Unmasking Chronic Spontaneous Urticaria

Medical Experts Provide Perspectives on Recognizing Symptoms and Disease Burden, the Role of BTK in the Disease Pathophysiology, and Exploring Unmet Needs in CSU

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BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria.

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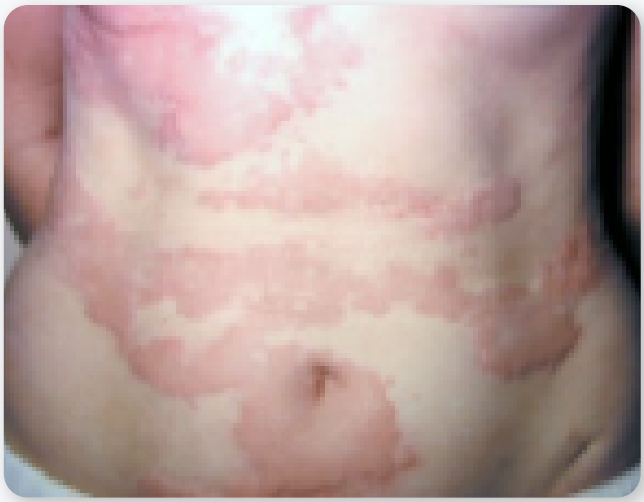
CSU Symptom Recognition

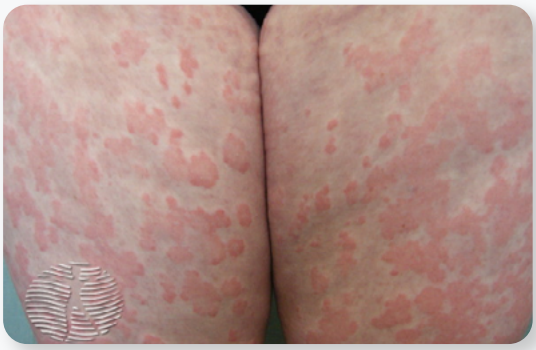
The Key to an Accurate and Timely Diagnosis

Chronic spontaneous urticaria (CSU) can have a profound impact on many aspects of patients' lives; understanding the common symptoms associated with the disease can guide recognition, lead to a prompt diagnosis, and ultimately improve disease management.



CSU is a mast cell–driven skin disorder thought to be caused by immune dysregulation.[1,2] CSU is marked by the spontaneous appearance of wheals, angioedema, or both for a cumulative period of more than 6 weeks.[3] Unfortunately, patients with CSU may experience a delay of up to 2 years or longer, in some cases, from symptom onset to diagnosis, with many suffering from debilitating symptoms before receiving treatment.[4]

Learning about symptoms and how to identify CSU is key to an accurate and timely diagnosis. CSU may affect the whole body. Wheals can vary in location and intensity and can appear on multiple areas, including the upper and lower extremities, chest, abdomen, and face, and angioedema can affect the face and extremities as well **(Figure 1)**.[5-7] The clinical morphology of urticaria can be quite diverse, deviating from the more classic "wheal and flare" textbook description. Focusing on the more pertinent findings and history that define and distinguish CSU from urticarial diseases is crucial for accurate diagnosis and, therefore, effective management of CSU.



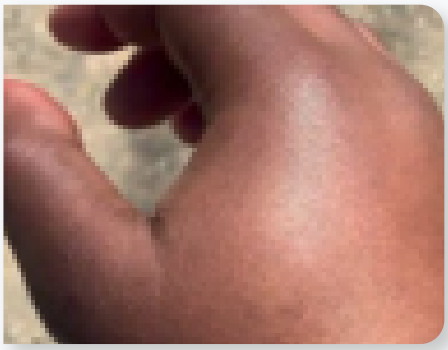


Figure 1.
CSU: Hives (left) and Angioedema (right)

CSU can be unrelenting, with daily or almost daily signs and symptoms.[3,9] While wheals disappear within 24 hours, new wheals in the same or different locations can appear concurrently.[7,10] CSU has no known external triggers and may remit spontaneously.[3] Despite spontaneous remission, severe disease can last decades, and even moderate disease can last for 5 years or more.[4,11]

CSU has no known external trigger. That's the most important thing. Patients come in thinking it's an allergy, or if you identify what's causing their CSU, it will go away if they remove that, and it's not true.

—Dermatologist, **Dr Friedman**

In up to ~30% of cases, CSU may coincide with chronic inducible urticaria (CIndU), which does involve external triggers, including cold, exercise, and pressure.[3,12-14] Therefore, it's critical to assess patients for both of these distinct conditions to optimize management practices and communicate appropriate disease-specific information to patients.

Assessing a patient's history is paramount to identifying CSU, as there is no predictable pattern, and almost every patient is going to present differently.[15,16] A key feature of CSU is the unpredictability of recurring hives and itch intensity. Because of this unpredictability, some patients may present without symptoms at the time of their office visit.[3,17]

I encourage patients to document their disease by taking photos because I tell them 'I always scare away the hives by the time they come in [to see me].'

—*Allergist*, **Dr Soong**

Getting answers to these questions is critical to uncovering CSU:

- Do the individual lesions last for more than 24 hours?
- Do the hives itch and, if so, how do they feel when scratched (ie, does scratching produce a burning sensation)?
- When did the hives begin?
- How often do the hives occur (daily, every few days/ weeks, or less often)?
- Has swelling accompanied the hives and, if so, on what parts of the body?
- Have you used any over-the-counter medications or corticosteroids to treat the symptoms?
- Have you gone to urgent care or the emergency room?

Disease Burden

The Heavy Toll of CSU on Patients' Quality of Life

For many patients, pruritus is their most bothersome symptom, especially at night, making it difficult for patients to sleep and, in some cases, leading to chronic fatigue.[1,18-20] Painful and intense pruritus is emotionally distressing, and symptoms can appear rapidly and unexpectedly at any time, causing immense stress if a patient experiences an unexpected CSU flare-up during important life events.[1,5,18,21,22]

CSU can significantly reduce a patient's quality of life (QoL), especially if symptoms persist for many months to years.[23] In fact, the QoL of patients with CSU or CIndU, who respond poorly to treatment, was worse compared to that of patients with other chronic diseases, like rheumatoid arthritis and insulin-dependent diabetes.[24] The presence of angioedema is also a strong predictor of impaired QoL.[25] Although angioedema in CSU is not life-threatening, misperceptions about the potential for angioedema-related anaphylaxis can add to patient distress.[7,26]

I tell everybody I think itching is a form of torture, especially not knowing when you're going to itch, and the unpredictability and nature of the itching.

—Dr Soong

Beyond physical discomfort, symptoms can have a serious impact on patients' psychological well-being and can interfere with their daily activities[1,18,27]

Patients are often embarrassed or feel shame over the visible signs of CSU and can have a negative view of their body, leading many to avoid social events and restrict their choice of clothing.[22,23,28] According to survey data, self-reported rates of depression and anxiety are twice as prevalent in patients with CSU compared with those without CSU.[22,a]

Compared to plaque psoriasis and atopic dermatitis, patients with CSU report higher levels of anxiety, depression, and impaired QoL[29,b]

CSU affects women twice as often as men.[9] The peak age of CSU occurrence is between 20 and 40 years old, a time when people are in their most productive years.[23] Patients with CSU reported that the disease also impacts their work performance and productivity.[30]

40% of patients, among those employed, experienced an impaired ability to work according to a retrospective, cross-sectional study of 369 patients with CSU[22,c]

> *CSU is a disease that may flare up at nighttime, and as a result, patients are not sleeping. Decreased sleep can lead to so many other comorbidities and problems such as absenteeism and presenteeism.*
>
> —Dr Friedman

Understanding the impact of CSU on a patient's QoL using validated patient-reported outcomes (PROs) is an important aspect of disease management and is recommended by the guidelines.[3] The weekly Urticaria Activity Score (UAS7) is one questionnaire for assessing disease activity in patients with CSU **(Figure 2)**.[3]

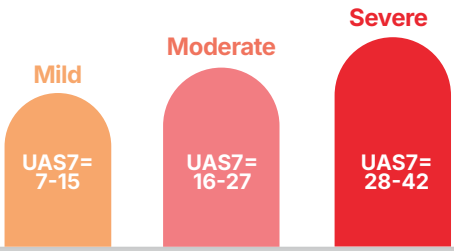
Figure 2. Monitoring Disease Activity With the UAS7[3]

To calculate the Urticaria Activity Score (UAS7), summarize the score for each day over 1 week (7 days)

- 0-3 for wheals (HSS) + 0-3 for pruritus (ISS)
- a maximum score of 42

A UAS7 score of 7 or greater indicates active urticaria

HSS, hives severity score; ISS, itch severity score.



The impact of CSU on patients' lives is more severe when urticaria is poorly controlled. CSU suffering can go unseen, so it is vital to monitor treatment responses and frequently communicate with patients about the impact of CSU on their lives to understand the full burden of CSU and not just the physical manifestations.

Where We Stand

Understanding the Current CSU Treatment Paradigm

According to guidelines, the goal of CSU treatment is to treat the disease until complete symptom control is achieved.[3] The guidelines recommend using second-generation H1 antihistamines as the first-line treatment, yet approximately 50% of patients remain symptomatic.[31]

~50% of patients will remain symptomatic despite the use of antihistamines[31]

If adequate control of symptoms is not achieved after the initial dose of the second-generation H1 antihistamine, then guidelines recommend that the dose of second-generation H1 antihistamine should be increased.[3]

However, even use of guideline-recommended increases of H1 antihistamines may not always result in symptom control.[32]

> *I think a lot of physicians make the mistake of thinking that if the guideline-recommended dose increase of antihistamines didn't cut it, they should stop treatment and start something else. One should not stop one and start another, rather add one or 'layer cake' your treatments.*
>
> —Dr Friedman

A brief course of oral steroids is sometimes used to help patients with a severe urticaria exacerbation; however, even after a short course of steroids, patients can develop adverse events, and urticaria may flare up when steroids are discontinued.[3,33] Treatment guidelines strongly advise against the prolonged use of steroids for CSU because long-term exposure is associated with safety risks.[33] Additionally, there is little evidence that using topical steroids to treat CSU flares has any effect.

59% of patients who take corticosteroids for their CSU have adverse events, even at moderate doses[33,d]

> *The biggest issue with steroids is rebound. It's a deal with the devil. They'll clear, feel great, and then it comes back even worse, usually. So, I think the risks don't outweigh the short-term, if any, benefits.*
>
> —Dr Friedman

For symptomatic patients who are refractory to increased doses of antihistamines, treatment options include advanced therapies.[3] However, advanced therapy options are limited in CSU and, despite their use, symptoms may persist. Escalating treatment to advanced therapy is patient specific, and factors to consider include the risks and benefits of treatment and patient preference.[34,35] In some instances, progressing to advanced therapies may result in additional treatment delays due to challenges with insurance approval.

Exploring CSU Disease Mechanism

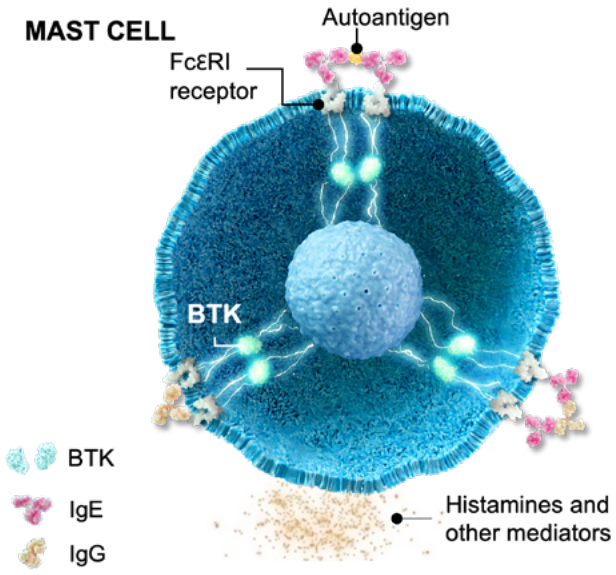
A Mast Cell–Driven Disorder

CSU has no detectable triggers; while the exact mechanism is unknown, it is an internally driven disease with a complex immunological pathophysiology.[36,37] Multiple cell types and inflammatory mediators contribute to the pathogenesis of CSU, but it is understood to be a primarily mast cell–driven disease.[36,38-40]

> *The inability of us as physicians to describe CSU pathophysiology to patients adds to the psychological burden. If we can't describe it well, just imagine what a patient's feeling. I like to tell patients that there's an on switch on your mast cells that your body somehow destabilizes, and then you fall off the cliff. When you fall off the cliff is very unpredictable.*
>
> —Dr Soong

Mast cells can be activated by immunoglobulin E (IgE) (autoallergic)- and/or immunoglobulin G (IgG) (autoimmune)-mediated pathways. In the IgE pathway, IgE antibodies bind autoantigens and activate mast cells through the high affinity IgE receptor, FcεRI, which is central to the disease process. In the IgG pathway, IgG antibodies and autoantibodies, such as anti-FcεRI and anti-IgE antibodies, also activate mast cells through the FcεRI receptor.[8,37] The activation of FcεRI triggers a cascade of downstream intracellular signaling, resulting in degranulation and a subsequent release of histamine and other proinflammatory mediators (eg, chemokines, cytokines, and leukotrienes).[8,37] This cascade is primarily responsible for the presentation of wheals and angioedema and the stimulation of histamine receptors, which cause itching **(Figure 3)**.[8,41]

Figure 3. Mast Cell Degranulation



In CSU, BTK has been implicated in the activation and degranulation of mast cells and basophils. In autoreactive B cells, overexpression of BTK may promote IgE- and IgG-autoantibody production.[8,41]

BTK is involved in both IgE- and IgG-mediated pathways leading to mast cell degranulation, and is one key driver of CSU pathophysiology[8,41]

Bringing It All Together

CSU is a devastating disease; uncontrolled CSU can distress patients in countless ways, affecting patients physically and psychologically and interfering with their ability to work and socialize. There is a need for better recognition of symptoms and patient burden (physical, social, and psychological) of the disease, and a further understanding of key disease drivers of CSU. Increased understanding of CSU pathophysiology and the role of disease mediators, such as BTK, provides insight into this complex disease.

> *These patients are miserable. Getting them better enables them to appreciate the things that we take for granted, that's the big thing. Not having to be in a constant state of paranoia or concern that their disease will flare up and people are going to stare at them, that is a goal that many patients feel is out of reach. Providing sufferers control over their disease is very rewarding.*
>
> —Dr Friedman

Health care providers have a distinct opportunity to recognize the burden CSU has on patients and treat them appropriately. This is essential to alleviating the significant impact CSU has on patients' physical, social, and psychological health.

[a]Based on real-world data.

[b]Results from a retrospective, cross-sectional analysis that incorporates data taken from the 5EU National Health and Wellness Survey in 2010 (N=57,805), 2011 (N=57,512), and 2013 (N=62,000) and estimates the burden of CSU among adults diagnosed with chronic urticaria in terms of health-related QoL, self-reported depression, anxiety, and sleep difficulties, work and activity impairment, and health care use.

[c]Results from a retrospective, cross-sectional analysis of survey data. The Work Productivity and Activity Impairment questionnaire was included in the study to measure health-related work and activity impairment. Only respondents who reported being employed full-time, part-time, or self-employed provided data for absenteeism (work time missed due to health), presenteeism (level of health-related impairment while at work), and overall work impairment (combined absenteeism and presenteeism). The overall work impairment of patients treated for chronic urticaria and for matched controls was 39.7% (N=369) and 20.1% (N=1476), respectively.

[d]Results from a retrospective cohort study that analyzed a commercial claims database from January 1, 2008, to December 31, 2012.

Key Takeaways

- **CSU is persistent**, with daily or near-daily symptoms characterized by **unpredictable** hives and **intense itch** with no identifiable external triggers
- **Despite treatment** with second-generation H1 **antihistamines, ~50%** of patients remain symptomatic
- **Treatment options are limited** for symptomatic patients who are refractory to antihistamines
- **BTK is a key mediator** of FcεRI mast cell degranulation. Mast cell degranulation is believed to be **central to the pathogenesis of CSU**
- **A better understanding of CSU's pathophysiology** is needed to **address unmet needs**

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