency and severity of HAE attacks have considerable interindividual variation and can even differ among patients within the same family,⁷¹ although, in general, functional C1-INH levels below 38% of normal have been associated with an increased risk of attacks.⁷²

An unmet need remains the identification of these biomarkers or mutations that will be able to predict attacks and their severity on top of distinguishing mast cell-mediated and BK-mediated angioedema. Recently, Bindke et al⁷³ have identified some promising biomarkers in angioedema, that is, Tie-2 for HAE, fibroblast activation protein- α (FAP- α), and tissue-type plasminogen activator (tPA) for angioedema in general, and sE-Selectin and Ang-2 for all BK-mediated angioedema. However, more research is needed to establish their validity and specificity.

Recently, some subtypes of HAE have been identified, which occur without any quantitative or qualitative irregularity of C1-INH, that is, normal C1-INH quantity/function (HAE with normal C1-INH- [HAE-nl-C1-INH]), and various underlying mutations have been discovered (detailed in Table 1). The pathophysiology of these HAE-nl-C1-INH conditions is complex, with some likely involving contact system dysregulation (factor XII, PLG, KNG1, and HS3ST6) and others with putative mechanisms related to vascular endothelial dysfunction (ANGPT-1, MYOF). Acquired C1-INH deficiency is an additional cause of BK-mediated angioedema, which is often caused by excess C1-INH consumption due to underlying lymphoproliferative or autoimmune conditions. Among acquired angioedema, the most common variety is induced by

TABLE III. Potential biomarkers in CSU to predict therapeutic response and improve disease management

Therapeutic response	Name of biomarker	Remarks
Antihistamines	Clinical ASST or BAT	Positively associated with no/insufficient response^{99,100}
	Serological/hematological - C-reactive protein - D-dimer/F 1+2	- Elevated levels are associated with nonresponse^{90,101} - Higher levels are associated with inadequate response^{88,90,101}
Omalizumab	Clinical ASST	Positively associated with insufficient response¹⁰²
	Serological/hematological Total serum IgE	- Higher baseline values and higher increase post-treatment are associated with a favorable response and faster relapse after omalizumab discontinuation^{103,104} - Notably, a lower week 4 IgE/baseline IgE ratio is a more accurate marker of nonresponse compared with baseline IgE alone ($P = .016$)¹⁰⁴ - However, the IgE level is not associated with time to response.⁸¹
	- BAT/BHRA - Basophil FcεR1 expression	- Negative, that is, reduced expression of CD63 and CD203 associated with a more favorable response^{81,105} - Higher expression is associated with a more favorable response¹⁰⁶
Cyclosporine	Serological/hematological - Total serum IgE - D-dimer - BAT/BHRA	- Lower baseline values associated with favorable response¹⁰⁷ - Lower levels associated with satisfactory clinical response¹⁰⁸ - Positive result (increased expression of CD63 and CD203) associated with better clinical response^{109,110}

ASST, Autologous serum skin test; BAT, basophil activation test; BHRA, basophil histamine release assay; CSU, chronic spontaneous urticaria.

angiotensin-converting enzyme inhibitors (ACEIs). These drugs block ACEI, which degrades BK, thus resulting in excess accumulation of BK and angioedema.⁷⁴ Table I highlights the various subtypes of “angioedema without wheals” with relevant details.

ROLE OF NOVEL PATHOGENETIC INSIGHTS OF URTICARIA AND ANGIOEDEMA IN IMPROVING PHYSICIAN-PATIENT COMMUNICATION AND DISEASE MANAGEMENT

The novel insights on the pathogenesis of urticaria and angioedema can help to improve patient-physician communication, especially in CSU. In the past, many patients with CSU did not receive consultations with their physician, the information they were looking for, or helpful answers to their questions. Physician communication on CSU was focused on the unpredictable and long course of CSU, that its cause is unknown, that little can be done to help, and that patients have to live with their disease. Moreover, patients were left without a concept of their disease, resulting in frustration, consulting with other physicians, and often giving up on using health care resources to help manage their disease. In addition, patients with CSU were rarely discouraged, and in some cases actively encouraged, to think that they have CSU because they are allergic to something they eat, breathe in, or have skin contact with. This erroneous concept, in turn, commonly resulted in allergy testing (linked to delayed treatment) without relevant results, further reinforcing the misconception that the cause of CSU cannot be detected. That management was therefore challenging.

The identification of autoimmunity and autoallergy as major drivers of the pathogenesis of CSU offers the opportunity to improve physician-patient communication. Rather than highlighting what is not known about CSU, today we focus, in our conversations with patients, on the fact that we know what happens in their skin, that mast cells get activated, histamine is released, and that this explains their signs and symptoms. We

further explain that most patients with CSU have their disease because they are allergic to themselves or because they are autoimmune, that is, because their immune system attacks and thereby activates their skin mast cells. This can help patients understand that their disease comes from the inside rather than their environment, that there is little use in allergy testing, and that they will experience spontaneous remission at some point. This basis of this line of communication, that is, that we do know what causes CSU, can lead to a meaningful conversation on treatment options and that many patients with CSU can be helped with the therapeutic options currently available and that novel and better treatment options are under development.

A recent systematic review identified that almost 1 of 3 patients with CU experiences at least 1 comorbid psychiatric disorder. There was no association between psychological functioning and CU severity and duration; however, the need for a multidisciplinary approach involving prompt recognition and management of any potential psychiatric comorbidities in addition to urticaria treatment was highlighted.⁷⁵

In another systematic review, the same group investigated the association between psychological stress and neuroimmune inflammation in CU. Complex neuroimmune-cutaneous cross-talk at the skin that could better explain the underlying pathophysiological mechanisms involved in the onset and maintenance of urticaria, or the stress-induced urticaria exacerbations, was underscored. This underlying complex psychoneuroimmune dysregulation may suggest new psychophenotypic or neuroendotypic CSU subsets.¹² It needs to be further investigated if pharmacological or nonpharmacological psychological/psychiatric intervention can help control or even treat some CU cases. Thus, mental health evaluations of patients with CU should be considered in routine clinical practice.⁷⁵

How can we use the recent novel insights to improve clinical outcomes in our patients? Several biological characteristics have been linked to the known endotypes of CSU, and they may help to forecast disease characteristics and therapeutic response before

TABLE IV. Selected MC-targeted therapies under development and their modes of action

Name of drug	Mechanism of action	Interesting facts	Stage of development
Ligelizumab	Reduction of total and specific IgE	- Humanized mAb against IgE, with greater affinity for IgE and FcεR1 receptors - Showed greater efficacy than omalizumab in a phase IIb trial, but not in the phase III PEARL1 and PEARL2 trials	Phase 2/3 ¹¹⁸ Further evaluation for CSU has stopped
Quilizumab	Inhibits proliferation of IgE-switched B cells and plasmablasts, thus reducing serum IgE ¹¹⁹	- Not significantly better in comparison with placebo¹²⁰ - May be tried in combination with omalizumab for better results	Proof of concept ¹²⁰
Tezepelumab	Blocking alarmin TSLP, one of the principal drivers of Th2 inflammation	- Anti-TSLP mAb prevents interaction with TSLP receptor - CSU wheals have upregulated TSLP - Effective in asthma, being tried in CSU - Reduced itch and hives compared with standard of care	Phase 2 ¹¹⁶
Dupilumab	Inhibiting IL-4 and IL-13 effect by blocking their common receptor IL-4α		Phase 3 ¹²¹ Part A (first study): in biologic-naïve patients, dupilumab significantly reduced itch and hives compared with standard of care Part B (second study): in patients refractory to omalizumab, dupilumab did not reach statistical significance in an interim analysis despite numeric improvements observed across key end points
Benralizumab (IL-5R Ab), mepolizumab, and reslizumab (anti-IL5 Ab)	IL-5 and IL-5 receptor blocker	- Approved in bronchial asthma - Currently being tried in CSU as IL-5 is one of the principal mediators of Th2 inflammation - IL-5 is an eosinophil chemoattractant, a cell involved in CSU	Phase 2 ¹²²⁻¹²⁴
AZD1981 (oral)	CRTH2/PGD2 receptor inhibitors	A role of PGD2 via CRTH2 has been speculated in CSU, as these receptors are constitutively expressed on eosinophils, basophils, and Th2 cells	Phase 2 trial conducted but primary end point not achieved (UAS7 reduction >9.5 from baseline) ¹²⁵ Further studies needed
Aprepitant, serlopitant, tradipitant, and orvepitant	Blockers of MRGPRX2 receptor and its agonists (substance P, EPO), for example, substance-P antagonist	- MRGPRX2 receptors preferentially expressed by skin MCs - This receptor mediated non-IgE-mediated activation and degranulation of mast cells - Substance P is a prominent neuropeptide involved in CSU pathogenesis via this receptor; thus its antagonists are a promising target	Preclinical ¹¹⁹
Remibrutinib and rilzabrutinib (GSK2646264)	Bruton's tyrosine kinase inhibitor and spleen tyrosinase kinase inhibitor	- These agents block the intracellular pathways of MC degranulation by blocking transduction of signals downstream - Promising targets in CU management	Phase 2/3 ¹²⁶

(continued)

TABLE IV. (Continued)

Name of drug	Mechanism of action	Interesting facts	Stage of development
Lirentelimab (LY3454738)	anti-Siglec-8 and anti-CD200Ra	• Most MC receptors are activating receptors, and 2 inhibitory receptors have been identified: Siglec-8 and CD200Ra • Compounds engaging these receptors silence MCs and prevent their degranulation and mediator release, thus relieving symptoms • Have been found to be beneficial in antihistamine and/or omalizumab refractory urticarias	Open-label proof of concept ¹²⁷ Phase 2 ¹¹⁶
Barzolvolimab (CDX-0159)	CD117 (KIT) receptor blocker	• MCs use SCF (stem cell factor) for their survival, differentiation, proliferation, activation, and degranulation • SCF acts via CD117 (KIT) receptor • A blocker of this receptor would prevent/reduce further accumulation and activation of MCs, and also reduce their survival, thereby improving CU (an MC-mediated disorder) • However, how skin MCs can be exclusively targeted, sparing lung and other MCs, is unclear	Phase 2 ¹²⁸

Ab, Antibody; *CRTH2*, chemoattractant receptor-homologous molecule expressed on Th2 cells; *CSU*, chronic spontaneous urticaria; *EPO*, eosinophil peroxidase; *mAb*, monoclonal antibody; *MC*, mast cell; *PEARL*, Study of Efficacy and Safety of Ligelizumab in Adolescents and Adults With Chronic Inducible Urticaria Who Remain Symptomatic Despite Treatment With H1- Antihistamines; *PGD2*, prostaglandin D2; *TSLP*, thymic stromal lymphopoietin; *UAS7*, weekly urticaria activity score.

treatment initiation. In CSU, these biological characteristics or biomarkers include demographic and clinical features and serological signals. They can and should be used to obtain, for individual patients, a risk profile for having CSU of long duration, high disease activity, major impact on quality of life, developing comorbidities, and responding to treatment. Working with biomarkers can immensely benefit physician-patient communication as physicians can better counsel patients regarding their disease prognosis and course from the very beginning. If the prognosis and course of the disease can be explained to patients with a fair degree of accuracy, it may improve their treatment compliance and rationalize their expectations. However, physicians who treat patients with CSU should know that biomarkers predict outcomes on a population level and that the experience of individual patients may differ from the predicted outcome. The combined use of several biomarkers, where available, can reduce this risk. Biomarkers that can be used to predict disease characteristics are listed in Table II.⁷⁶⁻⁹⁸

Currently, the identification of predictors of treatment responses is the most active area of biomarker research in CSU. Patients with CSU demonstrate variable therapeutic responses, with more than 50% nonresponse to treatment with antihistamine, the recommended first-line therapy. Omalizumab, the recommended second-line treatment, comes with response rates ranging from 26% to 83%, fast or slow response, and sustained remission or relapse after its discontinuation. Biomarkers that predict these treatments' efficacy, time to onset, and durability are emerging and can already help patients in routine clinical practice. Better biomarkers are needed, however, together with novel targeted treatments, to enable precise tailor-made treatment for each patient, with fast and complete control achieved by affordable treatment options. Biomarkers that can be used to predict CSU treatment response are listed in Table III.⁹⁹⁻¹¹⁰

ROLE OF NOVEL PATHOGENETIC INSIGHTS OF URTICARIA AND ANGIOEDEMA IN DEVELOPING NEWER TREATMENT OPTIONS

The currently accepted global treatment guideline for urticaria includes 3 therapies and their up dosing if necessary: second generation antihistamines, omalizumab, and cyclosporine as first, second, and third therapeutic lines, respectively.¹ Only 2 of them are licensed for this use, antihistamines for all types of urticaria and omalizumab only for CSU.

Although antihistamines constitute the first-line therapy for CSU, almost 61% do not respond to the standard dose, and up dosing is beneficial in only 63% of these nonresponders.¹¹¹ Omalizumab has revolutionized the treatment of CSU, as it directly affects the disease pathogenesis. It is the first in-class monoclonal antibody against IgE, which binds and lowers free IgE, subsequently resulting in downregulation of the FcεRI receptor on basophils and mast cells. Lowered FcεRI expression reduces the susceptibility of these cells to be activated by IgE and anti-FcεRI IgG, thus preventing histamine release and subsequent urticarial symptoms.¹¹² The licensed dose is 300 mg (Europe) and 150 or 300 mg (USA) by subcutaneous injection every 4 weeks. However, more than a third of patients remain symptomatic, even after receiving omalizumab for 6 months.¹¹³ The recent guidelines recommend dose increment and/or shortened interval of omalizumab in such cases (up to

600 mg every 4 weeks), as it has been found to be safe and effective.¹ In addition, omalizumab also improves several aspects of the quality of life of such patients, as demonstrated in real-life studies.¹¹⁴ Currently, omalizumab is approved for CSU in patients ≥ 12 years old, but it was also shown to be effective (although not yet approved) in CIndU, particularly symptomatic dermographism, cold urticaria, cholinergic urticaria, and solar urticaria.¹¹²

Today, many patients with CU do not achieve the goal of treatment, complete control, and the absence of signs and symptoms, with antihistamine or omalizumab treatment. Newer and better treatment options are needed, and several are currently under development. The development of these novel treatments is guided by recent insights into the pathogenesis of urticaria. All of them are mast cell targeted, based on the pivotal role of mast cells in the pathogenesis of urticaria. Novel approaches include mast cell silencing and mast cell depletion. Other treatments under development are endotype targeted, with targets that are specific for aaCSU or aiCSU. Novel treatments under development for urticaria as well as the underlying rationale and targets have recently been reviewed in detail.¹¹⁵⁻¹¹⁷ Table IV highlights and summarizes recent therapeutic advances in urticaria and their action modes.¹¹⁸⁻¹²⁸

Of note, none of these treatments aim to cure urticaria, although some of them can be expected to be disease modifying. Strategies to achieve a “complete cure” need to be developed and will need to be endotype specific. Thus, further research on known and additional endotypes of urticaria is needed, especially in acute urticaria and CIndUs.

Like for CU, several new and targeted therapeutic options have been approved for HAE in recent years, and additional therapies are in development for BK-mediated angioedema. The approval of hereditary-angioedema-specific therapies for both prevention and self-administration/caregiver administration of acute attacks has revolutionized the treatment of this disease. HAE treatment is currently focused on early treatment with rescue medication at the onset of attacks (on-demand treatment) and on reducing the frequency and severity of attacks with preventative medication (long-term prophylaxis treatment).¹²⁹ Modern effective HAE medications include C1-INH concentrates (plasma derived or recombinant), plasma kallikrein inhibitors, and a BK-2 receptor antagonist. Additional investigational medications targeting the contact system are in development for HAE including monoclonal antibodies, RNA-targeted therapies, orally administered targeted small molecules, and gene therapy through adeno-associated virus and clustered regularly interspaced short palindromic repeats associated protein 9 strategies. These emerging therapies have recently been comprehensively reviewed.^{117,130}

CONCLUSIONS

CSU is a chronic inflammatory disease with a complex pathogenesis. Skin mast cell activation can be induced via the IgE-Fc ϵ RI axis but also from several other distinct mechanisms, molecules, and receptors involved in CSU onset, preservation, and deterioration. These include autoallergy, autoimmunity, central or peripheral neuroimmune dysregulation, activation of both extrinsic and intrinsic coagulation pathways, and microbial infections. Besides mast cells, which play a central role in CSU pathogenesis, recent reports suggest the active and direct

involvement of basophils and eosinophils. Several biological characteristics or biomarkers have been linked with CSU's known endotypes and may help forecast therapeutic responses.

The cornerstone of angioedema pathogenesis is increased vascular permeability and plasma leakage into the deeper dermis and subcutis, either mediated by histamine or BK. C1-INH deficiency, hereditary or acquired, is the primary cause of BK-mediated angioedema due to increased plasma BK concentration. Other complex conditions have been identified, with some likely involving contact system dysregulation and others putative mechanisms related to vascular endothelial dysfunction. An unmet need remains the identification of these mutations or biomarkers that will predict angioedema attacks and their severity on top of distinguishing mast cell-mediated and BK-mediated angioedema, which is a crucial clinical dilemma.

Any new knowledge of the pathogenesis of CSU and angioedema offers the opportunity to improve patient information, physician-patient communication, prediction of therapeutic responses, selection of precise tailor-made treatment for each patient, and exploration of novel treatment options for those who do not achieve disease control with current medications. The development of these novel treatments will be guided by recent insights into urticaria's pathogenesis. Of note, none of these treatments aim to etiologically and permanently cure urticaria, although some of them can be expected to be disease modifying. Strategies in this direction are expected to arise only after the complex underlying pathophysiology is completely unraveled.

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