Management of Chronic Urticaria

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1 Conception of study
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Introduction

The management of urticaria, although complex, relies on two postulates:
- Recognition and eradication of the triggering factor(s)
- Provision of symptomatic relief

Recognition and eradication of the triggering factor(s)
Factors known are drugs, food, infections, and physical stimuli.
Drugs: Analgesics and NSAIDs can exacerbate already present urticaria and are also recognized triggers of new-onset urticaria.¹² When suspected, they should be withdrawn entirely or can be replaced. ACE inhibitors can cause angioedema.
Eradication of infectious agents
Infections and infestations should be treated where suspected, including infections of the GI tract e.g., H Pylori associated gastritis⁵, nasopharyngeal bacterial infections and intestinal worms.⁸

Management of diet
The allergens in food need to be avoided if a patient has type I hypersensitivity to any one of these allergens. Pseudo-allergic reactions⁵ which are not IgE mediated have been described for organic foods and food additives.⁹-¹³

Physical stimuli
They are usually recognized and controlled, e.g., in chronic pressure urticaria patients are advised to use bags with a wide handle and similarly, in symptomatic dermographism, simple avoidance of friction can give relief from symptoms.¹⁵

Symptomatic therapy
One of the objectives of symptomatic therapy is to mask the effects of histamine, platelet-activating factor, and other mast cell mediators. Histamine plays a primary role in inducing the symptoms associated with urticaria. The activation of receptors on endothelial cells by histamine results in wheals whereas this histamine receptor activation on sensory nerves results in itching. Different guidelines have been proposed for managing chronic urticaria including the EACCI [5] and BSACI [4].
Figure 1: Chronic Urticaria management algorithms.
(A) European Academy of Allergy and Clinical Immunology/ Global Allergy and Asthma European Network/ European Dermatology Forum/ World Allergy Organization (EAACI/GA2LEN/EDF/WAO) guidelines
(B) The US practice parameters for the diagnosis and management of chronic urticaria (CU).
According to EACCI guidelines, the first choice in treating chronic urticaria is second-generation histamine type I receptor blockers. However, continuous treatment is recommended because of their non-sedating or minimally sedating properties free of anticholinergic side effects. More than four-fold higher doses can be used in the majority. Table 1 enlists the commonly used H1 antihistamines in Pakistan.

### Table 1: Antihistamine (H1) commonly used for CU

| Drug       | Dose   | Class                        | References |
|------------|--------|------------------------------|------------|
| Cetirizine | 10 mg  | Second-generation antihistamine | (22)       |
| Desloratadine | 5 mg  | Second-generation antihistamine | (24)       |
| Fexofenadine | 120-180 mg | Second-generation antihistamine | (20)       |
| Levocetirizine | 5 mg  | Second-generation antihistamine | (25)       |
| Loratadine | 10 mg  | Second-generation antihistamine | (27)       |
| Ebastine   | 10 mg  | Non-sedating antihistamine    |            |
|            | 20 mg  |                              |            |

Safety data of H1 antihistamines are available regarding prolonged use. In the recent GA2LEN position paper, first-generation antihistamines are no longer recommended. This view is shared by the World Allergy Organization guideline for Allergic Rhinitis and its Impact on Asthma. Modern second-generation antihistamines (loratadine, and fexofenadine) are non-sedating metabolites of earlier sedative antihistamines. Astemizole and terfenadine are disregarded because of cardiotoxic effects. Seven of second-generation antihistamines (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, rupatadine, and bilastine) have been tested in detail. Studies show the benefit of dose more than four-fold of the recommended dose. It has been verified using bilastine, cetirizine, desloratadine, levocetirizine, fexofenadine, and rupatadine. H2-Antihistamines

There is little evidence for their use. A combination of cimetidine with hydroxyzine results in increased hydroxyzine levels hence recommended only in hydroxyzine unresponsiveness. Cimetidine is not recommended in combination with cetirizine. The combination of ranitidine with terfenadine was superior to terfenadine alone in terms of itch, but not in wheals or swellings.

### Treatment of refractory symptoms

Repeated courses of glucocorticoids may be used, but it may cause severe side effects without inducing remission or altering the course. So they are only advisable for short periods at the minimal effective dose while considering other options.

### Goal of Therapy

There is no standardized approach. Options include omalizumab, and anti-inflammatory or immunosuppressants. Therapy must be individualized, considering concomitant medical conditions and patient preferences.

### Treatment strategies

Any ineffective standard therapies should be discontinued. A baseline complete blood count and chemistry panel with liver function tests should be obtained prior to initiation.

Drugs for refractory urticaria can be divided into three groups:

1. **Anti-inflammatory group**
   - Predominantly anti-inflammatory, with low toxicity and less proven efficacy e.g., dapsone, sulfasalazine, and hydroxychloroquine.

2. **Immunosuppressant group**
   - Potent immune suppression with greater toxicity and efficiency e.g.; calcineurin inhibitors, sirolimus, and mycophenolate mofetil.

3. **Omalizumab**
1. ANTI-INFLAMMATORY AGENTS:
Table 2: Agents best studied in CU are dapsone, sulfasalazine, and hydroxychloroquine.

| Drug               | MOA                                      | Side Effects                                    | Dose         |
|--------------------|------------------------------------------|-------------------------------------------------|--------------|
| Dapsone            | Sulfone Antimicrobial; Addition of dapsone to antihistamines showed earlier response than with antihistamines. | Anemia, neuropathy, hepatotoxicity, methaemoglobinaemia, DRESS syndrome. | 100mg.       |
| Sulfasalazine      | 5-Aminosalicylic Acid derivative.        | Nausea, gastrointestinal discomfort, mild headache, leucopenia, and elevated liver function tests. | Start with 500 mg daily, increase by 500 mg per week to 2000 mg daily. |
| Hydroxychloroquine | Anti-inflammatory; Anti-malarial; Suppression of T-cell activation; Disruption of antigen processing of macrophages | Slow onset of action. | Adults: 200 mg twice daily. 3 months’ trial required. |

2. IMMUNOSUPPRESSIVE AGENTS:
Table 3: Immunosuppressant Agents.

| Drug               | MOA                                      | Side Effects                                    | Dose         |
|--------------------|------------------------------------------|-------------------------------------------------|--------------|
| Cyclosporine       | Inhibit the calcium-dependent release of histamine, leukotriene C4 and mediators in mast cells. Has anti-T lymphocyte activity; May disrupt TNF-alpha activity. | 3-5 mg per kg daily, tapering after remission. | 1mg twice daily for 1 week; increased to 2mg twice daily. |
| Tacrolimus         | Same as cyclosporine.                    |                                                 |              |
| Sirolimus          | The substrate of cytochrome P450 3A4.    | Headache, arthralgias, rash, dyslipoproteinaemia cytopenias, and immune suppression-related neoplasia or infections. |              |
3. Omalizumab:
This recombinant humanized monoclonal IgG antibody binds free IgE, down-regulates mast cell function and induces eosinophil apoptosis through the reduction of FcεRI in basophils and mast cells. It has proven efficacy in refractory CU. Add-on therapy with subcutaneous omalizumab 300 mg every 4 weeks for 12 or 24 weeks, reduced itching severity, hives, and angioedema. It is the second choice in the EAACI guidelines and officially approved by the European Regulatory Agency. Efficacy is proven in symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure, solar and cholinergic urticaria.

Dosing — Two doses approved by the FDA are 150 mg or 300 mg every four weeks. If the response is adequate, taper to a lower dose (e.g., 150 mg every four or six weeks). An algorithm for dose individualization has been proposed. Treated patients, who, after stopping therapy, had a recurrence, have been reported to respond to omalizumab again, suggesting that resistance does not develop readily.

Monitoring — No specific laboratory monitoring is required for patients receiving omalizumab.

Side Effects — There appears to be no reported side effect. However, transient hair loss was reported in three subjects who continued therapy despite it.

Therapies with Significant Limitations

Some additional agents that can be useful, albeit with limitations. Glucocorticoids remain the standard comparator.

Immunoglobulin
Used where immunomodulation is preferable to immunosuppression, e.g., history of malignancy. It alters cell adhesion, immunoregulatory molecules, complement function, cytokine levels, and autoantibody production. It can be administered intravenously [IVIG]) or subcutaneously [SCIG]. Adverse effects are generally predictable and manageable. It may be dosed individually, the optimal dose, number of infusions and schedule are unknown.

TNF-inhibitors
Tumor necrosis factor (TNF)-alpha is upregulated in the epidermis in lesional and nonlesional skin. Etanercept, adalimumab, and infliximab have been studied. However, the effectiveness is limited.

Colchicine

It acts by suppressing leukotriene generation or leukocyte adhesiveness and migration. It is safe at recommended doses, with a rapid onset of action.

Androgens
These are effective in hereditary angioedema and have been studied in chronic idiopathic urticaria and angioedema. Methotrexate
It reduces neutrophil accumulation, diminishes leukocyte adhesiveness, leukotriene synthesis, and alters cytokine activity. Efficacy is limited. Doses ranged from 5-25 mg/week and effects observed after four weeks.

Cyclophosphamide
Reserved where multiple alternative agents have failed. It is believed to act on plasma cells to reduce autoantibody production in autoimmune CU.

Antifibrinolytics
These are useful because coagulation and inflammatory pathways in urticaria are interconnected. Serine protease inhibitors decrease proteases including tryptase, kallikrein, complement, factor XII, and plasmin e.g., tranexamic acid.

Methylxanthines
Theophylline.

I/M or aerosolized epinephrine (BASCI):
Intramuscular epinephrine not routinely prescribed except for self-administration in angioedema affecting the upper airway.

Nondrug therapies
Nondrug treatments that have been studied in CU include phototherapy, autohemotherapy, and plasmapheresis.

Phototherapy
It is useful in solar and physical urticarias, suitable for patients who visit frequently or intolerant to systemic treatment. Narrowband UVB is effective, safe and affordable for steroid-dependent CRU.

Autohemotherapy
It involves the parenteral injection of autologous blood to desensitize patients to pro-urticarial factors in his serum and improved quality of life.

Plasmapheresis
It removes proteins and other substances and may be immunomodulatory. However, it is not easily available and not recommended for routine use.

Inducing Tolerance
It can be useful in physical, cholinergic, solar and cold urticarias. However, it lasts only a few days. A consistent exposure is required, which is often not acceptable.
Table 4: Recommendations for treatment of chronic urticaria: Representative sampling of clinical guidelines and expert panel opinions.

| Ref                          | Recommendations                                                                 |
|------------------------------|---------------------------------------------------------------------------------|
| EAACI/GA 2LEN/EDF/WAO guideline | Second-generation histamine type I receptor blockers should be the first choice for symptomatic relief. Sedating antihistamines should not be used for routine management as first-line agents |
| BSACI guidelines             | Non-sedating H1-antihistamines are the mainstay of therapy. Chronic use of these should be discouraged as it can lead to psychomotor dysfunction and heavy sedation |
| AAITO position paper         | Low-sedating H1-antihistamines as first-line therapy                             |
| SFD Consensus Conference Recommendations | Monotherapy with a second-generation H1-antihistamine is the preferred treatment. This drug controls the disease in the majority. |
| Joint Task Force on Practice Parameters | Symptomatic treatment with H1-antihistamines remains the mainstay of management; Sedation does not occur at recommended doses except for cetirizine. Sedation may reduce the discomfort of pruritus, but may cause undesirable and potentially dangerous side effects |
| BAD therapy guidelines       | Histamine type I receptor blockers which do not cause significant sedation are the mainstay of treatment. As the response and tolerance may vary among patients, the choice of a minimum of two non-sedating antihistamines should be offered to them. |
| Khan 2008                    | Second-generation of histamine type I receptor blockers should be the first choice |
| Muller 2004                  | 2nd generation H1-receptor antagonists should be used as first-line treatment |
| Kaplan 2002                  | There is general agreement that non-sedating antihistamines are the first choice for treatment |

**Special Populations**

**Children:** A significant proportion of children (50–80%) with chronic urticaria have concomitant angioedema. [BSACI] Cold and pressure are the most frequent precipitating factors. 4% have anti-thyroid antibodies. A detailed clinical history along with examination is needed. Allergy tests can be employed to diagnose the type I hypersensitivity reaction (IgE mediated allergies). An elimination and re-challenge diets may be required in some cases.

**Chronic urticaria and angioedema management in children**

The initial treatment depends on the severity of disease manifestation. The therapy is highly individualized, it is tailored and tapered according to the response of the patient. High dose steroid therapy (up to 40 mg/day) may be used for three days in case of severe exacerbations. Once the disease is under control the dose can be tapered. Latest Evidence on the mode of antihistamine action suggests that it is better to taper and stop than to stop such therapy suddenly. Histamine receptor blockers are the backbone of management. 2nd generation drugs are preferred and may be given in combination with sedating first-generation in case of unresponsiveness. However, these are not recommended for use in children < 6 months of age. Cetirizine and loratadine are licensed for use in 2 years and older and desloratadine to 1 year and older. 1st generation antihistamines that cause considerable sedation, can be used in childhood. These drugs include diphenhydramine, hydroxyzine, promethazine, and chlorphenamine. Among all these, only chlorphenamine and hydroxyzine are recommended for use in children under 2 years.

**Corticosteroids** are recommended in the resistance of the maximal dose of H1 antihistamines with the addition of H2 blockers and leukotrienes. More effective in delayed-pressure urticarias, but side-effects should be monitored.

**Pregnancy:** Most of the antihistamines are not contraindicated in pregnancy and can be used safely. Loratadine & hydroxyzine have shown teratogenicity at high doses in animals. Chlorpheniramine, loratadine & cetirizine have been recommended as Class B drugs in pregnancy. However, the lowest possible doses should be used.

**Breastfeeding:** Antihistamines are only recommended for breast-feeding if potential benefits outweigh the risk as the majority of the drugs are excreted in the
human breast milk. Chlorpheniramine can cause drowsiness and poor feeding.

**Conclusion**

Urticaria significantly affects the quality of life and therefore its early and effective treatment is imperative. Sound cooperation between the patient and the treating physician is required for successful therapy. The objective is to make the patient asymptomatic and hence elevate his quality of life. An individualized approach is required and the treatment of chronic urticaria needs to be tailored differently for each patient because of the highly variable disease presentation.

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