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The Itch That Won't Quit: A Comprehensive Review of Urticaria

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Abstract:

Urticaria is a skin condition that is categorized based on the duration of symptoms and the presence or absence of triggers. Urticarial vasculitis, contact urticaria, and special syndromes fall under the broader classification of urticaria. In recent years, there has been progress in understanding the pathogenesis of chronic urticaria, with the discovery of autoantibodies to mast cell receptors in almost 50% of patients with chronic idiopathic urticaria. These patients often require more aggressive therapies due to the severity of their condition. However, laboratory tests for chronic urticaria usually do not reveal significant findings, and there is no clear association between urticaria and chronic infections or cancer.Treatment for urticaria usually involves the use of first- and second-generation histamine H1 receptor antihistamines. For more severe and persistent cases, additional therapy may include leukotriene receptor antagonists, corticosteroids, and immunomodulatory agents. Despite advancements in understanding the pathogenesis of urticaria, it remains a frustrating condition for many patients, particularly those with chronic urticaria. Although there have been advancements in understanding the pathogenesis of urticaria, the condition can still be challenging to manage, and patients may require multiple treatments to achieve relief of their symptoms. Additionally, the psychological impact of chronic urticaria should not be overlooked, as it can significantly affect patients' quality of life. As such, a multidisciplinary approach to management, including education and psychological support, can be beneficial in treating patients with urticaria.

***Keyword*:** Urticaria, Mast cell, Food, Treatment, Prevention

1. Introduction

Urticaria is a common and diverse inflammatory skin disorder caused by the activation of skin mast cells, resulting in the release of mediators that cause itchiness, swelling, and inflammation. The condition known as urticaria or 'hives' has a well-documented history in medicine that dates back to ancient times. The Chinese referred to it as 'Feng Yin Zheng' as early as the 10th century B.C. and many cultures have described it in different ways. Hippocrates, in the 4th century B.C., identified the similarities between urticaria and nettle rash or insect bites and called it 'cnidosis.' Overtime, various terms have been used to describe urticaria, including 'Uredo,' 'essera,' 'urticatio,' 'scarlatina urticaria,' and even 'morbus porcinus,' which was a mistranslation of 'morbus pocellaneus' and referred to the white color of the central wheal. The term 'urticaria' was first used by William Cullen in 1769 [1,2,3,4].

2. Classification:

Classification of urticaria is most often based on upon clinical characteristics rather than etiology.

1. Ordinary Urticarias:
   - Acute
   - Chronic
   - Contact

2. Physical Urticarias

3. Special syndromes

4. Urticarial vasculitis

2.1 Acute Urticaria

Acute urticaria is a condition characterized by the presence of wheals for less than six weeks, with individual lesions usually disappearing in less than 24 hours. It is more common in children and often associated with atopy. About 20-30% of patients with acute urticaria progress to chronic or recurrent urticaria. The cause of acute urticaria is idiopathic in about 50% of cases, while upper respiratory tract infections, drugs, and foods are the main causes. Food allergies may contribute more often, but patients often self-diagnose and avoid the offending agent, which makes them under-represented in the data. Acute urticaria caused by certain foods, drugs (especially B-lactam antibiotics), insects, external agents, or parasites is often IgE dependent. On the other hand, opioids, muscle relaxants, radio-contrast agents, and vancomycin can cause urticaria by directly degranulating mast cells and releasing proinflammatory mediators. Complement-mediated acute urticaria can be triggered by serum sickness, transfusion reactions, viral or bacterial infections, while acetylsalicylic acid (aspirin) and NSAIDs can cause acute urticaria by affecting the metabolism of arachidonic acid [5, 6].

2.1.2 Chronic Urticaria

Chronic urticaria is the development of skin wheals that happen regularly (usually daily) for over six weeks with each lesion lasting from 4 to 36 hours. This can be a serious condition and can affect a person's health-related quality of life. Epidemiologic studies are not readily available, and published studies are problematic because they can include physical urticarias and urticarial vasculitis, or not. Identifying the cause and effect of chronic urticaria is also difficult, and many cases remain unknown. Physical urticarias make up around 35% of all chronic urticaria cases, while urticarial vasculitis accounts for about 5%.A small percentage of urticaria is caused by an infection or pseudo allergy. Although many cases remain idiopathic, new evidence suggests that some cases of idiopathic urticaria may have an autoimmune cause. Chronic urticaria is more common in females, occurring twice as often in females as in males [7].

2.1.3 Contact Urticaria

Contact urticaria is a condition where wheals or raised, itchy, and swollen bumps develop on the skin or mucous membrane after contact with an external substance. This can be divided into two types: allergic, which involves the activation of IgE, and non-allergic, which does not. Allergic contact urticaria happens in people who are sensitive to environmental allergens like animals or certain foods or occupational allergens like latex gloves. On the other hand, non-allergic contact urticaria occurs when urticants directly affect blood vessels. Some common urticants include sorbic acid found in eye solutions, cinnamic aldehyde found in cosmetics, and chemicals from the stinging nettle plant, which include histamine, acetylcholine, and serotonin [5].

2.2 Physical Urticaria

Physical urticarias are a type of urticarial disorder that can greatly affect a patient's quality of life. Lesions typically appear in the stimulated area and last less than 2 hours, except for delayed pressure and delayed dermatographism. Symptomatic dermatographism is the most common form and is not associated with systemic disease, atopy, food allergy, or autoimmunity. Delayed-pressure urticaria may cause systemic symptoms, while cholinergic urticaria is characterized by wheals surrounded by a flare in response to physical exertion or hot baths. Other categories include cold urticaria, solar urticaria, aqua genic urticaria, pressure urticaria, and vibrating angioedema. Challenge testing in the office setting can confirm the diagnosis, such as the ice cube test for cold urticaria or applying an 8-kg weight for pressure urticarial [8].

2.3 Special Syndromes

Schnitzler syndrome is a type of chronic urticaria characterized by recurrent non-pruritic wheals, fever, bone pain, and an elevated ESR. IgM may play a role in wheal formation and biopsies often show an increased polymorphonucleocyte count. Muckle-Wells syndrome is an auto inflammatory disorder characterized by urticarial, arthralgias, deafness, and amyloidosis. Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a common dermatosis in pregnancy characterized by urticarial lesions on the trunk, while pemphigoid gestations is a more serious disorder resembling bullous pemphigoid [9,10,11].

2.4 Urticarial Vasculitis

Urticarial vasculitis can be difficult to distinguish from chronic urticaria, but the characteristics of the lesions can help differentiate the two. Lesions of urticarial vasculitis tend to last longer than 24 hours, are associated with burning and pain, and may heal with purpura or petechiae. A skin biopsy can confirm the diagnosis by showing evidence of leukocytoclastic vasculitis. Urticarial vasculitis is rare, occurring in 1-10% of patients with chronic urticaria, and is typically associated with a chronic systemic illness such as lupus erythematosus, hypocomplementemic urticarial vasculitis syndrome, Sjögren syndrome, or mixed cryoglobulinemia [12].

3 Epidemiology:

2017, urticaria had a global prevalence of 86 million cases and an annual incidence of 160 million cases. The prevalence of urticaria varies among different populations depending on the subtype. Acute urticaria (AU) is most prevalent in children under 5 years of age, while chronic urticaria (CU), especially chronic spontaneous urticaria (CSU), is most prevalent in women over 30years old. All types of urticaria are more prevalent in women than in men, except for cholinergic urticaria, which is more prominent in both male adults and children. The prevalence of AU and CU is higher in non-white patients in some studies, but not all. The lifetime prevalence of all types of urticaria and AU is 3-22% and 6-19%, respectively. The overall lifetime prevalence of CU is 4.4%. The prevalence of CU ranges from≤1.5% in the USA and Europe to 3-4% in Mexico, Korea, and China. No significant changes in the global prevalence, incidence, and the years of life lived with disability were seen for urticaria between 1990 and 2017. The prevalence of CSU has consistently increased in South Korea, Italy, and Taiwan, which may be linked to country-specific demographic, environmental, and behavioral factors and changes. CIndU is less prevalent than CSU, with the most prevalent types being symptomatic dermographism, CholU, and ColdU. Aqua genic urticaria, solar urticaria, heat urticaria, vibratory angioedema, and contact urticaria are rare, seen in less than 2-3% of all CU cases. Delayed pressure urticaria is rarely seen as an isolated disorder but present in combination with CSU in up to 36% of patients with CU [13,14,15,16].

4 Etiology

Chronic urticaria is a condition whose cause often remains unknown. Autoimmunity is responsible for 35-50% of cases, as evidenced by the presence of autoantibodies to the FCER1 receptor on mast cells, which leads to chronic stimulation of these cells and release of vasoactive mediators. Non-immunologic causes include direct mast cell release, vasoactive stimuli, alterations in PG pathways due to NSAIDs, and alterations in the bradykinin pathway due to ACE inhibitors. Food allergies and additives are not significant causes. Hashimoto thyroiditis and Graves' disease are associated with chronic urticaria, with up to 27% of patients having ant thyroid antibodies, while H. pylori may indirectly contribute to chronic autoimmune urticaria. The link between chronic urticaria and thyroid disorders is uncertain, and there is no evidence that antibodies involved in thyroid disorders play a role in the pathogenesis of chronic urticaria. An evaluation for H. pylori infection may be considered since successful eradication may result in the resolution of chronic urticarial [17,18,19,20].

5 Pathophysiology

Mast cells are the main cause of urticaria and express high-affinity IgE receptors, which are involved in IgE-dependent allergic reactions. Mast cell degranulation occurs when IgE forms a complex with FCERI on the mast cell to which an allergen binds. Stimuli, such as opioids, C5a anaphylotoxin, and stem cell factor, can also cause degranulation via direct stimulation. Histamine, TNF-α, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, and GM-CSF are preformed cytokines that are released, and PGD2 and leukotrienes C4, D4, and E4 are newly synthesized mediators from arachidonic acid. Chronic urticaria demonstrates a perivascular non-necrotizing infiltrate of CD4+ lymphocytes, including monocytes, neutrophils, eosinophils, and basophils. Autoimmune involvement in chronic urticaria is shown by the presence of functional histamine-releasing anti-FcεRI autoantibodies in about 35-40% of patients with chronic urticaria[21, 22, and 23].

6 Diagnostic

Studies suggest that a detailed patient history is usually enough to diagnose chronic urticaria, but if necessary, an ESR and white blood cell count with differential should be considered. The ASST can help distinguish some cases of chronic autoimmune urticaria from chronic idiopathic urticaria, but it is not widely used. Screening for H. pylori infection is recommended if a cause for the urticaria is not found. Testing for thyroid function and antibodies is necessary only if clinical findings suggest the presence of thyroid disease, and challenge testing is indicated when physical urticaria is suspected. Skin biopsy is necessary to confirm the diagnosis of urticarial vasculitis, and C4 levels should be measured to screen for Cl-inhibitor deficiency in patients with angioedema but without urticaria. Differentiating autoimmune chronic urticaria from idiopathic chronic urticaria is clinically important, as patients with the autoimmune form typically have a more aggressive disease course and are more resistant to treatment. However, establishing a diagnosis of autoimmune chronic urticaria is difficult because there are no reliable laboratory tests to aid the clinician. The ASST is currently the most useful test for evaluating chronic urticaria, with a positive result indicating autoimmunity and a negative result indicating remission of symptoms. The diagnosis of chronic idiopathic urticaria is established when a patient does not have any identifiable autoantibodies to mast cells, and the clinical features of autoimmune chronic urticaria are indistinguishable from those of chronic idiopathic urticaria[24,25,26].

7 Treatment:

Pharmacotherapy and general trigger-prevention techniques are the cornerstones of urticaria management.

7.1 First-Line Therapy

The initial treatment for this condition involves educating the patient and using non-pharmaceutical methods, followed by a trial of antihistamines that target the histamine H1 receptor if the symptoms continue. The non-drug measures include avoiding things that make the condition worse, like stress, overheating, alcohol, acetylsalicylic acid, NSAIDs, and ACE inhibitors. Applying cooling antipruritic lotions containing menthol in aqueous cream or calamine lotion may also provide some relief. It's important to keep patients well-informed about the disease through both verbal and written communication. Specifically, patients should know that the condition usually doesn't have serious consequences, cannot be cured, and is often without a clear cause[4, 27].

7.1.1 Histamine H1 Receptor Antihistamines

Antihistamines are drugs that inhibit the H1 receptor and reduce inflammation by blocking the production of many important mediators of inflammation, such as IL-1ß, IL-6, TNFα, and GM-CSF. They can also inhibit histamine release and prevent the actions of mast cell and basophil-derived histamine on its target organs. Antihistamines are effective in reducing pruritus and the number of hives, although not all patients will respond. First-generation antihistamines have sedating and anticholinergic effects, whereas second-generation antihistamines, including cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, ebastine, and mizolastine, have fewer adverse effects. Fexofenadine is unique among second-generation antihistamines in that it is lipophobic and does not penetrate the blood-brain barrier, hence can be prescribed at doses of up to 360 mg/day without risk of sedation. Desloratadine is more potent than loratadine, and levocetirizine is more potent than cetirizine. More than one antihistamine should be tried, since efficacy is patient specific, and they are most effective if taken daily rather than on an as-needed basis[4, 28].

7.1.2 H2 Receptor Antagonists

Some patients with chronic urticaria can benefit from using H2 receptor antihistamines alongside H1 receptor antihistamines, as 15% of histamine receptors in the skin are of the H2 type. However, using H2 receptor antagonists alone is not recommended as they only have minor effects on itching. Cimetidine, ranitidine, nizatidine, and famotidine are examples of H2 receptor antagonists. It is important to note that there is limited evidence supporting the effectiveness of H2 receptor antagonists[29].

7.2 Second-Line Therapy

If antihistamines alone do not control urticarial symptoms, consider second-line therapies including pharmacologic and nonpharmacologic measures. Photo- or photo chemotherapy may be considered but results have been inconclusive. Relaxation therapies have also reported inconclusive results. Antidepressants, corticosteroids, calcium channel antagonists, levothyroxine sodium supplements, leukotriene receptor antagonists, and other drugs may be useful in second-line therapy[30].

7.2.1 Antidepressants

Doxepin, a tricyclic antidepressant, has potent H_1 and H_2 receptor antagonist activity and is more effective and less sedating than diphenhydramine in treating chronic urticaria. However, sedation is a greater problem for doxepin than for diphenhydramine or hydroxyzine, limiting its usefulness. Doxepin works best when taken at night and should be used with caution or avoided in patients taking other drugs metabolized by the CYP system. It may be especially useful in patients with chronic urticaria and coexisting depression. Only 10-30 mg/day is recommended for chronic urticaria. Mirtazapine, another antidepressant, has antipruritic activity and has been reported to be helpful in some cases of physical urticaria and delayed-pressure urticaria at doses of 30 mg/day[31, 32].

7.2.2 Corticosteroids

Short-term systemic corticosteroids may be prescribed for severe urticarial symptoms to rapidly and effectively control the disease. However, long-term corticosteroid therapy is not recommended due to the risk of developing tolerance and various adverse effects such as hyperglycemia, osteoporosis, peptic ulcers, and hypertension. If prolonged corticosteroid therapy is necessary, the lowest effective dose should be used along with corticosteroid-sparing immunosuppressive modalities. Clinicians should maximize antihistamine dosages, particularly first-generation antihistamines given up to four times daily, in an attempt to avoid corticosteroid courses[33].

7.2.3 Leukotriene Receptor Antagonists

Leukotriene receptor antagonists such as montelukast, zafirlukast, and zileuton have been shown to be effective in treating chronic urticaria, as they inhibit leukotrienes, which are potent mediators of inflammation that can cause wheal and flare responses. These antagonists may be used alone or in combination with antihistamines to control chronic urticaria, particularly in patients who are unresponsive to antihistamines alone or who have NSAID-induced exacerbations. However, their use remains controversial, as not all trials have shown a beneficial effect. For example, a recent double-blind, placebo-controlled, crossover study of 52 patients with chronic urticaria found that monotherapy with zafirlukast 20 mg twice daily did not provide any significant benefit over placebo[34,35,36].

7.2.4 Nifedipine

Nifedipine, a calcium channel blocker, has been reported to be effective in reducing pruritus and wheeling in patients with chronic urticaria, either used alone or in combination with antihistamines. However, some experts have found its clinical effect to be disappointing. Nifedipine has been shown to modify cases of physical urticaria and delayed-pressure urticaria at doses of 30 mg/day[37].

7.3 Third-Line Therapy

Third-line treatment options for chronic urticaria patients who do not respond to initial treatments consist of immunomodulatory agents such as cyclosporine, tacrolimus, methotrexate, cyclophosphamide, mycophenolate mofetil, and IVIG. These agents are commonly used for the autoimmune form of chronic urticaria. Other potential third-line therapies include plasmapheresis, colchicine, dapsone, albuterol (salbutamol), tranexamic acid, terbutaline, sulfasalazine, hydroxychloroquine, and warfarin[38].

7.3.1 Immunomodulatory Agents

Cyclosporine is effective in treating refractory chronic urticaria, benefiting about two-thirds of patients who do not respond to antihistamines. During treatment with cyclosporine, H1 receptor antihistamines should be continued and blood pressure and renal function should be monitored. Experience with other immunomodulatory agents, including tacrolimus, methotrexate, and cyclophosphamide, is more limited, but have shown success in some patients. IVIG has also shown effectiveness in managing severe refractory autoimmune chronic urticaria, but expense and potential morbidity are concerns, and controlled studies have not yet been conducted to evaluate this therapy[39, 40, and 41].

7.3.2 Plasmapheresis

Plasmapheresis has been reported to relieve symptoms in some patients with severe, treatment-resistant autoimmune chronic urticaria. However, this approach is expensive, potentially morbid, and not a long-term or standalone solution. Plasmapheresis should be investigated in combination with immunosuppressant pharmacotherapy to prevent the re-accumulation of histamine-releasing autoantibodies[42].

7.3.3 Other Drugs

Certain medications may be effective in managing urticaria depending on the underlying cause. Dispone, colchicine, and sulfasalazine may be beneficial for urticarial vasculitis and some types of chronic idiopathic urticaria. Hydroxychloroquine has shown promise in treating chronic idiopathic urticaria and hypocomplementemic urticarial vasculitis. The use of terbutaline for chronic urticaria is generally not recommended due to adverse effects. Studies on the effectiveness of warfarin for chronic urticaria have had mixed results, with some suggesting that it may be beneficial for certain patients with coagulation-dependent mediators such as kinins[43,44,,45].

7.4 Treatment for specific population

Special consideration is required for pregnant women, breastfeeding women, children, and geriatric populations in the management of chronic spontaneous urticaria (CSU). First-generation antihistamines and sgAHs are commonly used for allergic disease, but only cetirizine and loratadine have been shown to be safe during pregnancy and are therefore preferred. Nursing infants can develop sedation from first-generation antihistamines secreted into breast milk, so loratadine and cetirizine are advised for breastfeeding women. Omalizumab is safe for pregnant women and younger children, but currently licensed only for those aged 12 years and older. Several sgAHs have proven efficacy and safety in the pediatric population. Older populations are particularly sensitive to adverse effects from first-generation antihistamines and should be avoided. Standard doses of sgAHs and omalizumab are safe and effective in older patients, but some may be particularly susceptible to the sedative action of cetirizine and loratadine when recommended doses are exceeded. Risk-benefit profiles for immunosuppressive therapies need careful consideration in all three patient populations. Detailed reviews of CSU management in these groups are available[46, 47, and 48].

8 Impact quality of life

Patients with urticaria, especially chronic urticaria (CU), experience significant impairment to their quality of life, with physical, psychological, social, and emotional effects. Various instruments are available to assess this impairment, including generic questionnaires such as Short Form-36 (SF-36) and Nottingham Health Profile (NHP), and disease-specific questionnaires like Dermatology Life Quality Index (DLQI), Chronic Urticaria-Quality of Life Questionnaire (CU-Q2oL), Cholinergic Urticaria-Quality of Life Questionnaire (CholU-QoL), and Angioedema-Quality of Life Questionnaire (AE-QoL). Disease-specific questionnaires are recommended for all CU patients as per international guidelines. Acute urticaria (AU) has a limited impact on quality of life, with patients expressing greater satisfaction than CU patients. Patients with chronic inducible urticaria (CIndU) have slightly better quality of life than chronic spontaneous urticaria (CSU) patients, likely due to the transient nature of stimuli. CSU, characterized by unpredictable wheals and angioedema and severe pruritus, has the most significant impact on quality of life. Pruritus leads to lack of sleep, fatigue, and concentration, while the symptoms' daily occurrence leads to loss of control over patients' lives. Urticaria symptoms also cause embarrassment, frustration, sadness, and anxiety, exacerbated by the condition's underestimation by others, including treating physicians. CSU also limits social interactions, work

performance, and daily functioning, including interpersonal relationships and sexual life.CU has comparable quality of life impairment with moderate to severe psoriasis and atopic dermatitis. Social quality of life impairment in CU patients is similar to that in patients with coronary artery disease and worse than in patients with type I diabetes mellitus. Untreated CU has substantial negative effects on quality of life, but effective therapy results in a corresponding improvement in quality of life[49, 51, 52, and 53].

9 Prevention

Urticaria prevention options are limited. Breastfeeding for more than 6 months can reduce the risk of urticaria. Avoidance of triggers such as tight-fitting clothes or certain foods/drugs can be effective for secondary prevention. Moving to a different location with different temperatures may decrease the risk of ColdU. Tertiary prevention involves treating symptoms with antihistamines and omalizumab, or disease-modifying treatments such as allergen-specific immune therapy or cyclosporine. Novel mast cell-reducing therapies may also induce long-lasting remission[54, 55, and 56].

10 Conclusion

Urticaria can be diagnosed clinically and classified as idiopathic once other potential causes have been ruled out. While acute urticaria often has an identifiable trigger, chronic urticaria is usually idiopathic, although around 35-40% of chronic idiopathic cases may have an autoimmune etiology. Non-sedating H_1 receptor antihistamines are the first-line therapy for urticaria, followed by combinations with other medications. Severe chronic urticaria may benefit from short courses of corticosteroids and immunosuppressant therapies.

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