REVIEW ARTICLE

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Chronic Urticaria: Challenges in Diagnosis and Management

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Abstract

Urticaria encompasses a heterogeneous group of disorders characterised by transient wheals, angioedema, or both, with chronic spontaneous urticaria (CSU) posing several diagnostic and therapeutic challenges. Despite advances in understanding mast cell biology, a definitive aetiology remains elusive in most patients. Recent insights into disease endotypes, particularly autoimmune subtypes (CSU-1 and CSU-2), have reshaped management strategies. This review discusses a structured approach to diagnosis, highlights uncertainties in aetiological evaluation, and explores emerging targeted therapies, emphasizing a shift toward personalised, biomarker-driven care.

Key words: Urticaria, chronic spontaneous urticaria, mast cells, autoimmune mechanisms, endotypes, biomarkers, diagnosis, antihistamines, omalizumab, targeted therapy.

Introduction

Chronic urticaria is primarily a mast cell-driven disorder which is characterised by recurrent appearance of wheals, angioedema, or both for more than six weeks[1,2]. It is broadly divided into chronic spontaneous urticaria (CSU)and chronic inducible urticaria (CIndU). CSU, the more common subtype, occurs without any recognizable external trigger and has a complex interplay of immunological and non-immunological mechanisms. The condition markedly impairs quality-of-life and is difficult to manage due to its unpredictable course and variable therapeutic response.

Historically considered idiopathic, it is now increasingly understood as a mast cell-driven disorder with heterogeneous immunological mechanisms, including autoimmune and autoallergic pathways[3]. Recent literature emphasizes the importance of phenotypes and endotypes in guiding treatment decisions.

Aetiopathogenesis

Mast cells play a central role as the key effector cells in urticaria, showing both increased numbers in lesional skin and heightened sensitivity to activating stimuli[4]. They possess a wide array of surface receptors, enabling activation through multiple immunologic and non-immunologic pathways like IgE-dependent mechanisms through FcεRI, triggered by allergens or autoantibodies; IgE-independent pathways, particularly via MRGPRX2, responding to neuropeptides and eosinophil-derived proteins; cytokine-driven pathways (IL-33, TSLP), promoting Th2-skewed inflammation; complement activation (C5a - C5aR) and proteinase-activated receptors (PARs)[5].

Upon activation, mast cells degranulate and release preformed mediators such as histamine and tryptase, as well as newly synthesized substances (leukotrienes, prostaglandins, cytokines), producing the characteristic wheal, flare, and pruritus. Histamine plays a central role by increasing vascular permeability and stimulating sensory nerves via H1 receptors, while H4 receptor signaling sustains inflammation and promotes chemotaxis. It also contributes to coagulation activation, linking inflammation with vascular changes. In addition to histamine, mediators such as LTE4, PGD2, PAF, and multiple cytokines, (e.g., IL-33, IL-4, IL-5, IL-6, IL, TSLP) amplify inflammation (Table I)[5,6].

Mast cells participate in self-amplifying loops, where mediators like tryptase and histamine further enhance activation[4]. They also play a role in neuroimmune interactions, promoting nerve sensitisation and itch via nerve growth factor. Cross-talk with other inflammatory cells is crucial in the pathogenesis of urticaria[7]. Eosinophils interact closely with mast cells, enhancing each other's activation through direct contact and mediator release. Basophils contribute via both IgE and non-IgE pathways, including complement activation. Interactions with endothelial cells, nerves, and other immune cells sustain inflammation. Importantly, these inflammatory cells are a prominent source of cytokines besides mast cells[7].

Overall, urticaria represents a complex network of immune interactions including coagulation cascade activation, complement pathways, and neuroimmune interactions, with mast cells acting as central amplifiers of inflammation (Fig. 1).

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Table I: Key inflammatory mediators of chronic urticaria.

Category / Mediator	Source	Main Actions	Clinical Relevance
I. Preformed Mediators			
Histamine	Mast cells, basophils	Vasodilation, ↑capillary permeability, and stimulation of pruritus.	Central mediator of immediate wheal and flare reactions.
Tryptase	Mast cells	Cleaves C5 to C5a; activates PAR2 to amplify degranulation.	Marker of mast cell activation; induces non-histaminergic pruritus.
II. Lipid-Derived Mediators			
PGD2/LTE4	Mast cells, basophils	Chemotaxis of Th2 cells/eosinophils; sustains plasma extravasation.	Eicosanoids elevated in CSU and chronic inducible urticarias.
PAF	Most cells, basophils, platelets, eosinophils	Potent vasodilation and increased capillary permeability.	Linked to severe disease activity and antihistamine resistance.
III. Cytokines and Alarmins			
IL-33/TSLP/IL-25	Epithelial cells, keratinocytes	Th2 activation; sensitises mast cells to various ligands.	Key amplifiers; increased levels associated with increased disease severity and poor control.
IL-4/IL-5/IL-13	Th2 cells, mast cells	Drives IgE class switching and eosinophil recruitment/survival.	Essential for maintaining the Th2-skewed inflammatory milieu.
IV. Neuroimmune Factors			
NGF (Nerve Growth Factor)	Mast cells, eosinophils.	Promotes sensory nerve development and sensitisation; enhances itch and neurogenic flare.	Elevated in CSU; linked to stress-induced exacerbations and local mast cell accumulation.
Substance P	Sensory nerve endings	Direct mast cell activation via the MRGPRX2 receptor.	Mediates neurogenic inflammation and therapeutic refractoriness.
V. Complement Mediated Pathways			
C5a	Generated via complement activation.	Potent activator of mast cells and basophils via C5aR (CD88).	Primary mediator in Type II b autoimmune CSU; enables non-IgE degranulation.
C3a	Cleavage of C3 by tryptase or Factor Xa.	Stimulates histamine release and enhances vascular permeability.	Involved in the alternative complement pathway triggered by autoantibodies.
VI. Coagulation Factor Pathways (Cascade Activation)			
Tissue Factor (TF)	Eosinophils, monocytes, endothelial cells.	Activates the extrinsic coagulation pathway.	Expressed in lesional skin; triggers systemic thrombin and C5a generation.
Thrombin (FIIa)	Activated coagulation cascade.	Increases vascular permeability; activates PAR1 and PAR4 on mast cells.	Links systemic coagulation activation with CSU severity and mast cell "releasability".
Factor Xa/PF 1+2	Transudate plasma components.	Activates PARs and converts prothrombin to thrombin.	Elevated markers (D-dimer, PF 1+2) rise in proportion to disease activity.

Autoimmune urticaria and endotypes

Autoimmune urticaria is a form of CSU in which the disease is driven by autoantibodies that activate mast cells and basophils. Clinically, autoimmune urticaria often shows greater severity and variable response to standard therapy. The classification of autoimmune urticaria is based on molecular endotypes which forms the basis of targeted precision based management (Table II)[8]. This approach identifies CSU as a spectrum of disorders driven by different immune pathways leading to mast cell activation, rather than a single disease.

Major endotypes includes type I autoimmune urticaria, also called autoallergic endotype and type IIb autoimmune urticaria (CSU-1 and CSU-2)[9]. In the former endotype, IgE autoantibodies recognise and bind to self-antigens. These autoantigens include a wide range of endogenous proteins such as IL-24, thyroid peroxidase, thyroglobulin, and nucleic acids. These IgE autoantibodies bind to FcεRI on mast cells and basophils, leading to cross-linking and degranulation, mimicking classical allergic reactions but in the absence of external allergens.In type IIb autoimmune endotype,IgG autoantibodies (and less commonly IgM or IgA) develop against IgE or FcεRI. This binding activates mast cells directly.

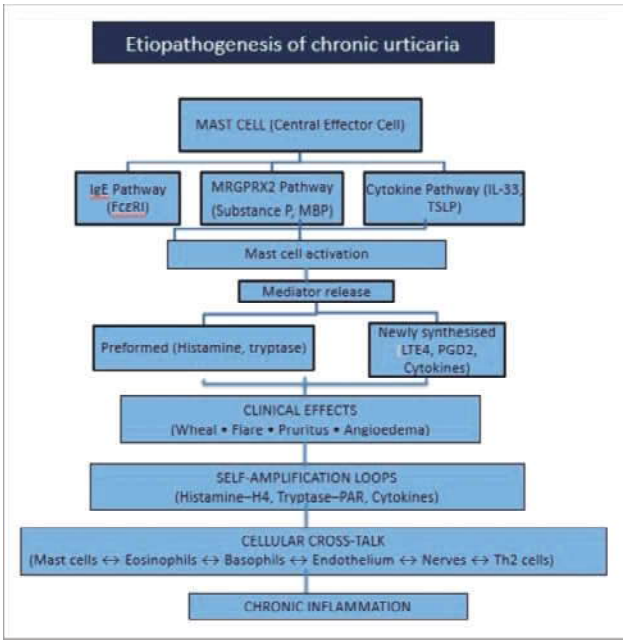

Fig. 1: *Aetiopathogenesis of chronic urticaria.*

However, not all detected autoantibodies are pathogenic, and their clinical relevance depends on functional activity. This subtype is often associated with low total IgE levels, suggesting reduced receptor occupancy facilitates autoantibody binding. However, emerging evidence suggests that chronic spontaneous urticaria endotypes are not mutually exclusive. Many patients show a mixed phenotype encompassing both type I and type IIb disease, forming a continuum rather than discrete categories. Notably, type IIb frequently coexists with type I features. Some patients may transition over time, possibly progressing from IgE-mediated to IgG-mediated disease. Additionally, some patients do not clearly fall into either subtype, indicating the presence of non-FcεRI-mediated mechanisms, further underscoring disease heterogeneity[8,9].

Various autoimmune diseases have been associated with urticaria with around one quarter to one third of patients having at least one coexisting autoimmune condition and about 30 - 40% of CSU cases mediated by autoimmune mechanisms like autoantibodies targeting IgE of FcεRI receptors. The common autoimmune diseases are thyroid disorders (Hashimoto's thyroiditis, Graves' disease), vitiligo, Type 1 diabetes mellitus, celiac disease, pernicious anaemia, Sjögren disease, SLE, inflammatory bowel disease (IBD) and Rheumatoid arthritis (RA)[2]. Thyroid autoimmunity accounts for roughly 6 - 23% of CSU patients in most series, with some studies documenting thyroid-related autoantibodies in up to about 22 - 25% of cases. Other organ specific autoimmune disorders, including pernicious anaemia, vitiligo, and haematologic autoimmune diseases, occur in about 27 - 28% of CSU cohorts, while systemic conditions such as RA, IBD, celiac disease, and psoriasis show a modestly increased risk but lower absolute prevalence, typically under 5 - 10% each in urticaria populations[10,11].

Approach to diagnosis

Urticaria is predominantly a clinical diagnosis. Since patients often do not present with active lesions during consultation, reviewing photographs or videos of previous episodes can be useful for confirming the diagnosis. The typical lesion is a transient, erythematous, or skin-colored swelling with ill-defined borders that resolves in less than 24 hours without leaving behind any pigmentation or scar (Fig. 2). Intense pruritus is the hallmark symptom and may significantly impair sleep and quality of life. Angioedema occurs in a substantial proportion of patients and involves deeper tissues, presenting as non-pitting swelling of the lips, eyelids, or extremities, often associated with pain or a burning sensation and lasting up to 72 hours. Lesions are usually migratory and can involve any part of the body, with no fixed distribution. Systemic symptoms are generally absent in uncomplicated chronic urticaria, and their presence should prompt evaluation for alternative diagnoses.

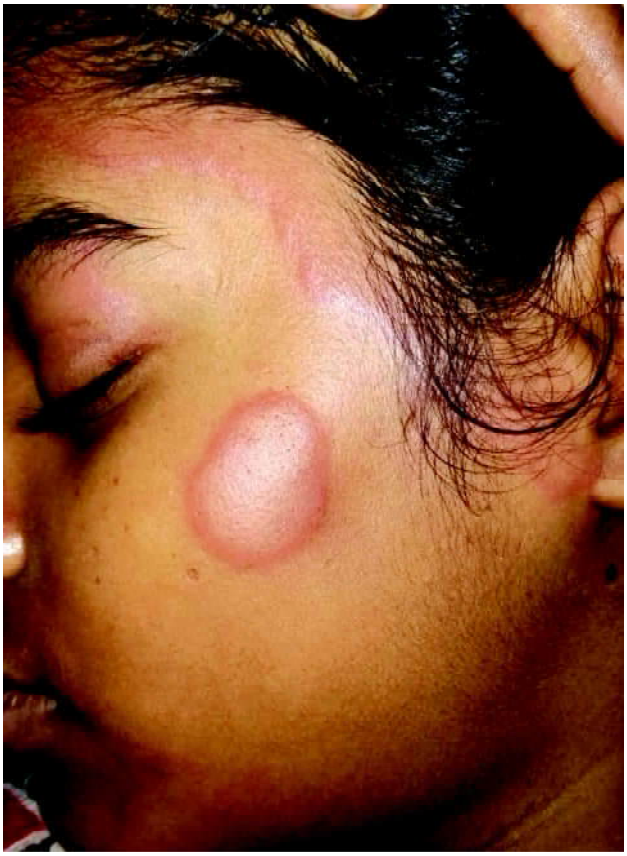

Fig. 2: *Typical wheal in a case of chronic spontaneous urticaria.*

Table II: Characteristics of various endotypes in chronic spontaneous urticaria.

Feature	Type I Autoimmune (Autoallergic) CSU	Type IIb Autoimmune CSU	Overlap / Mixed CSU	Non-autoimmune CSU
Primary mechanism	IgE autoantibodies to self-antigens	IgG (± IgA/IgM) autoantibodies	Combined IgE + IgG mechanisms	to IgE/FcαRI-independent pathways
Target	Autoallergens (e.g., IL-24, TPO)	IgE or to IgE/FcαRI receptor	Shared targets (e.g., TPO)	Unknown/diverse
Mast cell activation	IgE cross-linking	Direct receptor activation by IgG	Dual activation	Alternative pathways (e.g., MRGPRX2)
Total IgE levels	Normal to high (>43 IU/mL, usually >100 IU/mL)	Low(<43 IU/mL)	Variable	Variable
Biomarker Ratio	Low IgG anti-TPO to total IgE ratio.	High IgG anti-TPO to total IgE ratio (>2.88)	Variable	Usually absent
Haematology	Typically, normal counts	Basopenia (<0.01 × 103/μL) and Eosinopenia (<0.05 × 103/μL) are common[8].	May show basopenia/eosinopenia.	Typically, normal counts.
Autoantibodies	IgE autoantibodies	Functional IgG autoantibodies	Both present	Usually, absent
Autologous serum skin test)	May be positive/negative	Often positive	Often positive	Usually negative
Basophil tests (BAT/BHRA)	Variable	Frequently positive	Positive	Negative
Disease severity	Moderate	Often severe	More severe	Variable
Thyroid autoimmunity	May be present	Common (anti-TPO high)	Common	Variable
Treatment response	Good response to omalizumab	Poorer response to omalizumab; better to cyclosporine	Delayed/partial response	Variable
Clinical course	Relatively responsive	More refractory	Prolonged disease	Heterogeneous

Differentials of urticaria include a broad spectrum of cutaneous and systemic disorders such as urticarial vasculitis, mastocytosis,urticarial dermatitis, contact dermatitis, arthropod bite reactions, drug reactions, autoimmune bullous diseases, (e.g., bullous pemphigoid), and pregnancy-related dermatoses (PUPPP), along with rarer entities like Wells syndrome and neutrophilic eccrine hidradenitis. In addition, important systemic causes include connective tissue diseases, (e.g., SLE, Sjögren disease), other vasculitides, (e.g., polyarteritis nodosa), haematologic disorders, (e.g., Schnitzler syndrome, lymphoma, hypereosinophilic syndrome), and autoinflammatory syndromes such as cryopyrin-associated periodic syndrome[12,13].

Masquerades of urticaria should be suspected when clinical features deviate from typical transient wheals. Red flags include lesions lasting >24 - 36 hours,resolve with pigmentation or are associated with pain and burning sensation instead of pruritus, and the presence of additional lesion types (purpura, bullae, scaling). Systemic symptoms such as fever, arthralgia, malaise, or organ involvement strongly suggest alternative diagnoses. Additionally, poor response to antihistamines and abnormal laboratory findings (elevated inflammatory markers, hypocomplementaemia, eosinophilia, or monoclonal gammopathy) should prompt evaluation for underlying conditions such as urticarial vasculitis, autoimmune, autoinflammatory, or hematologic disorders (Table III).

A detailed history is essential to identify potential triggers such as recent infections,vaccinations, medications or food items (Table IV)[14,15]. In cases of chronic inducible urticaria, certain provocation tests may be help in confirmation of diagnosis[16]. These include the cold stimulation test for cold urticaria, wherein an ice cube wrapped in plastic is applied to the skin for 5 - 10 minutes and a wheal forming after rewarming confirms the diagnosis[17]. In dermographism, a blunt object is used to stroke the skin and linear wheals appearing within minutes indicate symptomatic dermographism, while in pressure urticaria a graded weight or sandbag is left on the skin for 15 - 30 minutes to elicit delayed swelling. Solar urticaria is tested by exposing small skin areas to UV or visible light, and cholinergic urticaria may be provoked by controlled exercise or passive warming to induce small, itchy wheals[16]. Assessment of disease activity and impact is done using tools like the Dermatology Life Quality Index (DLQI), Urticaria Activity Score (UAS7), Angioedema Activity Score (AAS), and Urticaria Control Test (UCT).

Table III: Differential diagnosis of chronic urticaria.

Feature	Chronic Spontaneous Urticaria	Urticarial Vasculitis	Cutaneous Mastocytosis	Autoinflammatory syndromes	Urticarial Dermatitis	Drug Eruptions	Arthropod Bite Reaction	Autoimmune Bullous Diseases
Lesion duration	<24 hours (transient wheals)	>24 - 48 hours (persistent plaques)	Persistent lesions	Variable, often prolonged	Days to weeks	Days to weeks	Days to weeks	Persistent; may precede blistering
Predominant symptoms	Intense pruritus, fleeting lesions	Burning sensation, pain >pruritus, fixed lesions	Pruritus, flushing	Fever, systemic inflammatory symptoms	Severe pruritus	Pruritus ± low-grade fever	Pruritic papules/ nodules	Pruritus, occasionally burning
Residual skin changes	Absent	Post-inflammatory hyperpigmentation, purpura	Hyperpigmented macules	Variable	May show residual pigmentation	Desquamation, transient pigmentation	Excoriations, post-inflammatory changes	Possible pigmentation or scarring
Angioedema	Frequently associated	May be present	Uncommon	May occur	Rare	Rare	Rare	Rare
Blanchability	Typically present	Often reduced/absent	Present	Variable	Variable	Present	Variable	Variable
Systemic involvement	Absent	Common (fever, arthralgia, organ involvement)	Rare (unless systemic disease)	Prominent (fever, arthritis, systemic inflammation, bone pains, etc.)	Absent	Occasionally mild systemic symptoms	Absent	Usually absent in early phase
Histopathology	Superficial dermal oedema with sparse perivascular infiltrate (mast cells, eosinophils)	Neutrophils in and around vessels, fragmentation of neutrophil nuclei forming dust, RBC extravasation, fibrinoid necrosis	Dense dermal mast cell infiltrate (CD117+)	Dense infiltrate composed of neutrophils in the superficial and mid-dermis without fragmentation of neutrophils, fibrinoid necrosis (neutrophil)	Mild epidermal spongiosis, papillary dermal oedema, superficial perivascular lymphocytic infiltrate with eosinophils	Perivascular lymphocytic infiltrate with eosinophils, epidermal involvement	Mixed inflammatory infiltrate with eosinophils	Subepidermal blister with eosinophil-rich infiltrate
Key diagnostic clues	Evanescent wheals, no sequelae	Lesions >24 h with pain and residual changes	Positive Darier sign (urticaria elicited by rubbing or stroking a skin lesion	Recurrent fever with urticarial rash	Combined urticarial and eczematous morphology	Temporal relation to drug exposure	Central punctum, exposed site predilection	Evolution to tense bullae
Response to antihistamines	Good response	Poorer response	Partial response	Poor response	Poor response	Variable	Partial response	Poor response

Investigations

Since the diagnosis is often clinical, a basic set of investigations are recommended like differential blood count, inflammatory markers (CRP, ESR), thyroid function test (± anti-TPO antibodies). Urine and stool routine microscopy to rule out parasitic infection may also be undertaken. Additional investigations are often reserved for unresponsive or refractory cases of autoimmune urticaria. Autologous serum skin test (ASST) is one such traditional test found to be useful in autoimmune urticaria. Here we detect functional autoantibodies in chronic spontaneous urticaria by an intradermal injection of a small volume (about 0.05 - 0.1 mL) of the patient's own serum into normal skin and comparing the response with a saline control. A wheal–flare reaction at the serum site ≥1.5 mm greater than the saline site within 15 - 30 minutes is considered positive, suggestingactivation of mast cells or basophils by circulating histamine releasing factors present in the serum.

Other tests that may indicate autoimmune urticaria are elevated CRP or ESR, basopenia and eosinopenia, low IgE levels, increased IgG anti-TPO antibodies, elevated IgG anti-TPO to total IgE ratio, positive basophil activation test or histamine release assay, andhigh levels of D-dimer. Various biomarkers are available for the diagnosis of autoimmune urticaria, some of which have prognostic role as well (Table V). Nevertheless, most of these investigations have not been validated and many of these are not routinely available.

Skin biopsy of a typical urticarial wheal shows a predominantly perivascular infiltrate composed of lymphocytes with scattered eosinophils in the papillary and upper dermis and mild oedema. Delayed pressure urticaria may show upper dermal predominantly perivascular inflammatory infiltrate, composed of mononuclear cells, eosinophils, neutrophils, and some lymphocytes, with variable mast cell degranulation and mild dermal oedema;

Table IV: Triggers for chronic urticaria.

Category	Specific Triggers	Mechanism	Clinical Relevance
Food and Dietary Triggers			
True Allergy (Rare)	Milk, egg, peanuts, tree nuts, fish, shellfish[24]	IgE-mediated (Type I) hypersensitivity	Extremely rare cause in CSU (<2%)[23]. More relevant in acute urticaria or cases with intermittent symptoms appearing within one hour of exposure[22].
Alpha-gal Syndrome[31]	Red meat (beef, pork), dairy products	Sensitisation to galactose-alpha-1,3-galactose via tick bites	Causes delayed reactions (3 - 6 hours post-ingestion) manifesting as urticaria or anaphylaxis (Information from outside sources; not found in provided snippets).
Pseudoallergens	Tomatoes, citrus fruits, strawberries, chocolate, spices, and aromatic compounds	Non-IgE-mediated mast cell activation; direct effect on cell releasability	May exacerbate preexisting CSU in approximately 30% of patients. Benefit may be seen with a 3 - 4-week elimination diet in selected cases.
Histamine-Rich Items	Fermented foods, aged cheese, processed meat, canned fish, alcohol	Exogenous histamine increases the total mediator load	Benefits from low-histamine diets are reported but lack proof from double-blind, placebo-controlled studies.
Food Additives[32]	Tartrazine, benzoates, sulphites, artificial colorants, and preservatives	Pseudoallergic reactions	Improvement seen in a subset of patients after 10–14 days of an additive-free diet.
Medications[23]			
NSAIDs and Aspirin	Ibuprofen, diclofenac, naproxen, high-dose aspirin	COX-1 inhibition leads to increased synthesis of pro-inflammatory cysteinyl leukotrienes	Common exacerbating factors in up to 25% of CSU patients. Paracetamol and selective COX-2 inhibitors (e.g., celecoxib) are usually safer alternatives.
ACE-Inhibitors	Lisinopril, Enalapril, and other "prils"	Non-immunologic accumulation of bradykinin	Primary cause of angioedema without wheals. Reactions can occur weeks or even years after starting the drug.
Direct Degranulators	Opioids (morphine, codeine), fluoroquinolones, neuromuscular blockers, radiocontrast media	Activation of mast cells via the MRGPRX2 receptor rather than IgE pathways	Common triggers for exacerbation; should be avoided or substituted if a temporal relationship with flares is suspected.
Infections			
Bacterial and Viral	EBV, Hepatitis (A/B/C), COVID-19, Streptococcal tonsillitis	Immune activation, induction of autoimmunity, or "priming" of mast cells	Common triggers for the initial onset of CSU or acute flares.
Helicobacter pylori	Chronic gastritis	Immune activation and induction of autoimmunity	Eradication therapy may improve CSU symptoms, but only if the underlying gastritis or inflammatory process is also healed[22].
Parasitic	*Anisakis simplex* (raw fish)[23], *Strongyloides*, *Blastocystis hominis*	Polyclonal IgE stimulation; induction of autoreactive IgE	More relevant in endemic areas; *Anisakis* is a major trigger in certain regions like the Mediterranean.
Stress and physical factors			
Psychological Stress	Emotional distress, anxiety, psychiatric comorbidities	Neuroimmune interaction; release of neuropeptides like Substance P, VIP, and NGF	Affects up to 1/3 of CSU patients. The cycle of stress, insomnia, and the itch-scratch cycle aggravates chronic inflammation.
Physical Factors	Pressure, heat, cold, friction, UV radiation	Direct mast cell degranulation or neoallergen formation in the skin	Inducible forms (CIndU) co-exist with CSU in 30 - 40% of patients and require specific provocation testing for diagnosis.
Others			
Vaccination	COVID-19 vaccines and standard immunisations[24]	Systemic immune response and release of pro-inflammatory cytokines	Reported as an occasional trigger for both acute flares and the initial onset of CSU.
Hormonal Changes	Menstruation cycle, puberty pregnancy, menopause	Multifactorial immune modulation; potential stimulation of autoimmunity	Flares are frequently linked to the menstrual cycle. During pregnancy, activity often follows a "one-third rule" (improve, worsen, or stay the same).
Metabolic Factors	Vitamin D deficiency	Reduced T-regulatory (Treg) cell function	Low Vitamin D levels are linked to higher disease activity; supplementation may serve as an adjuvant therapy.
Microbiome Dysbiosis	Gut microbiome alterations	Increased intestinal permeability ("leaky gut") and systemic inflammatory tone	Emerging evidence suggests that gut microbial alterations facilitate CSU; probiotics are being investigated as a complementary strategy.

fibrin deposits may be seen in the interstitium, but there is no vasculitis. A biopsy is often not needed and is reserved for ruling out differential diagnoses like urticarial vasculitis, mastocytosis, etc. Presence of neutrophils, RBC

extravasation, leukocytoclasia, fibrin degeneration indicates alternate diagnosis than urticaria.

Skin prick tests (SPT) can identify IgE mediated triggers in urticaria but play a limited and selective role, especially in CSU. In one Indian study of 100 urticaria patients, SPT was positive in 88%, with the most common sensitisations being house dust mites (*Dermatophagoides pteronyssinus* 30%, *D. farinae* 24%), grass (*Cynodondactylon* 24%), and peanuts (24%), suggesting SPT can cost effectively detect clinically relevant aero and food allergens when the history points to an external trigger[18]. Another hospital based study in chronic urticaria found SPT positivity in about two thirds of patients, reinforcing that SPT may help in selected populations where an underlying allergy is suspected[19]. However, guidelines note that SPT is not routinely indicated in chronic urticaria, because many positive tests are not clinically relevant: in one assessment of food allergic patients, only about 35% of those with positive SPT for food allergens developed urticaria upon exposure, so SPT findings must always be interpreted alongside the clinical history[20]. Overall, SPT is most useful in acute or inducible urticaria with a clear atopic background or suspected allergen, where it can guide avoidance and adjunctive therapy, but it has low yield in idiopathic chronic cases and should not replace standard urticaria management.

Diet elimination tests have a limited role in CSU and are offered only when there is a strong history of a food trigger, (e.g., reproducible symptoms after specific foods). A review of 1,668 CSU patients on systematic elimination diets (pseudoallergen free, low histamine, or fish avoidance) reported complete remission in about 4.9% and partial remission in 37.5%, with the best outcomes seen after at least 3 weeks on a pseudoallergen or low histamine diet, suggesting that a subset of patients are sensitive to food additives, natural pseudoallergens, or histamine rich foods[15]. Controlled low histamine trials show significant reductions in urticaria activity scores, while paediatric and oligoantigenic diet studies also report improved symptom control in some children, although the added benefit over pharmacotherapy alone is not always statistically robust[2]. Thus, such trials should be time-limited to 2 - 4 weeks and conducted with caution to avoid nutritional deficiencies[22].

Treatment

Treatment of chronic spontaneous urticaria (CSU) follows a stepwise strategy integrating general measures and targeted therapy. The immediate objective is to achieve complete symptom relief, while the long-term goals are to maintain sustained disease control, enhance quality-of-life, and prevent severe exacerbations.

General measures

Patients should be counselled to minimise identifiable triggers such as NSAIDs, stress, inducible urticaria triggers, etc. Dietary restrictions often are not advised, only indicated whenever there is a very strong clinical correlation supported by diet elimination test. In patients with angioedema, it is advised to stop use of ACE inhibitors. Infectious triggers for urticaria, ranging from viral and bacterial to parasitic and fungal agents, should be identified and ruled out as part of a comprehensive diagnostic workup. In acute urticaria, symptoms typically resolve spontaneously once the underlying infection – most commonly upper respiratory tract infections – is controlled or heals[23]. For CSU, *Helicobacter pylori* should be eliminated if detected; although meta-analyses show low overall evidence for consistent symptom improvement, studies indicate that successful eradication benefits CSU activity specifically when the associated gastritis or inflammatory process is also healed. Globally, parasitic infections show an average comorbidity of 10% with CSU, and their treatment leads to clinical improvement in approximately one-third of patients[14]. Additionally, ruling out and treating focal infections of the nasopharynx, ears, and conditions like tinea (fungal infection) or Lyme disease can significantly improve the clinical course for select individuals[2,23,24].

Based on international guidelines and recent research, identifying triggers and cofactors is a cornerstone of the diagnostic workup to better disease control and enhanced quality-of-life (Table IV).

Documentation of disease activity using validated scores like Urticaria Activity Score and Urticaria Control Test are indicated especially in refractory cases where complete symptom control may not be achieved. Stress relieving techniques like mindfulness, relaxation techniques, and psychotherapy, specifically cognitive-behavioural therapy (CBT), brief talking therapies, have been shown to improve symptoms[14,25].

Pharmacological therapy

Second-generation H1 antihistamines are the first line therapy with dose escalation up to four-fold if required[22]. Around 50 - 60% patients achieve control with antihistamines alone. Short course of oral steroids (prednisolone 0.5 mg/kg in adults, 0.5 - 1 mg/kg in children and adolescents, not exceeding 20 mg/day) up to a maximum of 2 weeks for acute flares is recommended[22]. For inadequate responders, add-on agents like omalizumab are preferred, with cyclosporine reserved for selected refractory cases. Increasingly, endotype-based and precision approaches are being explored, with newer biologics such asligelizumab, dupilumab, remibrutinib are expanding therapeutic options.

Table V: Diagnostic and prognostic role of various biomarkers in chronic urticaria[24,33].

Biomarker	Diagnostic/Endotyping Role	Disease Activity/Severity	Treatment Response Prediction	Prognostic Implications
Total IgE	High → Type I autoallergic; Low → Type IIb	Inconsistent correlation with severity	High IgE → good response to omalizumab; Low IgE → better response tocyclosporine	High IgE → higher relapse risk after omalizumab; possible persistence
IgG anti-FcεRI/anti-IgEantibodies	Marker of Type IIb autoimmune CSU	Linked with severe phenotype	Predict poor response with antihistamines and omalizumab; better response to cyclosporine	Suggest chronic, refractory disease course
IgE autoantibodies (e.g., anti-TPO, IL-24)	Support Type I autoallergic CSU	May reflect immune activation	Associated with good response to omalizumab	May indicate relapsing but treatment-responsive disease
Anti-TPO (IgG)	Indicates autoimmune association/ endotype	Linked with severe disease	May predict poor response with antihistamines. Raised IgG-anti-TPO/Total IgE ratio (>2.88) is a key predictor of omalizumab failure.	Associated with longer disease duration
Basopenia	Suggests Type IIb CSU	Correlates with higher disease activity	Predicts poor response to omalizumab	Marker of severe, persistent disease
Eosinopenia	Seen in autoimmune CSU	Associated with high disease activity	Linked to treatment resistance	Suggests unfavorable prognosis
CRP	Non-specific inflammatory marker	Correlates with disease activity	High CRP → poor antihistamine response; better cyclosporine response	Reflects high inflammatory burden
D-dimer	Reflects coagulation pathway activation	Associated with disease severity (variable evidence)	May indicate severe/refractory CSU	Potential marker of active disease
ASST (Autologous serum skin test)	Indicates autoreactivity	Often linked to more severe disease	May predict poorer response to standard therapy	Suggests autoimmune phenotype
BAT / BHRA (functional assays)	Type IIb	Associated with high disease activity	Predict refractoriness to antihistamines/ omalizumab	Strong marker of severe, persistent CSU
Basophil activation markers (CD63, CD203c)	Reflect mast cell–basophil activation	Correlate with disease activity	Potential predictors of response (emerging)	Under investigation
Complement (C4)	Not diagnostic	May correlate with severity	Unclear	Limited prognostic role. Primary role in ruling out mimics.

Table VI: Characteristics of second generation antihistamines used in CSU.

Drug	Usual Adult Dose	Common Side Effects	Renal Impairment	Hepatic Impairment	Pregnancy Category	Lactation Safety
Cetirizine	10 mg once daily (up to 20 mg in urticaria)	Mild sedation, dry mouth	Dose reduction required	Usually safe	B	Safe (minimal transfer)
Levocetirizine	5 mg once daily (up to 20 mg)	Somnolence, fatigue	Dose reduction required	Not required	B	Safe
Loratadine	10 mg once daily	Headache, dry mouth (non-sedating)	Caution in severe renal	Dose adjustment in severe hepatic disease	B	Safe
Desloratadine	5 mg once daily	Headache, fatigue	Caution	Caution	C	Probably safe
Fexofenadine	120 - 180 mg once daily	Headache, dizziness (least sedating)	Dose adjustment required	Safe	C	Safe (minimal secretion)
Bilastine	20 mg once daily	Headache, drowsiness (rare)	Not necessary	Not necessary	B	Limited data (avoid if possible)
Rupatadine	10 mg once daily	Somnolence, headache	Limited data	Avoid in hepatic impairment	C	Avoid (insufficient data)

Second-generation H1 antihistamines primarily act as inverse agonists of H1 receptors, stabilizing the inactive receptor state. Treatment is started at the usual recommended dose which may be increased four-fold if needed. Combining multiple second-generation antihistamines does not provide additional benefit. Some patients may benefit from the use of montelukast (10 mg at night, for adults). They typically begin acting within 1 - 4 hours and the effect lasts for about 24 hours (Table VI). If symptoms remain controlled for 3 - 6 months, treatment can be gradually tapered. Most second-generation H1 antihistamines demonstrate comparable efficacy in CSU, with no single agent consistently outperforming others. Evidence from comparative analyses shows only minor differences in effectiveness and tolerability. Hence, treatment choice is best individualised based on patient

response and safety profile. First-generation H1 antihistamines are generally not recommended due to adverse effects such as sedation, anticholinergic effects, and disruption of REM sleep.

H2-blockers like ranitidine can be considered an alternative add-on therapy in CSU patients who do not achieve adequate control with H1-antihistamines, and they may be particularly beneficial for patients whose urticaria is associated with dyspepsia[26,27]. Despite these potential benefits, current international guidelines do not provide a clear recommendation for or against their use owing to a lack of strong evidence of their efficacy in the majority of patients[22].

hypertension, nephrotoxicity, hypertrichosis, and gingival hyperplasia, necessitating regular blood pressure and renal function assessment. In contrast to omalizumab, patients with low IgE tend to respond better, and remission may be more sustained after discontinuation, while those with higher IgE levels may show comparatively less robust responses.

Agents such as azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, dapsone, and hydroxychloroquine have been used in refractory CSU, mainly as steroid-sparing or add-on therapies[24]. Their evidence base is limited and heterogeneous, largely derived from small studies and observational data. Meta-analyses suggest these drugs may provide benefit in

Table VII: Characteristics of various oral immunosuppressants used in CSU.

Drug	Mechanism of Action	Dose (Typical)	Evidence/Efficacy	Adverse Effects/Limitations	Clinical Role
Azathioprine	Purine synthesis inhibitor → ↓ T- and B-cell proliferation	1 - 2 mg/kg/day	Moderate evidence from small studies; steroid-sparing effect	Myelosuppression, hepatotoxicity, infections	Alternative in refractory CSU, especially autoimmune
Methotrexate	Folate antagonist → ↓ lymphocyte proliferation	10 25 mg/week	Limited evidence; mixed results	Hepatotoxicity, marrow suppression, GI intolerance	Occasional use in resistant cases
Cyclophosphamide	Alkylating agent → profound immunosuppression	1 - 2 mg/kg/day (oral) or pulse IV	Sparse evidence; used in severe refractory disease	Haemorrhagic cystitis, infertility, malignancy risk	Rarely used due to toxicity
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase → ↓ lymphocytes	1 - 2 g/day	Some supportive observational data	GI upset, infections, teratogenicity	Safer alternative to other immunosuppressants
Dapsone	Anti-inflammatory; inhibits neutrophil function	50 - 150 mg/day	Beneficial in some cases, especially with neutrophilic urticaria	Hemolysis (G6PD), methemoglobinaemia	Selected phenotypes
Hydroxychloroquine	Immunomodulatory; interferes with antigen presentation	200 - 400 mg/day	Limited evidence; slow onset	Retinopathy (long-term), GI upset	Mild/moderate refractory CSU

Omalizumab, amonoclonal antibody targeting IgE, is widely used as an effective second-line treatment for chronic spontaneous urticaria refractory to antihistamines. It is given subcutaneously at 300 mg every 4 weeks (150 mg in selected cases), usually for at least 6 months, with longer use based on response. Efficacy rates of up to 90% has been seen in certain cohorts with rapid symptom control within the first 12 weeks, particularly in patients with elevated baseline IgE levels and type 1 autoimmune urticaria[28]. Interestingly, higher levels of IgE have also been linked to greater relapse rates after discontinuation of omalizumab, whereas low IgE may predict a more sustained remission. It is generally well tolerated with headache and injection site reactions described as common adverse effects, while anaphylaxis is rare.

Cyclosporine, a calcineurin inhibitor, is used as a third-line therapy in patients not adequately controlled with antihistamines and omalizumab[20]. The usual dose is 3 - 5 mg/kg/daygiven for 3 - 6 months, depending on clinical response. It is particularly effective in patients with type IIb autoimmune CSU, low baseline IgE levels, positive ASST test, but requires careful monitoring. Common adverse effects include

selected patients, particularly those with autoimmune CSU, but their overall efficacy and safety remain less predictable and adverse effects often limit long-term use (Table VII).

Biologicals and targeted therapy are now being tried in refractory CSU. Dupilumab (targeting IL-4/IL-13 signaling) has shown reductions in wheal activity and itch, although responses may be slower and somewhat variable[29]. BTK inhibitors liker remibrutinib and rilzabrutinib act by suppressing mast cell and basophil activation and have shown encouraging results[30]. Barzolvolimab (CDX-0159), anti- KIT monoclonal antibody has shown marked disease improvement in early studies. Benralizumab, through eosinophil depletion, may offer benefit in selected cases. Collectively, these therapies reflect a move toward mechanism-based, individualised treatment approaches in refractory CSU (Table VIII)[30].

Challenges in diagnosis and management

The main challenge faced by the physicians or the patient is establishing an etiological diagnosis of CSU. It is due to its varied and often unclear pathogenesis, with most cases

being autoimmune or idiopathic rather than trigger-driven. Up to 80 - 90% of patients have no identifiable external cause, and there is no single diagnostic test, so the diagnosis is mainly by exclusion. Factors such as infections, drugs, stress, and comorbid autoimmune conditions – often coexist, but their causal role is not fully established. Additionally, overlapping phenotypes (autoimmune *versus* autoallergic, inducible components) and variability in disease response to treatment further complicates interpretation[9].

and symptom control, keeping in mind that a definitive cause may not be found in most cases.

Beyond diagnosis, other challenges include variable response to standard therapies. Some patients may remain symptomatic despite high-dose antihistamines. Access, cost, and long-term safety considerations of advanced therapies such as biologics can limit their use especially in a resource-limited setup. There is uncertainty about the optimal duration of treatment, timing of step-down,

Table VIII: Biologicals and targeted therapy in CSU[34,35]

[34]Drug	Target Molecule	Mechanism of Action	Dose	Frequency	Route	Indications	Contraindications	Common Adverse Effects
Omalizumab	Free IgE	Binds circulating IgE → ↓ FcεRI expression on mast cells/basophils	150 - 300 mg	Every 4 weeks	SC	Antihistamine-refractory CSU	Hypersensitivity	Injection site reactions, headache, rare anaphylaxis
Ligelizumab (investigational)	IgE (high affinity)	Stronger IgE neutralisation vs omalizumab	72 - 240 mg	Every 4 weeks	SC	CSU (trials) Phase 3 trials failed to show superiority over omalizumab[34].	Hypersensitivity	Injection reactions, URTI, headache
Dupilumab	IL-4Rα (IL-4/IL-13 pathway)	Inhibits Type 2 inflammation signaling	600 mg loading → 300 mg	Every 2 weeks	SC	CSU refractory to antihistamines ± omalizumab; atopic overlap	Hypersensitivity	Conjunctivitis, injection reactions, eosinophilia
Remibrutinib	BTK (Bruton tyrosine kinase)	Inhibits mast cell and basophil activation (FcεRI signaling)	25 mg	Twice daily	Oral	FDA Approved as of September 2025 for antihistamine-refractory adult CSU.	Severe hepatic impairment, hypersensitivity	Headache, URTI, mild infections, petechiae
Rilzabrutinib (investigational)	BTK	Reversible BTK inhibition → ↓ mast cell activation	400 mg	Twice daily	Oral	CSU (trials)	Hypersensitivity	GI upset, diarrhoea, headache
Fenebrutinib (investigational)	BTK	Non-covalent BTK inhibition	Variable (trial-based)	–	Oral	CSU (trials)	–	Headache, infections
Barzolvolimab (CDX-0159)	KIT receptor (CD117)	Mast cell depletion via KIT inhibition	IV doses (trial-based)	Monthly	IV/SC	Refractory CSU	Pregnancy (caution), hypersensitivity	Hair depigmentation, taste changes, infusion reactions
Tezepelumab (investigational)	TSLP	Blocks upstream epithelial cytokine → ↓ Th2 cascade	210 mg	Every 4 weeks	SC	CSU with Type 2 inflammation	Hypersensitivity	Injection reactions, URTI
Secukinumab (exploratory)	IL-17A	Modulates inflammatory pathways (limited role)	300 mg	Monthly	SC	Selected refractory CSU (limited evidence)	Infection risk	URTI, candidiasis
Benralizumab (exploratory)	IL-5Rα	Eosinophil depletion	30 mg	Every 4 - 8 weeks	SC	CSU with eosinophilic phenotype. Ddiscontinued for SCU after the Phase 2b ARROYO trial failed to reach its therapeutic primary endpoint[34].	Hypersensitivity	Headache, pharyngitis

To address these challenges, physicians should focus on detailed history-taking, examination, and basic baseline investigations, rather than extensive workup. Identification of triggers should be history-driven, confirmed by short elimination trials or symptom diaries when appropriate. Emphasis should be placed on excluding differentials, identifying comorbidities, and assessing disease activity. Thus, management should prioritize pragmatic evaluation

and predicting relapse. In addition, there are no widely available biomarkers for endotype-driven therapy which hinders precision medicine approaches. Patient-related factors, including poor adherence, psychosocial stress, and impaired quality-of-life, further complicate management. Collectively, these challenges necessitate an individualised, stepwise, and patient-centered approach to care (Fig. 3).

In conclusion, CSU remains a complex condition and its exact causes are not fully understood despite advances in pathophysiological understanding. The recognition of distinct endotypes, especially autoimmune forms, has improved our understanding and helped develop more targeted interventions. However, uncertainties in diagnosis and variability in treatment response continue to pose challenges in routine practice. A structured, stepwise approach based on clinical evaluation with judicious use of investigations is essential. In the future, the use of validated

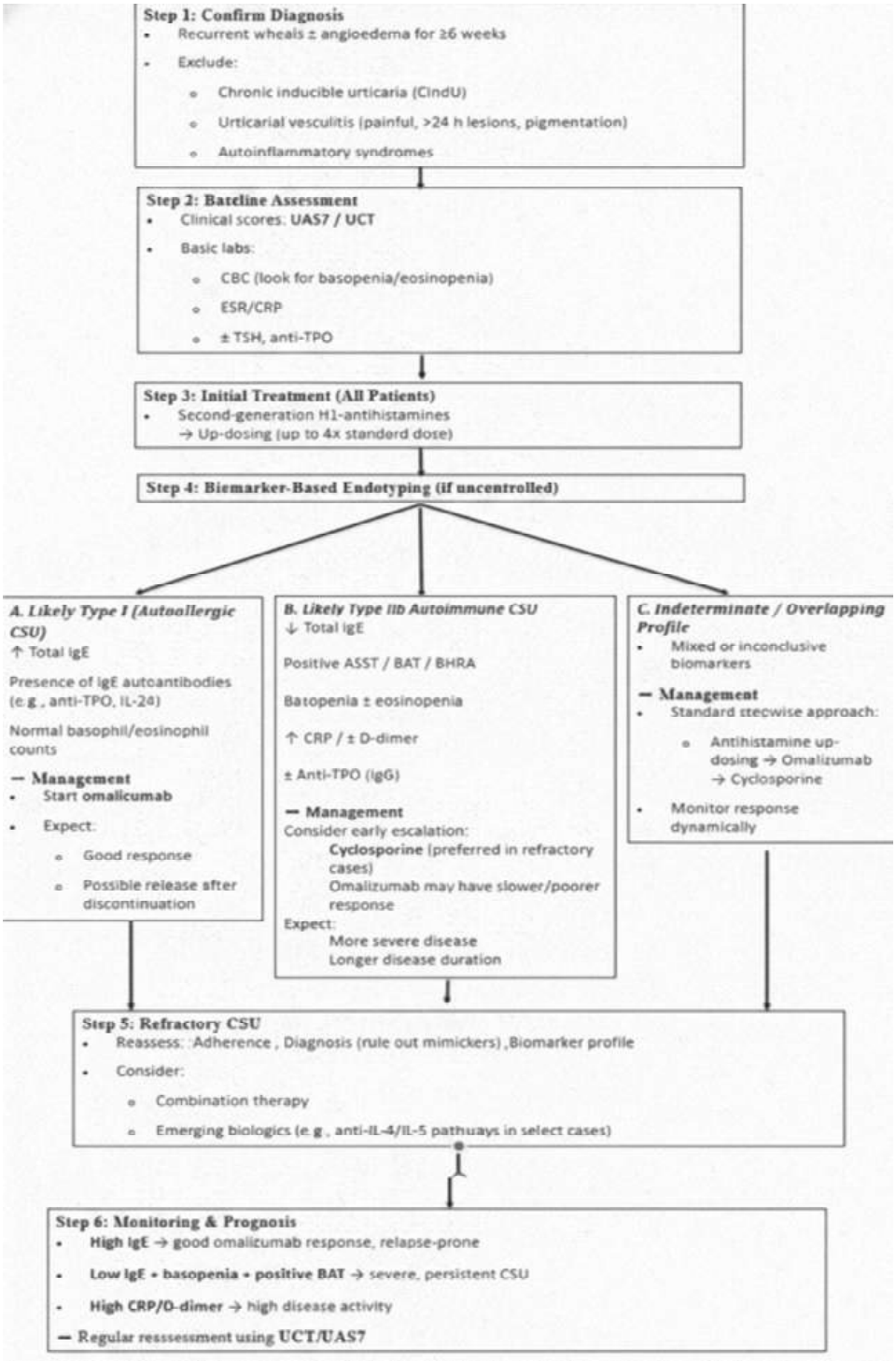

Fig. 3: *Biomarker-Guided Management Algorithm in Chronic Spontaneous Urticaria (CSU).*

biomarkers and endotype-driven strategies may help improve outcome allowing more personalised care.

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