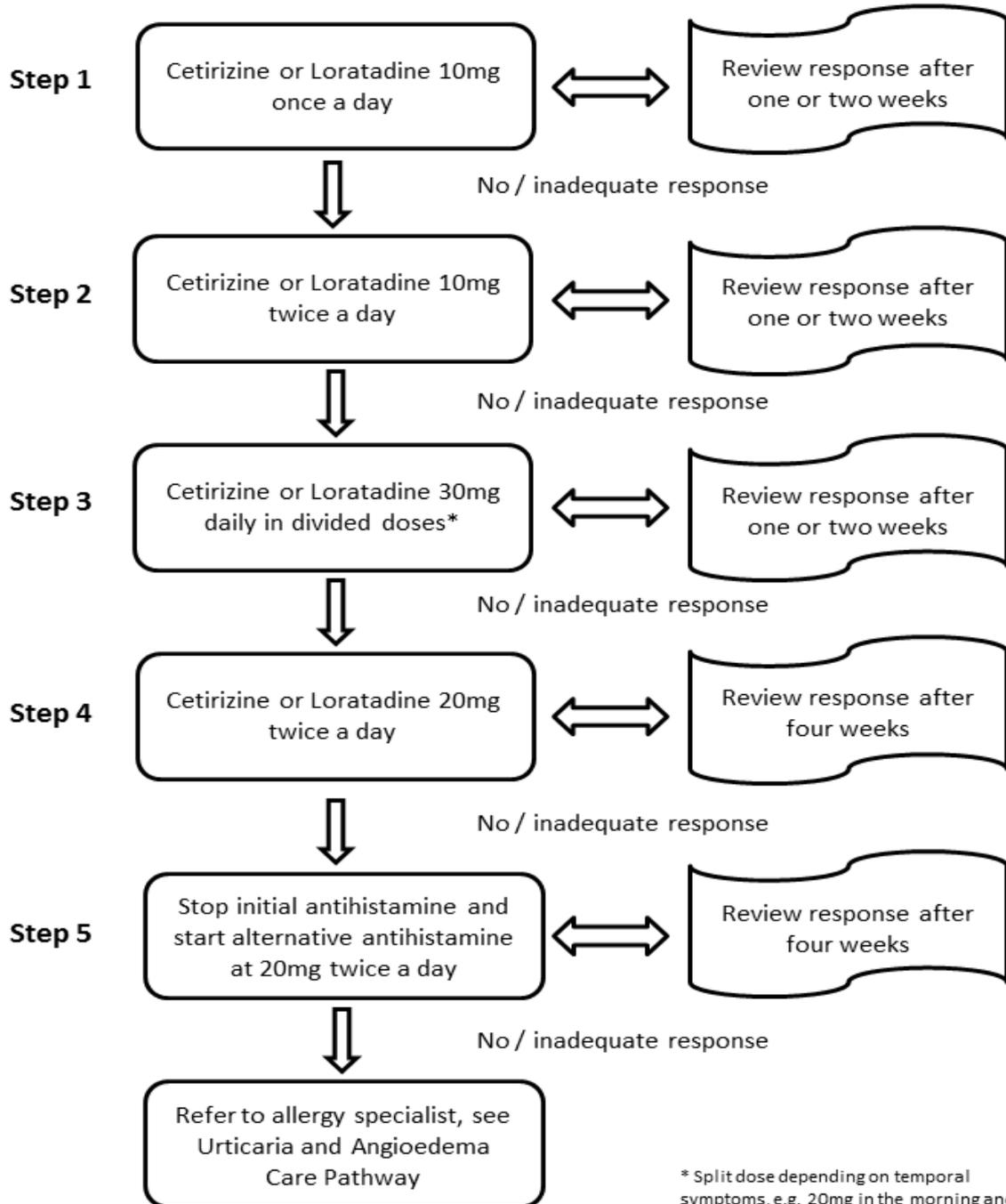


High Dose Antihistamines for Chronic Idiopathic Urticaria



Notes:

- Cetirizine and loratadine are the drugs of choice due to cost, availability on formulary and lack of evidence demonstrating superiority of newer non-formulary antihistamines. Patients and prescribers should be aware that the doses of antihistamines in this pathway are higher than the licensed doses.
- Sedating antihistamines (chlorpheniramine, hydroxyzine) are discouraged, even at night, due to their shorter duration of action. The focus of therapy is on the antihistamine activity rather than the sedating activity.
- This guideline does not apply to pregnant or breast feeding women. These patients should be referred to a specialist.
- Higher doses of non-sedating antihistamines are not recommended in children because their safety has not been assessed in this age group.
- Hepatic and renal function should be checked prior to initiation. Counsel patient to monitor for sedation. Nil other routine monitoring required.
- Loratadine should be avoided in patients with risk factors for torsades de pointes or who are taking CYP 450 enzyme inhibitors – see section on Safety.

Background

Urticaria is a superficial swelling of the skin (epidermis and mucous membranes) that results in red, raised, itchy wheals. The symptoms of urticaria are a result of pro-inflammatory mediators in the skin, among which histamine appears to be pivotal. Acute urticaria may be caused by allergy to foods, drugs, irritants, insect bites and stings, physical stimuli and viral infection. It is usually a self-limiting, one-off episode. By contrast, the cause of the most common form of urticarial, chronic idiopathic urticarial (CIU) cannot be identified and it may remit and relapse. In CIU, symptoms last for more than 6 weeks (recurrence of acute symptoms or persistent symptoms) and may last for months or years. CIU is rarely life-threatening; it can however have a negative impact on quality of life though anxiety and embarrassment.

Second generation antihistamines such as cetirizine and loratadine, are selective H1 receptor antagonists, which reduce histamine, reduce the migration of inflammatory cells, and prevent the release of mediators associated with the late phase allergic response. These form an important part of the treatment plan for patients with CIU. These antihistamines have a long duration of action and are less likely to cause anticholinergic and sedative effects associated with first generation antihistamines.

The approach to use higher than licensed doses of second generation antihistamines for chronic urticaria (CU) in patients unresponsive to standard doses is supported by the British Society of Allergy and Clinical Immunology¹, British Association of Dermatology², and European Academy of Allergy and Clinical Immunology (EAACI)³ guidelines for the treatment of this condition. The EAACI guidelines propose that up to a fourfold increase of a second generation antihistamine could be recommended for the unresponsive patient.

Efficacy

Staevska *et al*, evaluated 80 patients with CU in a randomized, double blind study; patients were assigned to levocetirizine (n=40) or desloratadine (n=40) with increasing dosage of up to 4-fold. 13 patients became symptom-free at the conventional dose and 28 at higher doses. This shows that increased doses of these second generation antihistamines has benefit in certain patients and that patients who do not respond to one antihistamine may indeed respond to an alternative. In regards to safety there were no discontinuations due to adverse events, and no serious adverse events were noted⁴.

Kameyoshi *et al*, showed that cetirizine at twice the recommended dose has benefit in CU⁵.

Safety

Antihistamines rarely cause cardiovascular adverse events; tachycardia and palpitations. Clinical data suggests that doses of loratadine of up to 40mg are not associated with cardiac adverse events when compared to placebo⁶. Loratadine undergoes extensive first pass metabolism via CYP3A4 and CYP2D6, and therefore its metabolism may be affected by drugs that inhibit these enzymes (e.g. amiodarone, macrolides, HIV protease inhibitors), resulting in high plasma levels which may lead to toxicity⁹. Loratadine should be avoided in patients taking medication which inhibit CYP450 enzymes or who are at risk of torsades de pointes. Cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of the QT interval⁹. Cetirizine is renally excreted and therefore requires dose reductions in renal impairment.

[1] Powell RJ, Du Toit GL, Siddique N et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clinical and Experimental Allergy*. 2007. 37: 631-650

[2] Grattan CEH, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *British Journal of Dermatology*. 2007. 157: 1116-1123

[3] Zuberbier T, Bindslev-Jensen C, Cananica W et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy*. 2006. 61: 321-331

[4] Staevska M, Popov TA, Kralimarkova T et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. 2010. *J Allergy Clin Immunol*. 125 (3): pp 676-682

[5] Kameyoshi Y, Tanaka T, Mihara S et al. Increasing the dose of cetirizine may lead to better control of chronic idiopathic urticaria: an open study of 21 patients. 2007. *Br J Dermatol*. 157: pp803-804

[6] Philpot EE. Safety of second generation antihistamines. 2000. *Allergy and Asthma Proceedings* 21(1): pp15-20

[7] Loratadine SPC <http://www.medicines.org.uk/emc/medicine/22603/SPC/Boots+One-a-Day+Allergy+Relief+10+mg+Tablets> (accessed on 12/08/2015)

[8] Cetirizine SPC <http://www.medicines.org.uk/emc/medicine/29498> (accessed on 12/08/2015)