Antihistamine-refractory urticaria: when standard care falls short

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Chronic urticaria, characterised by recurrent wheals, angioedema, or both, presents a significant challenge for both patients and clinicians. While antihistamines remain the cornerstone of initial management, a substantial proportion of patients experience persistent symptoms despite standard doses. This necessitates a clear understanding of step-up therapy, as outlined in current clinical guidance, to achieve adequate disease control and improve quality of life.

KEY TAKEAWAYS

- The Pivot: Patients with chronic urticaria who do not achieve symptom control with standard-dose antihistamines require a structured approach to therapy escalation.
- The Data: Current guidelines advocate for increasing antihistamine dosage up to four-fold before considering advanced therapies.
- The Action: Clinicians should systematically escalate antihistamine doses and, if symptoms persist, consider referral for biologic treatment or other immunosuppressants.

Chronic urticaria (CU) is a mast cell-driven disease defined by the spontaneous appearance of wheals, angioedema, or both for more than six weeks. It affects approximately 0.5% to 1% of the global population, with a significant impact on quality of life due to pruritus, sleep disturbance, and psychological distress. The condition is broadly classified into chronic spontaneous urticaria (CSU), where no external trigger is identified, and chronic inducible urticaria (CIndU), where specific triggers like cold, pressure, or sunlight are involved. Both forms share a common pathway of mast cell activation and histamine release, making antihistamines the logical first-line treatment.

The initial management strategy for chronic urticaria universally involves second-generation H1-antihistamines. These agents, such as cetirizine, loratadine, fexofenadine, and desloratadine, are preferred over first-generation antihistamines due to their improved safety profile, particularly the reduced sedative and anticholinergic effects. The standard approach begins with a regular, once-daily dose. But a significant subset of patients, estimated to be around 30% to 50%, will not achieve satisfactory symptom control with this initial step. This lack of response defines antihistamine-refractory urticaria and necessitates a structured escalation of therapy.

Escalating Antihistamine Doses

When a patient with chronic urticaria reports persistent symptoms despite adherence to a standard daily dose of a second-generation H1-antihistamine, the first step in current guidelines is to increase the antihistamine dosage. This involves up-dosing the chosen antihistamine up to four times the standard daily dose. For example, if a patient is on 10

mg of cetirizine daily, the dose can be increased to 20 mg, then 30 mg, and finally 40 mg daily. This strategy aims to achieve a higher receptor occupancy, thereby more effectively blocking histamine's effects on H1 receptors. The rationale for this approach is rooted in the understanding that higher doses can overcome individual variations in antihistamine metabolism and receptor sensitivity, leading to improved symptom control.

The up-dosing strategy should be implemented systematically, with each dose increase maintained for a period of two to four weeks to assess efficacy. Patients should be counselled on the potential for increased side effects, although second-generation antihistamines generally maintain a favourable safety profile even at higher doses. Sedation, while less common than with first-generation agents, can still occur, particularly at the maximal four-fold dose. Clinicians should monitor for any adverse events and adjust the regimen if necessary. The Oxford Handbook of Clinical Immunology and Allergy provides a practical guide to managing such conditions, including detailed dosing strategies.

If a patient remains symptomatic despite a four-fold increase in antihistamine dosage, they are considered to have truly antihistamine-refractory chronic urticaria. At this juncture, further escalation of antihistamine dosage is generally not recommended, as the likelihood of achieving additional benefit diminishes, while the risk of side effects may increase. This is the point where clinicians must consider moving to advanced therapeutic options, often requiring referral to a specialist, with the stake being the patient's quality of life.

Beyond Antihistamines: Biologics and Immunosuppressants

For patients who do not respond to high-dose antihistamines, current guidelines recommend the introduction of omalizumab, a monoclonal antibody targeting immunoglobulin E (IgE). Omalizumab works by binding to free IgE in the circulation, thereby reducing IgE levels and preventing its binding to mast cell receptors. This mechanism leads to a reduction in mast cell activation and histamine release, alleviating urticaria symptoms. It is administered subcutaneously, typically at a dose of 300 mg every four weeks. The onset of action can vary, with some patients experiencing rapid improvement within weeks, while others may require several months of treatment to achieve optimal control.

Omalizumab has demonstrated efficacy in both CSU and CIndU, significantly reducing symptom severity and improving quality of life. Its safety profile is generally favourable, with injection site reactions being the most common adverse event. Anaphylaxis, while rare, is a known risk, necessitating administration in a clinical setting with immediate access to resuscitation equipment, particularly for the initial doses. The duration of omalizumab treatment is often prolonged, with many patients requiring continuous therapy to maintain symptom control. Discontinuation can lead to symptom recurrence, highlighting the need for careful patient selection and ongoing assessment.

But what if omalizumab fails? For the small percentage of patients who do not respond adequately to omalizumab, or for whom omalizumab is contraindicated or unavailable, the next step involves considering immunosuppressive agents. Cyclosporine A is the most commonly recommended option in this scenario. It acts by inhibiting T-cell activation, thereby reducing the inflammatory response and mast cell degranulation. Cyclosporine A is an effective treatment for severe, refractory urticaria, but its use is limited by a significant side effect profile. This includes nephrotoxicity, hypertension, hyperlipidemia, and increased risk of infections. Close monitoring of renal function, blood pressure, and lipid profiles is essential during treatment. The decision to initiate cyclosporine A should be made in consultation with a specialist, weighing the potential benefits against the risks.

Other immunosuppressants, such as methotrexate, mycophenolate mofetil, and tacrolimus, have been explored in refractory urticaria, but their evidence base is less robust compared to cyclosporine A. These agents are generally reserved

for highly selected cases under specialist supervision, often when other options have failed or are not tolerated. The choice of agent depends on individual patient factors, comorbidities, and the clinician's experience. For example, some clinicians might consider JAK inhibitors in RA for other autoimmune conditions, but their role in urticaria is still evolving.

Guideline Recommendations and Practical Considerations

International guidelines, such as those from the European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA2LEN), European Dermatology Forum (EDF), and World Allergy Organization (WAO), provide a clear algorithm for managing chronic urticaria. These guidelines consistently recommend a step-wise approach: first, standard-dose second-generation H1-antihistamines; second, up-dosing antihistamines up to four times; third, adding omalizumab; and fourth, considering cyclosporine A or other immunosuppressants. This structured approach ensures that patients receive appropriate and evidence-based care, progressing to more potent therapies only when less intensive options have failed.

A critical aspect of managing antihistamine-refractory urticaria is patient education and adherence. Patients must understand the chronic nature of the disease and the importance of consistent medication use. Non-adherence to antihistamine regimens is a common reason for perceived treatment failure. Regular follow-up appointments are crucial to assess symptom control, monitor for side effects, and adjust therapy as needed. Validated tools, such as the Urticaria Activity Score (UAS7), can be used to objectively measure disease activity and treatment response. The UAS7, which assesses the number of wheals and intensity of pruritus over seven days, provides a standardized method for tracking progress and guiding therapeutic decisions.

The diagnostic work-up for chronic urticaria should also be revisited in refractory cases. While CSU is often idiopathic, a thorough initial evaluation is important to rule out underlying causes or associated conditions, such as autoimmune thyroid disease, infections, or physical urticarias. In patients who do not respond to standard treatments, re-evaluation may uncover a missed diagnosis or a contributing factor that requires specific management. For instance, some patients with CIndU may benefit from strict avoidance of triggers in addition to pharmacotherapy. The distinction between CSU and CIndU is important, as the latter may respond differently to certain treatments or require specific trigger avoidance strategies.

The role of diet and lifestyle modifications in chronic urticaria is often debated. While there is limited evidence to support widespread dietary restrictions, some patients report symptom exacerbation with certain foods or additives. A trial of a pseudoallergen-free diet may be considered in selected patients, but it should be done under medical supervision to ensure nutritional adequacy. Stress management techniques can also be beneficial, as psychological stress is a known trigger for urticaria flares in many individuals. The overall management plan should be holistic, addressing not only the pharmacological aspects but also the psychosocial impact of the disease.

Still, the journey for many patients with chronic urticaria is long and frustrating. The lack of a definitive cure for most cases means that long-term management is often necessary. The development of new therapies, particularly biologics, has significantly improved outcomes for those with severe, refractory disease. But access to these advanced treatments can be a barrier in some healthcare systems, and their cost remains a consideration. The challenge for clinicians is to navigate these options effectively, ensuring that patients receive timely and appropriate care according to established guidelines. This often involves a multidisciplinary approach, collaborating with allergists, dermatologists, and immunologists to optimise patient outcomes.

> **CLINICAL IMPLICATIONS**
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> The persistent challenge of antihistamine-refractory urticaria highlights the need for a systematic approach to treatment. Simply prescribing another antihistamine at the same dose is a disservice to patients experiencing

debilitating symptoms. Clinicians must be confident in escalating antihistamine doses up to four-fold, a step often overlooked in busy general practice settings.

But the real shift in management comes with the introduction of biologics. Omalizumab has transformed the treatment landscape for many patients, offering significant relief where traditional therapies have failed. GPs should not hesitate to refer patients who remain symptomatic on high-dose antihistamines to a specialist for consideration of this therapy; delaying referral only prolongs patient suffering.

The use of immunosuppressants like cyclosporine A, while effective, carries a substantial burden of side effects. This necessitates careful patient selection and rigorous monitoring, making it a treatment best initiated and managed by specialists. The complexity of these advanced therapies highlights the importance of adherence to established guidelines, ensuring patients receive care that is both effective and safe.

Managing chronic urticaria requires patience and persistence, both from the clinician and the patient. The goal is not just symptom suppression, but a significant improvement in quality of life, which for many, means moving beyond the limitations imposed by persistent itching and swelling.

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