INTERNATIONAL JOURNAL
of PEDIATRIC DERMATOLOGY

Special Issue, 2025
ISSN 3035-1006 online

Narrative Review

How to Manage a Severe Urticaria

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KEYWORDS

Chronic urticaria,
CSU,
Hives,
Angioedema

ABSTRACT

Chronic spontaneous urticaria (CSU) is a condition characterized by the recurrent appearance of wheals (hives) and/or angioedema lasting for more than six weeks without an identifiable trigger. It is often difficult to treat but recent advances in the understanding of pathophysiology allows for the adoption of more personalized treatments (1). The author reports the most recent findings regarding diagnosis, monitoring and therapeutic approach (2).

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Definition and epidemiology

Urticaria is defined by transient, itchy, raised skin lesions (wheals) that typically last less than 24 hours and are often associated with a burning sensation. Angioedema, which involves swelling of deeper skin layers and mucous membranes, may accompany chronic urticaria (40-50% of cases) or occur independently (10% of cases) (1).

In pediatric populations, the prevalence of CSU ranges from 0.7% in Europe to 1.8% in Korea. Prognosis varies: remission occurs in about 10–32% of cases after one year, and up to 72% after five years (1).

Pathophysiology and classification

Chronic Urticaria is classified into:

• **Spontaneous forms** (idiopathic, allergic, or pseudo-allergic) representing 80% of cases.

• **Inducible forms** (triggered by physical stimuli like cold, heat, pressure, or sunlight) (Fig.1), representing 20% of cases.

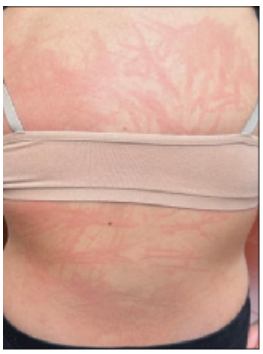

Fig. 1. *Symptomatic dermatographism.*

CSU involves mast cell activation, which is driven by multiple pathways:

• IgE receptors (FcεRI)
• MRGPRX2 receptors
• Complement system components (e.g. C5a)
• Cytokine and protease-activated receptors

Two main CSU endotypes are discussed:

• **Type I (autoallergic)**: mediated by IgE autoantibodies (IgE anti TPO, IgE anti Il-24, IgE anti dsDNA);
• **Type IIb (autoimmune)**: characterized by IgG autoantibodies against IgE or its receptor (3).

Phenotypes

Allergic Type I CSU affects 30-40% of children with CSU. They are characterized by the presence of high comorbid atopic diseases; high/normal total IgE; good response to omalizumab. This disease has usually a shorter duration when compared with autoimmune Type IIb CSU, it is not accompanied by angioedema and children are younger than those with autoimmune Type IIb CSU.

Autoimmune Type IIb CSU affects only 10% of children with CSU. They are characterized by the presence of high comorbid autoimmune diseases, low total IgE; poorer/slower response to omalizumab, longer duration of the disease which could be associated with angioedema. Children affected are older than those with allergic Type I CSU (4).

Diagnosis and monitoring

First-level diagnostic tests mostly include:
• Complete blood count, liver and kidney function, thyroid tests;
• Autoantibodies (e.g., anti-TPO), total IgE levels;
• Celiac disease screening.

There are not biomarkers to be used for diagnosing the correct phenotype. The cutoff value for IgG anti-TPO/total IgE ratio of 2.88 was defined for the detection of type IIb CSU on the basis of data from the PURIST study and it seems to be promising (5).

Disease activity is monitored using:
• **UAS7 (Urticaria Activity Score)**: a 7-day scoring system assessing daily hives and itching
• **UCT (Urticaria Control Test)**: a simple patient-reported tool for disease control assessment
CU-Q2oL is a questionnaire used to monitor quality of life.

Treatment approaches

Treatment follows a stepwise approach as recommended by international guidelines (EAACI/GA²LEN/WAO):
1. **Second-generation H1 antihistamines** (standard dose);
2. **Increased dose of antihistamines** (up to 4x);
3. **Biologic therapy**: **Omalizumab**, a monoclonal antibody targeting free IgE, is the only currently approved biologic for CSU.

Omalizumab is generally effective, with significant reductions in symptoms (UAS7) and improvement in quality of life. However, about 30% of patients are **non-responders**, and half may relapse after discontinuation. The treatment does not alter the long-term course of the disease but can be resumed with good efficacy (6-8).

Emerging therapies and research

Several new therapeutic strategies are under investigation, including:
• Next-generation anti-IgE therapies: Ligelizumab, UB-221;
• BTK inhibitors: Remibrutinib, Fenebrutinib – promising results in patients unresponsive to Omalizumab (9);
• Cytokine-targeting biologics: Dupilumab (IL-4/IL-13), Tezepelumab (TSLP), and others;
• Mast cell modulation strategies: JAK inhibitors, Siglec-8 agonists, and KIT inhibitors.

Conclusion

CSU is a heterogeneous and often difficult-to-treat condition. While many patients respond well to standard therapies, a significant subset remains refractory. Recent advances in the understanding of pathophysiological mechanisms are paving the way for more personalized, targeted treatments, which hold promise for improving outcomes in patients with severe, treatment-resistant CSU.

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