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Clinical practice guideline for H1 antihistamine-resistant Chronic Spontaneous Urticaria

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Abstract

Chronic spontaneous urticaria (CSU), characterized by recurrent wheals and/or angioedema persisting for more than 6 weeks, represents a substantial clinical challenge. Although international guidelines endorse second-generation H1-antihistamines (sgAHs) as first-line therapy, up to 50% of patients remain refractory even at quadruple doses, significantly compromising quality of life and mental well-being. Notably, standardized guidelines for managing H1 antihistamine-resistant CSU are currently lacking. To address this gap, we aimed to develop an evidence-based clinical practice guideline for the diagnosis, assessment, and step-wise treatment of H1 antihistamine-resistant CSU. A multidisciplinary panel conducted a systematic literature review and through multiple rounds of group discussions, both offline and online, to draft recommendations. Evidence was graded using the Oxford CEBM 2011 system and recommendations assigned GRADE strengths. This guideline provides a standardized, personalized treatment algorithm for H1 antihistamine-resistant CSU, aiming to improve clinical efficacy, reduce socioeconomic burden, and direct future research toward validating novel agents such as JAK inhibitors and optimizing long-term outcomes.

Key words: Chronic Spontaneous Urticaria, Antihistamines, Resistant, Omalizumab, Guidelines

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Abbreviations:

CSU	chronic spontaneous urticaria
sgAHs	second-generation H1-antihistamines
CSD	Chinese Society of Dermatology
CDA	China Dermatologist Association
IgE	Immunoglobulin E
CRP	C-reactive protein
ASST	autologous serum skin test
BTK	Bruton's tyrosine kinase
NB-UVB	narrowband ultraviolet B
JAK	Janus kinase
OCEBM	Oxford Centre for Evidence-Based Medicine
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
CIndU	chronic inducible urticaria
IgG	Immunoglobulin G
FcεRI	high-affinity IgE receptor
MRGPRX2	mas-related G protein-coupled receptor member X2
PAR	protease-activated receptor
TNF-α	tumor necrosis factor-α
ACE	angiotensin-converting enzyme
C4	Complement component 4
C1INH	C1 esterase inhibitor
AIDs	auto-inflammatory diseases
CAPS	cryopyrin-associated periodic syndromes
NUD	neutrophilic urticarial dermatosis
AECT	angioedema control test
AE-QoL	angioedema quality of life questionnaire
TPO	thyroid peroxidase
ESR	erythrocyte sedimentation rate
UAS7	urticaria activity score over 7 days
ISS7	itch severity score over 7 days
BTKis	Bruton's tyrosine kinase inhibitors
TSLP	thymic stromal lymphopoietin
IVIG	intravenous immunoglobulin
CRTh2	chemoattractant receptor-homologous molecule expressed on Th2 Cells
TCM	traditional Chinese medicine
RCTs	randomized controlled trials
UCT	urticaria control test

Introduction

Chronic spontaneous urticaria (CSU) is a prevalent clinical condition, characterized by recurrent spontaneous wheals and/or angioedema lasting for more than 6 weeks.[1] In China, the prevalence of chronic urticaria is as high as 2.6%, with over half of these cases being CSU.[2,3] Both international and domestic guidelines recommend second-generation H1-antihistamines (sgAHs) as the first-line treatment for CSU.[4,5] However, studies have shown that standard-dose sgAHs achieve complete symptom control in less than half of CSU patients, and even when the antihistamine dose is increased up to fourfold, 10-50% of patients still fail to respond adequately.[6,7] Clinically, patients who fail to achieve complete symptom control despite standard or increased doses of antihistamines, or even when used in combination, are defined as H1 antihistamine-resistant CSU.[4]

H1 antihistamine-resistant CSU significantly impairs patients' quality of life and mental health, posing a substantial medical burden and socioeconomic impact.[8,9] Currently, there are no clinical guidelines or consensus for the diagnosis and treatment of H1 antihistamine-resistant CSU, and existing urticaria guidelines fail to meet the demands for high-quality standardized management. Based on the latest evidence-based data and clinical practice, this guideline aims to standardize the diagnosis and treatment of H1 antihistamine-resistant CSU, improve clinical efficacy, and enhance overall disease management.

Methods

We reviewed the published literature on H1 antihistamine-resistant CSU and combined it with the latest research evidence. A team of 29 senior clinical experts in the field of urticaria was formed. The team included dermatologists, allergists, and immunologists. After multiple rounds of group discussions, both offline and online, the initial version of the guideline was drafted. Subsequently, other authors reviewed and modified the guideline based on their expertise, local conditions, relevant guidelines, and literature. This guideline adopts the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence system to grade the quality of evidence for therapeutic interventions.[10] The strength of recommendations was categorized using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach into three levels: strong recommendation, moderate recommendation, and weak recommendation. Clinical opinions with very low-quality evidence that require individualized decision-making based on comprehensive consideration of patients' specific conditions and clinical practice were designated as "limited recommendations".[11]

Definition and diagnosis of H1 antihistamine-resistant CSU

H1 antihistamine-resistant CSU should be considered when the following criteria are met: (1) inadequate response after 1-2 weeks of standard-dose sgAHs therapy, (2) persistent poor control following either combination therapy with additional H1-antihistamines or dose escalation up to fourfold for another 1-2 weeks, and (3) exclusion of alternative diagnoses. The clinical profile of H1 antihistamine-resistant CSU typically includes: (1) more severe disease manifestations, (2) prolonged disease duration, (3) numerous wheals, frequently with annular/semi-annular morphology, (4) frequent disease flares, and (5) common coexistence with angioedema and/or chronic inducible urticaria (CIndU).

Potential mechanisms of H1 antihistamine-resistant CSU

Current evidence suggests that H1 antihistamine-resistant CSU may primarily involve the following mechanisms: 1) heterogeneity of mast cell activation pathways: H1 antihistamine-resistant CSU is frequently associated with type IIb autoimmunity mediated by autoantibodies (e.g., IgG-anti-FcεRIα and IgG-anti-IgE)[12] and non-IgE-mediated pathways (e.g., MRGPRX2, PAR-1, and PAR-2 activation)[13] which are more likely to exhibit treatment resistance; 2) broad activation of multiple inflammatory cells: beyond mast cells, H1 antihistamine-resistant CSU typically demonstrates extensive involvement of various immune cells including basophils, eosinophils, neutrophils, and lymphocytes, suggesting a complex inflammatory network;[14] 3) participation of non-histaminergic mediators: Mast cells and basophils release numerous inflammatory mediators besides histamine - including leukotrienes, prostaglandins, tumor necrosis factor (TNF-α), interleukins (IL-4, IL-5, IL-13, IL-17), and various neuropeptides - which contribute to urticarial symptoms but remain unaffected by antihistamine therapy.[15]

Differential diagnosis of H1 antihistamine-resistant CSU

The differential diagnosis algorithm for H1 antihistamine-resistant CSU is shown in **Figure 1**. In general, H1 antihistamine-resistant CSU primarily needs to be differentiated from H1 antihistamine-resistant CIndU, hereditary or acquired angioedema, auto-inflammatory syndromes (AIDs), urticarial vasculitis (UV), and neutrophilic urticarial dermatosis (NUD). Key differentiating features of these conditions include:

1) If the patient's wheals and pruritus refractory to H1-antihistamines and consistently correlate with specific triggers, prompt provocation tests for CIndU should be conducted (e.g., dermatographism test, cold/heat contact test, exercise challenge test for patients with cholinergic urticaria, etc.).
2) If the patient presents with recurrent isolated angioedema unresponsive to H1-antihistamines, acquired angioedema induced by medications (e.g., ACE inhibitors), malignancies, or autoimmune diseases, as well as hereditary angioedema, should be investigated. A systematic review of the patient's medical history, medication use, and family history is required, along with C4 and C1 esterase inhibitor (C1INH) testing. Genetic screening may also be considered if available.[16]
3) Patients presenting with H1 antihistamine-resistant urticarial lesions accompanied by systemic symptoms such as fever, arthralgia, and fatigue should raise high suspicion for AIDs. AIDs are a group of recurrent or persistent systemic inflammatory disorders caused by hereditary or acquired innate immune defects or dysregulation. They can be classified into hereditary AIDs with identified pathogenic gene mutations (e.g., cryopyrin-associated periodic syndromes, CAPS) and acquired AIDs without known genetic etiology (e.g., adult-onset Still's disease and Schnitzler syndrome). For infants or children with recurrent antihistamine-resistant urticaria, periodic fever, and arthralgia, genetic testing (e.g., NLRP3 mutation analysis) should be performed to rule out hereditary AIDs such as CAPS; In elderly patients with recurrent antihistamine-resistant urticaria accompanied by bone pain or other osteoarticular symptoms, serum protein electrophoresis should be conducted to evaluate for Schnitzler syndrome.[17]
4) UV, usually refractory to H1 antihistamines, can usually be distinguished clinically due to its characteristic features, including wheals persisting for more than 24 hours and residual hyperpigmentation or purpura/ecchymosis upon resolution. However, definitive diagnosis requires skin biopsy for histopathological examination. If no definitive vasculitis changes are identified, a diagnosis of urticarial vasculitis should be made with caution.[18]
5) NUD is totally resistant to H1 antihistamines, but the wheals may resolve without residual marks. Histopathology shows prominent neutrophilic infiltration without vasculitis. However, key distinguishing features include lesions persisting > 24 hours, elevated CRP and peripheral blood neutrophil levels, and frequent association with extra-cutaneous systemic symptoms.[19]

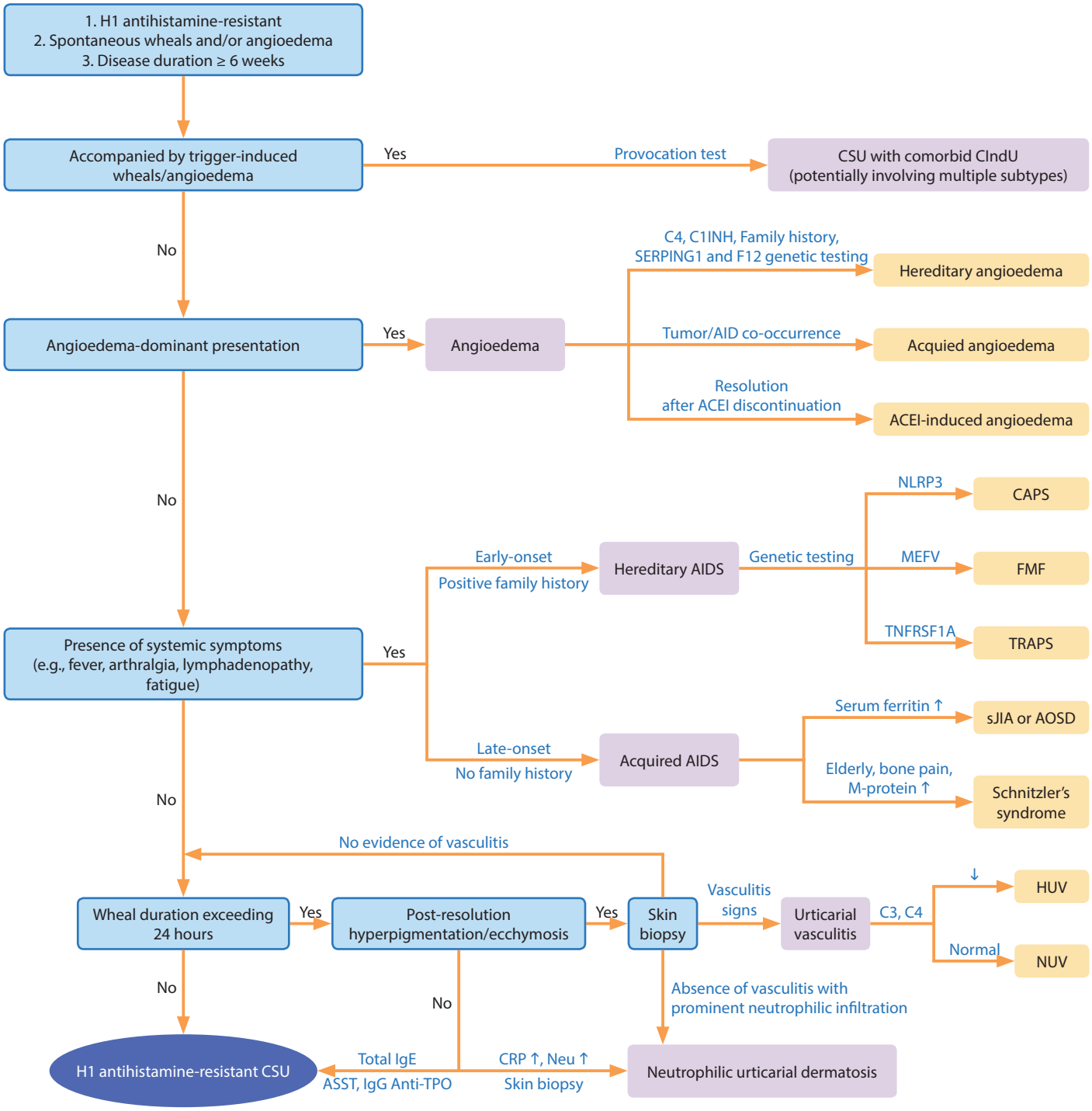

Figure 1. Differential diagnostic algorithm for H1 antihistamine-resistant CSU.

CSU, Chronic spontaneous urticaria; CIndU, Chronic inducible urticaria; C4, Complement 4; C1INH, C1 esterase inhibitor; AID, Autoimmune disease; ACEI, Angiotensin converting enzyme inhibitor; CRP, C-reactive protein; SAA, Serum amyloid A; CBC, Complete Blood Count; AIDs, Autoinflammatory diseases; CAPS, Cryopyrin-associated periodic syndrome; FMF, Familial Mediterranean fever; TRAPS: TNF receptor-associated periodic syndrome; sJIA, Systemic juvenile idiopathic arthritis; AOSD, Adult-onset Still's disease; C3, Complement 3; HUV, Hypocomplementemic urticarial vasculitis; NUV, Normocomplementemic urticarial vasculitis; ASST, Autologous serum skin test; TPO, Thyroid peroxidase; Neu, Neutrophils.

The clinical assessment of H1 antihistamine-resistant CSU

1) **Disease status assessment:** Assess H1-antihistamine-resistant CSU with validated tools.
2) **Comorbidity assessment:** A comprehensive comorbidity assessment is essential in H1 antihistamine-resistant CSU.[20] Notably, approximately 30% of CSU patients present with at least one autoimmune comorbidity, most commonly Hashimoto's thyroiditis and vitiligo.[21] The presence of autoimmune conditions suggests an autoimmune CSU endotype that demonstrates increased propensity for treatment resistance. Similarly, CSU patients with concomitant CIndU - most commonly symptomatic dermographism, followed by delayed pressure urticaria, cold contact urticaria, and cholinergic urticaria[22] - typically show poorer treatment responses.[23] While atopic comorbidities (primarily allergic rhinitis, asthma, and atopic dermatitis) do not influence antihistamine efficacy, they are associated with enhanced responsiveness to omalizumab and increased relapse rates following treatment discontinuation.[24,25] Furthermore, CSU with poor treatment response shows a strong association with psychiatric comorbidities, particularly sleep-wake disorders, anxiety, and depression.[20]

The laboratory investigations of H1 antihistamine-resistant CSU

For patients with H1 antihistamine-resistant CSU, routine laboratory tests can be performed to assist in endotyping or to guide and predict treatment responses, as shown in **Table 1**. Key biomarkers include:

1) **Tests for CSU phenotype:** Elevated total IgE levels are indicative of type I autoimmunity, whereas the presence of anti-thyroid peroxidase (TPO) antibodies and a positive autologous serum skin test (ASST) support type IIb autoimmunity.[26]
2) **Inflammatory markers and disease activity:** Elevations in CRP, ESR, or D-dimer levels and/or reductions in eosinophil/basophil counts reflect heightened inflammatory activation and disease activity in CSU, correlating with poor treatment response.
3) **Additional workup should be tailored to clinical presentation:** Patients with atopic predisposition should be evaluated by allergen-specific IgE testing or skin prick tests, while those of H1 antihistamine-resistant cases with gastrointestinal symptoms should undergo *Helicobacter pylori* testing or esophagogastroduodenoscopy to assess for autoimmune gastritis.[27] In cases of atypical skin lesions (morphologically unusual, lasting > 24 h, leaving residual hyperpigmentation, and refractory to H1-antihistamines), histopathological examination via biopsy is essential to exclude alternative diagnoses such as UV or NUD.

Table 1. Recommended Laboratory Tests for H1 Antihistamine-Resistant CSU.

Category	Item	Clinical Significance and Applicability
Routine Examinations	Complete blood count	**Neutrophils:** Elevated in acute exacerbation of CSU, suggesting infection, steroid use, or systemic inflammation (e.g., neutrophilic urticarial dermatosis). **Eosinophils/Basophils:** Decreased levels link to disease activity and poor response; elevated eosinophils may indicate drug, parasitic, or hematologic disorders.
	Total IgE	Atopic background; predicts omalizumab treatment response.
	ASST	ASST positivityindicates autoimmunity, suggests Type IIb autoimmune endotype, and often correlates with poor response to antihistamines and omalizumab.
	IgG anti-TPO	Indicates autoimmunity; for CSU endotyping.
	CRP	Inflammatory markers.
	ESR	Inflammatory markers.
	D-dimer	Inflammation marker; potential treatment response correlation.
Special Examinations (if necessary)	Allergen specific IgE/SPT	History suggestive of allergic comorbidities and other atopic diseases.
	Provocation test	History indicative of chronic inducible urticaria.
	C3, C4, C1q	Consider comorbid autoimmune diseases, urticarial vasculitis, or hereditary angioedema.
	serum ferritin	Inflammatory markers; suspect adult-onset Still's disease or other autoinflammatory syndromes.
	ANA	Autoimmune marker; consider comorbid autoimmune diseases.
	SAA	Inflammatory markers; screen for autoinflammatory syndromes.
	HP related tests and gastroscopy	Patient with recurrent gastrointestinal discomfort clinically associated with urticarial symptoms.
	Skin biopsy	Wheals persisting >24 hours with post-inflammatory pigmentation or purpura; suspect urticarial vasculitis or neutrophilic urticarial dermatosis.
	C1INH	Suspect hereditary angioedema.

CSU, chronic spontaneous urticaria; IgE, Immunoglobulin E; ASST, autologous serum skin test; IgG, Immunoglobulin G; TPO, thyroid peroxidase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SPT, skin prick tests; C3, Complement component 3; C4, Complement component 4; C1q, Complement component 1q; ANA, antinuclear antibodies; SAA, serum amyloid A; HP, *Helicobacter pylori*; C1INH, C1 esterase inhibitor.

Treatment of H1 antihistamine-resistant CSU

Treatment of H1 antihistamine-resistant CSU should follow the principles of individualization, efficacy, and safety, aiming to achieve complete (UAS7 = 0) or near-complete symptom control (UAS7 ≤ 6) and improve patients' quality of life.

1. Etiological management

Identification and management of underlying triggers and etiologies (e.g., medications, foods, psychological stress, infections, allergens, gastrointestinal disorders, or chronic inflammatory comorbidities) constitute a pivotal therapeutic strategy for H1 antihistamine-resistant CSU. Targeted intervention for confirmed causes may significantly improve disease control. However, given the complex and often multifactorial nature of CSU, this guideline recommends pursuing etiological investigations only when strongly supported by clinical history and presentation (as shown in **Table 2**).

2. Pharmacological management

Omalizumab (strong recommendation, level 1a evidence): Omalizumab is generally well-tolerated, although a small proportion of patients may experience transient injection site reactions or temporary exacerbation of urticarial symptoms following administration. Clinical studies in Chinese populations demonstrate: 1) Overall response rate: 87%-98.7% at 12 weeks; 2) Complete response rate: 65.2%-91.1%; 3) Median time to onset: ≤ 1 month in 50% of patients.[28-30] Studies indicate that different endotypes of CSU show similar response rates to omalizumab, but with varying onset speeds: Type I autoimmune CSU responds more rapidly, whereas type IIb autoimmune CSU has a relatively slower response.[31] For patients who do not achieve a sufficient response after 12 weeks of standard-dose omalizumab treatment, continuing the original dose or increasing the dose for another 12 weeks can lead to a good response in nearly 60% of cases.[32] Therefore, if standard-dose omalizumab treatment fails to achieve a sufficient response

Table 2. Precipitating/Etiologic Factor Management.

Precipitating/Etiologic Factor Management	Evidence-Based Evidence	Recommendations
Avoiding NSAIDs	Nearly one-fourth of patients with CSU experience symptom exacerbation due to oral nonsteroidal anti-inflammatory drugs (NSAIDs). For those with a history of recurrent use of such medications and clinical evidence linking NSAIDs to symptom worsening, avoidance of NSAIDs is recommended to prevent disease exacerbation.[1]	Limited
Dietary intervention	A low-pseudoallergen diet (e.g., avoiding foods containing sulfites, artificial colors, preservatives, and alcohol) and a low-histamine diet (e.g., minimizing the intake of pickled foods, fermented products, and unfresh fish and seafood) have demonstrated some efficacy in certain CSU patients.[2]	Limited
Anti-infection/ antiparasitic treatment	Studies suggest that infections with certain microorganisms, such as Helicobacter pylori or Anisakis, are closely related to CSU. For patients with confirmed infections, targeted anti-infective treatment may alleviate CSU symptoms and reduce recurrence.[3,4]	Limited
Low-dust-mite environment	Studies have shown that patients with CSU sensitized to dust mites experience significant exacerbation of symptoms in environments with high dust mite density. Avoidance of dust mite allergen exposure can alleviate symptoms.[5]	Limited
Treatment for thyroid disease	Studies have shown that refractory CSU is closely associated with autoimmune thyroid diseases. Effective treatment for Hashimoto's thyroiditis, such as medical therapy for thyroid dysfunction and thyroidectomy if indicated, may improve the therapeutic response in patients with CSU.[6]	Limited
Treatment for autoimmune gastritis	Studies have suggested an association between refractory CSU and autoimmune gastritis (AIG). Targeted treatment for AIG, such as vitamin B12 and iron supplementation, may help alleviate CSU symptoms.[7]	Limited

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after 12 weeks, the original dose can be continued, or the injection dose (450 mg or 600 mg per injection) can be increased and/or the injection interval shortened (to once every 2 weeks) for another 12 weeks before reassessing the treatment response.

Cyclosporine (strong recommendation, level 1a evidence): Cyclosporine, a calcineurin inhibitor, demonstrates clinically significant efficacy in H1 antihistamine-resistant CSU, with a meta-analysis reporting response rates of 54.2%, 65.9%, and 73.1% at 4, 8, and 12 weeks of treatment, respectively.[33] The standard dosage is 3.0-5.0 mg/kg, with subsequent individualized adjustments based on therapeutic response, blood drug concentration monitoring, and patient tolerance. Clinical studies confirm that responders can maintain symptom stability for over 6 months with low-dose maintenance therapy (1-1.5 mg/kg).[34] Cyclosporine can be considered the first-line treatment for H1 antihistamine-resistant CSU patients unresponsive to or ineligible for omalizumab therapy. Notably, patients with type IIb autoimmune CSU exhibit more rapid and robust responses to cyclosporine.[35] The primary adverse effects of cyclosporine include gastrointestinal reactions, hypertension, renal impairment, headache, and hypertrichosis, all of which are dose-dependent.

Dupilumab (strong recommendation, level 1a evidence): Dupilumab is a fully human monoclonal antibody targeting the IL-4 receptor α subunit. Two independent randomized, placebo-controlled, multicenter phase III clinical trials (CUPID A and CUPID B) were recently reported.[36] CUPID A enrolled H1 antihistamine-resistant CSU patients who had never received omalizumab, while CUPID B included H1 antihistamine-resistant CSU patients with intolerance or incomplete response to omalizumab. The CUPID A results demonstrated that at Week 24, the dupilumab group exhibited significant improvements in UAS7 and Itch Severity Score over 7 days (ISS7), with reductions of -20.5 and -10.2, respectively, compared to -12.0 and -6.0 in the placebo group. These findings suggest that dupilumab significantly reduces disease activity and pruritus in H1 antihistamine-resistant CSU patients naïve to omalizumab. Although the primary endpoint of CUPID B did not reach statistical significance, dupilumab still showed moderate efficacy in patients with omalizumab intolerance or incomplete response. Overall, dupilumab provides a novel therapeutic option for H1 antihistamine-resistant CSU. Dupilumab demonstrates an overall favorable safety profile, with a minority of patients experiencing mild-to-moderate adverse reactions such as injection-site reactions, conjunctivitis, and blepharitis. This biologic agent represents a safe and effective alternative therapeutic option for H1 antihistamine-resistant CSU, with particular added value in patients exhibiting concomitant type 2 inflammatory comorbidities (e.g., allergic rhinitis, asthma, atopic dermatitis). However, its current use for CSU constitutes off - label application across the vast majority of regions worldwide, as regulatory approval for this indication has been granted only in Japan and the United States to date. The standard dosing regimen consists of an initial 600 mg loading dose, followed by 300 mg administered subcutaneously every 2 weeks. Pediatric dosing should be adjusted according to age and body weight.

BTK inhibitors (strong recommendation, level 1a evidence): BTK inhibitors (BTKis) exert anti-inflammatory effects by inhibiting the activation of mast cells and basophils while modulating the function of other immune cells such as B cells and T cells, thereby demonstrating therapeutic potential in CSU.[37] Currently, several BTKis including remibrutinib, rilzabrutinib, and TAS5315 are under clinical investigation for H1 antihistamine-resistant CSU. Remibrutinib, a novel oral highly selective BTKi, functions through irreversible covalent binding to BTK in its inactive conformation.[38] Results from two Phase III clinical trials (REMIX-1 and REMIX-2) showed that remibrutinib demonstrated significant efficacy and favorable safety in patients with H1 antihistamine-resistant CSU.[39] At Week 12, UAS7 scores decreased by 20.0 points (REMIX-1) and 19.4 points (REMIX-2) in the remibrutinib group, compared to reductions of 13.8 points (REMIX-1) and 11.7 points (REMIX-2) in the placebo group. The complete remission rate (UAS7 = 0) was 31.1% (REMIX-1) and 27.9% (REMIX-2) in the remibrutinib group, versus 10.5% (REMIX-1) and 6.5% (REMIX-2) in the placebo group. Additionally, the rate of good disease control (UAS7 ≤ 6) was 49.8% (REMIX-1) and 46.8% (REMIX-2) in the remibrutinib group, compared to 24.8% (REMIX-1) and 19.6% (REMIX-2) in the placebo group. The therapeutic efficacy was observed regardless of prior anti-IgE treatment, with sustained UAS7 improvement maintained through 52 weeks of treatment.[40] Remibrutinib demonstrates an overall favorable safety profile with predominantly mild-moderate adverse events, only marginally elevated skin purpura incidence (3.8% vs. 0.3%) without increased bleeding events. As BTK inhibition mechanism carries theoretical bleeding risks, individualized risk assessment is recommended for patients receiving concomitant antiplatelet or anticoagulant therapy. A meta-analysis further demonstrated that remibrutinib outperformed both omalizumab and dupilumab in terms of efficacy and safety for H1 antihistamine-resistant CSU.[41] Having successfully completed Phase III trials and met all endpoints, remibrutinib is currently under regulatory review for market approval. It is poised to become an important therapeutic alternative for H1 antihistamine-resistant CSU patients who are ineligible for or unresponsive to omalizumab. The recommended dosage is 25 mg twice daily.

JAK inhibitors (moderate recommendation, level 2b evidence): Studies have demonstrated that certain inflammatory cytokines (e.g., IL-4, TSLP) contribute to the pathogenesis of autoimmune CSU via the JAK/STAT pathway.[42] Currently, aside from a case report documenting the successful use of ruxolitinib in a patient with primary myelofibrosis and comorbid H1 antihistamine-resistant CSU,[43] two retrospective studies reported the efficacy of tofacitinib in 11 patients with H1 antihistamine-resistant CSU who were also unresponsive to glucocorticoids, cyclosporine, or omalizumab. Among them, nine achieved complete remission, one showed significant improvement, and all exhibited good tolerability.[44,45] Another case series described the treatment of six omalizumab-refractory CSU patients with abrocitinib, resulting in complete remission in five and marked improvement in one, with no significant adverse effects reported.[46] Furthermore, a phase Ib clinical trial demonstrated that a JAK1/TYK2 inhibitor (TLL-018) exhibited significant efficacy and favorable safety in moderate-to-severe H1 antihistamine-resistant CSU.[47] Another JAK1 inhibitor (povorcitinib) is also under investigation in a phase II study for H1 antihistamine-resistant CSU (NCT05936567). Prior to initiating JAK inhibitor therapy, screening for hepatitis B and tuberculosis is mandatory. During treatment, close monitoring for serious infections, cardiovascular events, and venous thromboembolism risks is essential, along with regular laboratory assessments.

Other clinically available agents: Current studies have reported several other drugs used in the treatment of H1 antihistamine-resistant CSU. This guideline summarizes the available evidence, levels of evidence, and recommendation grades based on clinical practice and expert consensus (see **Table 3**). It should be noted that these drugs are currently used off-label currently, and informed consent must be obtained before administration when clinically necessary. Additionally, due to insufficient evidence and safety concerns, this guideline does not recommend the long-term systemic use of glucocorticoids for H1 antihistamine-resistant CSU. They should only be considered for acute severe exacerbations or in special populations (e.g., pregnant women or children) when no better alternatives are available, with a short-term course (≤ 10 days) after careful risk-benefit assessment. Other anti-inflammatory agents (e.g., dapsone, sulfasalazine, colchicine) and H2-receptor antagonists have been reported for H1 antihistamine-resistant CSU treatment, either as monotherapy or in combination with H1-antihistamines and omalizumab,[48,49] However, the overall quality of evidence is low, with inconsistent outcomes or significant safety concerns, warranting only limited recommendations in this guideline. Furthermore, anti-CD20 monoclonal antibodies (rituximab)[50] and intravenous immunoglobulin (IVIG)[51] have also been reported in H1 antihistamine-resistant CSU management. Nevertheless, the evidence remains limited, and their use is complicated by high costs and complex administration, leading to only limited recommendations.

Other preclinical drug candidates: Ligelizumab is a next-generation, high-affinity, humanized monoclonal antibody against immunoglobulin E (IgE). It exhibits 40- to 50-fold higher affinity for IgE compared to omalizumab. However, results from its two Phase III trials in CSU (PEARL 1 and PEARL 2) did not demonstrate a significant therapeutic advantage; specifically, Ligelizumab was superior to placebo but not superior to omalizumab.[52] This outcome has impeded its developmental progress toward approval. While Ligelizumab remains an important candidate drug for CSU (strong recommendation, level 1a evidence), it has not yet crossed the threshold for market authorization and remains distant from clinical availability. Besides, other several novel biologics and small-molecule targeted therapies for H1 antihistamine-resistant CSU, such as MRGPRX2 inhibitors, CRTh2 antagonists, and the c-Kit-targeting monoclonal antibody barzolvolimab, are still in early-phase clinical development or have failed to meet primary endpoints in trials. Given their considerable distance from clinical approval and routine use, they are not specifically recommended in this guideline.

3. Non-pharmacological and traditional Chinese medicine (TCM) therapies

Narrowband ultraviolet B (NB-UVB) phototherapy may enhance the therapeutic response to antihistamines in H1 antihistamine-resistant CSU when used in combination (weak recommendation, Level 3b evidence).[53] Additionally, autologous whole blood/serum injection therapy has shown efficacy in H1 antihistamine-resistant CSU patients with a positive autologous serum skin test (ASST), though its effectiveness remains controversial (weak recommendation, Level 2b evidence).[54] In recent years, studies have explored TCM for CSU management. While high-quality randomized controlled trials (RCTs) have reported benefits of acupuncture in general CSU cases, current evidence does not sufficiently support its efficacy in H1 antihistamine-resistant CSU.[55] Beyond acupuncture, the evidence for Chinese herbal medicine and other TCM modalities in CSU treatment is heterogeneous in quality. Therefore, this guideline provides only a limited recommendation for TCM in H1 antihistamine-resistant CSU.

Table 3. Other Clinically Available Medications in the Treatment of H1 Antihistamine-Resistant CSU.

Types	Medications	Evidences	Recommendation with Evidence Level
Conventional Drugs	Tripterygium glycosides	Results of the meta-analysis based on randomized controlled trials (RCTs) suggest that the combination of Tripterygium glycosides and H1 antihistamines has good efficacy and safety in the treatment of adult refractory chronic spontaneous urticaria (CSU), but further high-quality studies are needed to confirm these findings.[1] The drug is associated with potential risks of hepatotoxicity, nephrotoxicity, reproductive system damage, and bone marrow suppression.	Moderate Level 1a
	Leukotriene receptor antagonist (Montelukast)	A meta-analysis based on RCTs demonstrated that the combination of leukotriene receptor antagonists and H1 antihistamines may provide additional therapeutic benefits in the treatment of refractory CSU, while the evidence for its efficacy as monotherapy is insufficient. The drug was well-tolerated with no serious adverse reactions reported.[2]	Moderate Level 1a
	Azathioprine	In a randomized controlled trial involving 80 patients with refractory CSU, azathioprine demonstrated non-inferiority compared with cyclosporine.[3] Potential adverse effects of the drug may include myelosuppression, hepatotoxicity and nephrotoxicity, increased risk of infection, and gastrointestinal reactions.	Moderate Level 1b
	Hydroxychloroquine sulfate	A retrospective study involving 264 patients with refractory CSU compared the efficacy of omalizumab and hydroxychloroquine. Results showed that although the omalizumab group exhibited a higher complete remission rate, 66% of patients in the hydroxychloroquine group achieved complete and sustained remission within 1 year.[4] In another RCT conducted in patients with refractory CSU, it was found that 20.8% of patients who were additionally treated with hydroxychloroquine daily achieved disease remission after 12 weeks, while no patients in the control group treated solely with H1 antihistamines achieved remission.[5]	Moderate Level 1b
	Methotrexate (MTX)	A retrospective study involving 16 patients showed that MTX can be used to reduce corticosteroid dosage in corticosteroid-dependent patients with refractory chronic urticaria (CU), with therapeutic effects observed from week 3 to month 6.[6] Another retrospective study with 10 patients reported that MTX demonstrated good responsiveness and tolerability in patients with CU who were unresponsive to omalizumab plus high-dose second-generation H1-antihistamines (sgAH).[7] Two RCTs and one meta-analysis have demonstrated that MTX, although well-tolerated overall, lacks definitive efficacy in refractory CU.[8-10]	Weak Level 2b
	Tacrolimus	In a retrospective study, 36 patients were treated with high-dose tacrolimus, achieving a response rate of over 75%, with more than half experiencing complete remission and 25% maintaining remission after discontinuation of the drug.[11] In another prospective study, 17 patients received low-dose treatment for 12 weeks, with a 70.5% response rate, 9 patients experiencing significant symptom improvement and discontinuing antihistamines, 2 patients discontinuing corticosteroids, and 3 patients achieving moderate remission.[12]	Weak Level 4
	Mycophenolate mofetil (MMF)	A single-arm study involving 9 patients reported significant symptom improvement and successful tapering of corticosteroids in patients with CU who had an inadequate response to H1-antihistamines and/or corticosteroids after treatment with MMF.[13] Another retrospective study with 19 patients found that MMF showed good efficacy in autoimmune CSU refractory to H1-antihistamines, with good tolerability among patients.[14] There are also case reports of successful treatment with MMF in severe CU patients intolerant to cyclosporine.[15]	Weak Level 4
	Doxepin	A retrospective study involving 36 patients reported the use of doxepin in the treatment of refractory CSU. Among the 36 patients, 27 (75%) responded to doxepin either as monotherapy or in combination with H1-antihistamines, with 16 (44.4%) achieving complete remission and 11 (30.6%) achieving partial remission. The main adverse reactions were mild sedation, dry mouth, and occasional blurred vision, with no systemic adverse reactions and no patients discontinuing treatment due to adverse effects.[16]	Weak Level 4

Table 3. (Continued)

Types	Medications	Evidences	Recommendation with Evidence Level
Biologics	IL-2	A retrospective study of 15 patients with refractory CSU demonstrated that low-dose IL-2 injection therapy achieved a 73.3% complete response rate after 12 weeks, with good tolerability and no serious adverse events reported.[17]	Weak Level 4
	TNF-α inhibitor -Adalimumab -Etanercept	A retrospective study involving 9 patients showed that adalimumab demonstrated a good response and tolerability in 7 patients with refractory CSU.[18] In another study, 20 patients with chronic urticaria received adalimumab or etanercept, with 60% of patients achieving complete or almost complete remission of urticaria symptoms.[19]	Weak Level 4
	IL-17 inhibitor -Secukinumab	In a single-arm study involving 8 patients with refractory CSU who were resistant to both H1-antihistamines and omalizumab, the UAS7 scores decreased by 55% and 82% from baseline at day 30 and day 90, respectively.[20]	Weak Level 4
	IL-23 inhibitor -Tildrakizumab	A case report involving 3 patients with refractory CSU who were resistant to omalizumab treatment demonstrated significant therapeutic efficacy with tildrakizumab.[21]	Weak Level 4
	IL-5 inhibitor -Benzralimab -Mepolizumab	Both drugs have case reports of successful treatment of refractory CSU.[22,23] However, a recently published Phase II clinical trial of benralizumab for the treatment of CSU showed that benralizumab did not produce significant therapeutic effects in patients with refractory CSU.[24]	Weak Level 4

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Proposed Treatment algorithm for H1 antihistamine-resistant CSU

Based on the synthesized evidence and recommendations outlined above, this guideline developed a Proposed Treatment Algorithm (**Figure 2**) incorporating currently available therapeutic options to assist clinicians in clinical decision-making. Special considerations are highlighted as follows:

1) For patients demonstrating inadequate response (UCT < 12) after 12 weeks of omalizumab therapy, dose escalation, interval shortening, or combination with cyclosporine/other anti-inflammatory agents may be considered. Once optimal control is achieved, cyclosporine or adjunctive therapies should be tapered first.
2) Patients with partial rather than complete resistance to H1-antihistamines may continue concomitant antihistamine therapy during subsequent treatments, with gradual tapering guided by symptom control.
3) Dupilumab is recommended after optimized omalizumab or cyclosporine, based on comprehensive consideration of current evidence (demonstrated efficacy in omalizumab-naïve patients, limited data in refractory settings), comparative cost-effectiveness, global accessibility constraints, established alternatives, and its favorable safety profile with particular value for specific subgroups (e.g., patients with significant comorbid atopy).
4) Combination with H1-antihistamines is recommended during treatment with tripterygium glycosides, leukotriene receptor antagonists, hydroxychloroquine sulfate, doxepin, NB-UVB phototherapy, or autologous whole blood/serum injection.

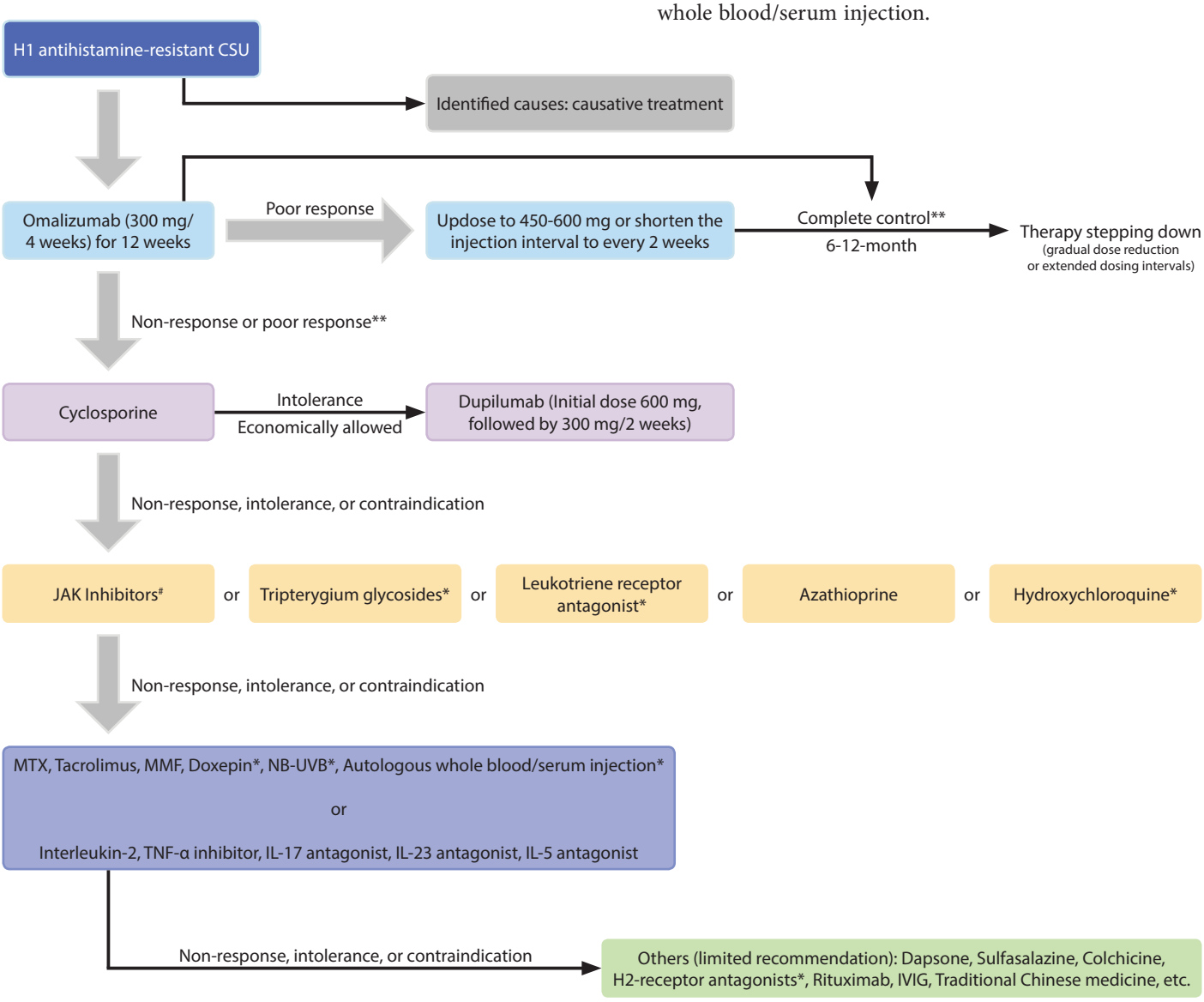

Figure 2. Proposed Treatment Algorithm for H1 antihistamine-resistant CSU.

CSU, Chronic spontaneous urticaria; MTX, Methotrexate; MMF, Mycophenolate mofetil; NB-UVB, Narrowband ultraviolet B phototherapy; IVIG, Intravenous immunoglobulin; **Response to omalizumab was assessed using UAS7: Complete control: UAS7 = 0, Poor response: UAS7 = 7-15, Non-response: UAS7 > 15; ‡Currently approved and clinically available JAK inhibitors with reported efficacy in H1-antihistamine-resistant CSU treatment include: tofacitinib, abrocitinib; *Used in combination with H1-antihistamines. ‡NOTE: Remibrutinib and ligelizumab are excluded from this algorithm due to current lack of market authorization globally. They remain candidate options pending availability.

5) Remibrutinib and ligelizumab (Level 1a evidence, strong recommendation) are excluded from this algorithm due to lack of global regulatory approval. These remain candidate therapies awaiting market authorization. The algorithm prioritizes currently accessible interventions to ensure practical clinical implementation. Future updates will incorporate these agents upon formal approval and availability confirmation.

Conclusions and future perspectives

H1 antihistamine-resistant CSU remains a clinically challenging condition due to its complex pathophysiology, frequently severe and protracted disease course, and substantial burden on both patients and society. Although multiple therapeutic options exist, a subset of H1 antihistamine-resistant CSU patients still fail to achieve optimal symptom control. Furthermore, many currently available treatments lack high-quality evidence-based support for H1 antihistamine-resistant CSU, and their off-label use presents additional challenges. Both conventional and novel targeted therapies require further high-quality clinical studies to validate their efficacy and safety in the management of H1 antihistamine-resistant CSU. Future research should focus on elucidating disease mechanisms, optimizing treatment strategies, and developing more effective therapeutic approaches to improve long-term outcomes for these patients.

Conflict of interest

All authors declare no conflicts of interest. The development of this guideline did not receive sponsorship from any commercial entity.

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