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# Urticaria: Pathogenesis and Treatment Progress

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## Abstract

**Urticaria is a common inflammatory skin disease that may possibly occur in about one in five humans. It is now believed that IgE-mediated degranulation of mast cells to release substances such as histamine is an important pathogenetic mechanism of urticaria. The clinical manifestation of urticaria is the random appearance of irregular itching wheals, angioedema with on the skin. Urticaria can be divided into acute urticaria (AU) and chronic urticaria (CU), depending on whether the urticaria has been recurrent for more than 6 weeks. Chronic urticaria (CU) is characterised by a long-term and recurrent course, which can lead to a reduced quality of life, increased incidence of psychosomatic illness and higher healthcare costs, and can be divided into chronic spontaneous urticaria (CSU) and chronic induced urticaria (CIndU), which may be associated with autoantibodies, complement activation or activation of the coagulation pathway. Current treatments for urticaria are mainly H1 antihistamines, omalizumab and cyclosporine. Various new targets for the pathogenesis of urticaria are being explored and investigated. The precise discovery of the specific pathogenesis of urticaria and the development of individualized treatment regimens are new prospects for the treatment of urticaria.**

## Keywords

**Urticaria; Pathogenesis; Treatment; Progress.**

## 1. INTRODUCTION

Urticaria is an inflammatory skin disease caused by a variety of triggers[1]. Urticaria occurs and develops primarily through a pathophysiological course that mediates the release of various inflammatory factors such as histamine by mast cell degranulation leading to pruritus perception by nerve endings, vasodilation, increased vascular permeability and inflammatory cell recruitment.

The classification of urticaria into acute urticaria (AU) and chronic urticaria (CU) depends on whether the disease lasts longer than six weeks or not[2]. Depending on the etiology, urticaria can be divided into spontaneous and inducible types. Inducible urticaria can be caused by various triggers, such as cold stimulation, water-induced, cholinergic-induced. In clinical practice, most patients with urticaria do not have a clear trigger. The majority of patients with urticaria could be secondary to infection, stress or other possible triggers[3].

## 2. CLINICAL CHARACTERISTICS OF URTICARIA

It has been discovered that different populations are affected by different urticaria subtypes. Of these, AU is more common in children; the population's chance of having AU is roughly 6 –

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19%[4]. The prevalence of CU is about 4.4%, and 80% of these are CSU. High risk factors for urticaria include high population density, personal history of allergic disease or parental history of atopic disease.

There is an association between the development of urticaria and genetic diversity such as IFN-γ, IL-6 and TNF[5]. The pathogenesis of autoimmune CSU may be associated with HLA-DR4 gene diversity. Some studies have found that HLA-DR4 gene diversity may be associated with multiple autoimmune diseases[6]. Patients with CSU are associated with comorbid hypothyroidism, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes[7]. Recently, it has been discovered that CIndU may be influenced by a number of environmental elements, including latitude, temperature, and sun exposure.

## 3. PATHOGENESIS OF URTICARIA

Localized mast cell degranulation in the dermis and subcutaneous tissue stimulates nerve endings, resulting in perceived itching and increased local vascular permeability (wheals, angioedema)[8].

### 3.1. Pathogenesis of AU

AU is generally associated with Type I hypersensitivity due to food, drugs and corresponding allergens. IgE can cause mast cell activation or degranulation by binding to the allergen complex and then the high-affinity receptor FcRI on the surface of basophils or mast cells[9]. Certain substances can induce AU development through direct contact with the skin.

### 3.2. Pathogenesis of CU

3.2.1. Mast cell

Several direct or indirect factors mediate mast cell degranulation to cause clinical manifestations of wheals or angioedema[5]. Mast cells and vascular endothelial cells secrete stem cell factor (SCF), which can then bind to CD117 receptors on the surface of mast cells to promote cell differentiation, migration, proliferation, and other activities[10].

Activation of the FcεRI receptor further mediates the activation of LYN, spleen tyrosine kinase (SYK) and Bruton's tyrosine kinase (BTK), which in turn promote mast cell activation[11]. In addition to the above cytokines and receptors that may be involved in mast cell activation, inhibitory receptors such as Siglec 8, CD200R, CD300a and FcγRIIb are also involved in inhibiting mast cell degranulation and other activities[12].

Besides histamine, clinical symptoms of CSU may also be associated with inflammatory responses of T cells, eosinophils and basophils mediated by trypsin-like proteases, prostaglandin D2, TNF, IL-4, IL-5, IL-13, IL-17 and IL-31[7].

3.2.2. Cell infiltration

Inflammatory cells can be seen locally in the skin of patients with CSU. Various inflammatory cells migrate into the lesions and are closely involved in the allergic late-phase reaction. Local basophils in the blood and skin can secrete histamine, leukotrienes and cytokines by activating the cell surface receptors FcεRI and C5aR[13]. Fujisawa et al. suggest that eosinophils may be involved in the development of CSU by secreting major basic protein (MBP) that mediates the activation of the mast cell inflammatory pathway[14]. Lymphocytes of Th1, Th2 and Th17 phenotypes were found in CSU lesions. Among them, the Th2 mediated type 2 inflammatory response may play an important role in the pathogenesis of CSU through the secretion of various cytokines such as IL-4, IL-13 and IL-31[15].

3.2.3. Coagulation cascade and complement

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Eosinophils and localised vascular endothelial cells in the skin are promoted by tissue factors such as VEGF, histamine, IL-6 and IL-1β to express coagulation factor III on their surface, which further activates thrombin (FIIa) and coagulation factor Xa (FXa)[16]. These reactions can activate protease-activated receptor (PAR) 1 and 2 to induce mast cell degranulation[17]. Activated fibrinolytic enzymes, FXa and FIIa, convert C5 and C3 into C5a/b and C3a/b respectively, which in turn bind to mast cell receptors to promote histamine release[18]. Products of both the coagulation cascade and fibrinolysis may be involved in the pathogenic activity of CSU. It has been found that CSU disease severity scores and D-dimer levels are positively correlated. In addition, CRP, IL-4, C3 and C4 levels are strongly and positively correlated with the level of CSU disease activity[19].

3.2.4. Autoantibodies

IgE, IgA, IgM and IgG may all be involved in the pathogenesis of CSU[20]. Of these, IgE acts by binding to the mast cell receptor FcεRI. Self-antigens and IgG, which can bind to IgE, can also mediate the development of mast cell and basophil-mediated allergic inflammatory factors by binding to IgE and through the corresponding receptors. Thyroid peroxidase (TPO), eosinophil peroxidase (EPO), double-stranded DNA, TF, FcεRI, thyroglobulin, and IL-24 may all act as autoantigens to bind to IgE and induce allergic reactions. IgG may have an important mechanism in the pathogenesis of CSU by binding to IgE or FcεRI[21]. Numerous studies have shown that autoantibodies are present in 20-50% of CSU patients[22]. There is still no conclusive evidence as to whether auto-IgE or other types of autoantibodies are co-expressed in patients with CSU.

3.2.5. Neurogenic inflammation

In patients with CU, mast cell, eosinophil and lymphocyte-mediated inflammatory responses can lead to vasodilation, plasma exudation, pruritus and neuropeptide secretion from nerve endings. Substance P (SP) is a neuropeptide whose levels have been found to correlate positively with disease severity scores in CSU[23]. SP can promote degranulation by activating the mast cell expression receptor MRGPRX2[24].

3.2.6. Other pathogenesis

The specific pathogenesis of CIndU has not been fully elucidated[25]. Among them, it is currently thought that symptomatic dermographism, cold urticaria (ColdU) and solar urticaria (SolarU) may be closely related to autoallergic IgE[26]. In addition, local molecular, cellular and tissue structural changes in the skin induced by various physical stimulants are also a mechanism for the development of CIndU. The receptor CHRM3 expressed in the cutaneous sweat gland (eccrine sweat gland) may induce acetylcholine to bind to mast cells and release histamines. IL-1, IL-6, IL-3 and TNF may also be involved in mediating the pathogenesis of CIndU[27].

## 4. TREATMENT OF URTICARIA

As new mechanisms in the pathogenesis of urticaria have been uncovered and investigated in recent years, our knowledge of developments in urticaria treatment has been steadily growing. Current research focuses on targeted treatments for various urticaria pathogenesis targets. These new targets and therapeutic agents are expected to further enhance the effectiveness of urticaria treatment.

### 4.1. Avoidance of triggers

We should try to avoid the specific triggers in patients who have known urticaria triggers[28]. It is important to treat the underlying infection in patients who have urticaria triggered on by viral or bacterial infections. Significant improvement in CU has been observed in patients receiving standard treatment for chronic H. pylori infection with concurrent CU[29]. After

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receiving standard anti-thyroid medication or thyroid supplementation, there was no discernible improvement in the condition of patients with CU who had Graves' disease or Hashimoto's thyroiditis[30]. We need additional RCT trials in addition to the aforementioned to clarify the precise effect.

### 4.2. Second-generation H1 antihistamines

For patients with urticaria that cannot be controlled by avoiding triggers, treatment with second-generation H1 antihistamines is now routinely recommended[31]. These drugs exert their therapeutic effect mainly by reversibly binding to H1 receptors. Most guidelines do not recommend the use of 1st generation H1 antihistamines for the treatment of urticaria due to significant drowsiness, anticholinergic and drug-drug interactions[32]. Second-generation H1 antihistamines are more effective in the treatment of urticaria and are better tolerated and safer when used in larger doses than indicated[33]. Currently commonly used 2nd generation H1 antihistamines include bilastine, ebastine, fexofenadine, rupatadine, desloratadine. high doses can increase the likelihood of drowsiness. The UK urticaria guidelines do not recommend increasing the dose when treating urticaria with mizolastine[34]. The length of time for these drugs to treat CU is usually about 2 weeks. For patients with CSU, the probability of efficacy with second-generation H1 antihistamines is approximately 60%[35]. For patients who do not respond well with the above treatments, treatment with omalizumab is recommended.

### 4.3. Omalizumab

Omalizumab is a neutralising antibody to human IgE, which exerts its therapeutic effect mainly by reducing IgE concentrations and lowering FcεRI on the surface of mast cells and basophils. the reduction in FcεRI expression also reduces the probability of binding IgE and IgG antibodies to it. The addition of omalizumab is recommended as an effective treatment for CSU patients over 12 years of age who have had unsatisfactory results with second-generation H1 antihistamines. A review on the treatment of CSU with omalizumab found a 72% and 18% probability of complete and partial control, respectively. Omalizumab can also be used to treat CIndU, dermographism, ColdU, CholU and SolarU, but the treatment of these diseases is currently over-indicated. CSU without a significant increase in blood IgE levels or autoimmune associated CSU may result in poor treatment with omalizumab. There are no authoritative conclusions regarding the medication duration of omalizumab, dosage of omalizumab, dosing interval and discontinuation of the drug. In cases of poor outcome with omalizumab, the addition of other immunosuppressive agents (e.g. cyclosporine, aminophenazone or colchicine) may be considered.

### 4.4. Cyclosporine

Cyclosporine can dampen basophil and mast cell activity by suppressing T-lymphocyte activity[29]. Current guidelines suggest that the addition of cyclosporine may be considered for patients with CSU who have failed to respond to combination antihistamines and omalizumab therapy. Statistically, the overall effectiveness of this regimen can currently reach 73%[36]. Nephrotoxicity may occur in more than half of patients. Therefore, most guidelines do not currently recommend the use of cyclosporine for the treatment of urticaria[37]. However, given the price of cyclosporine and the low level of side effects compared to glucocorticoids, there are still many countries that use cyclosporine as a complementary treatment option for CSU patients who have had poor results with antihistamines.

### 4.5. Alternative treatments

Intravenous or oral glucocorticosteroids can also be used in patients with AU or severe flares in CSU. Given the side effects of glucocorticosteroids, it is currently recommended that it should not be administered for more than 10 days. The use of aminophenone, sulfasalazine,

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methotrexate, interferon, and haemodialysis for urticaria has also been reported, but more RCT clinical trials are needed to enhance the level of evidence for their use[38].

### 4.6. Therapies in development

Ligelizumab is a human anti-IgE antibody currently in phase 2 trials for the treatment of CSU[26]. Fenebrutinib is an oral BTK inhibitor that has been found to be effective in the treatment of urticaria that is ineffective against antihistamines[39]. Barzolvolimab may act therapeutically by inhibiting IL-5Rα, thereby suppressing eosinophil activity. Lirentelimab is an anti-Siglec 8 antibody that acts therapeutically by inhibiting mast cell activity and the degranulation response[40]. Secukinumab has also been reported to be effective in controlling CSU patients who do not respond to omalizumab, but the time to achieve therapeutic efficacy is longer[41]. There are other therapeutic targets that may have a role in the treatment of urticaria, such as tryptase, SYK, C5aR, MRGPRX2, IL-33, thymic stromal lymphopoietin (TSLP) and H4R. Some of these drugs are in development.

## 5. CONCLUSIONS

Urticaria is a common inflammatory skin disease, part of the cause of which is known. Depending on the duration of urticaria, it can be classified as AU or CU, which can be further classified as CSU or CIndU. CU can have a serious impact on the quality of life of patients and can be a serious financial burden. The current treatment options for urticaria are second-generation H1 antihistamines, omalizumab and cyclosporine. There are new drugs in development and clinical trials for known targets in urticaria. It is essential to develop individualised treatment plans for patients with urticaria. We believe that in the near future, as we elucidate the pathogenesis of urticaria. Ultimately, the treatment of urticaria will not be a challenge.

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