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How to manage chronic urticaria ‘beyond’ guidelines: a practical algorithm.

Running title: Chronic urticaria: a practical algorithm

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ABSTRACT

Chronic urticaria (CU) is a disease characterised by pruritic weals, angio-oedema or both occurring for at least 6 weeks. It encompasses spontaneous and inducible urticarias. The national and international guidelines outline the principles of treatment. Omalizumab, an anti-immunoglobulin E monoclonal antibody has transformed the management of many severe and treatment-refractory patients. However, current UK guidance on its use does not address the needs of those with less severe disease, inducible urticarias, idiopathic histaminergic angio-oedema without weals as a presentation of CU and omalizumab non-responders. Our algorithm and a summary of the evidence to support its principles offers guidance and a more systematic targeted approach to using a range of 'off-label' agents for specific phenotypes of CU. It will be of use when guideline-recommended mast cell mediator antagonists fail to control symptoms and/or using omalizumab is ineffective, not practical or unfunded.

Chronic urticaria (CU) is a disease characterised by itchy weals, angio-oedema or both occurring for 6 weeks or more. Around half of patients present with weals alone; 40% with weals and angio-oedema and 10% with angio-oedema only [1]. CU can be classified as spontaneous (CSU) and inducible (CIndU) although overlaps often occur (Fig 1).

I. CU impacts on quality of life and generates high direct and indirect costs:

CSU is not just a skin disease. It impacts negatively on multiple aspects of patients' lives. Disfiguring and unpredictable episodes of swellings interfere with social interactions and cause absenteeism.

Nocturnal pruritus leads to insomnia and fatigue during the day resulting in reduced productivity (presenteeism) [3]. The chronic and unpredictable nature of symptoms often forces patients to seek medical attention (GP and/or A&E), which is stressful for them and puts limited healthcare resources under greater pressure. CU may impact on quality of life (QoL) of patients recruited in

secondary care as much as ischaemic heart disease in patients awaiting coronary artery bypass grafting, more than respiratory allergy in patients with perennial rhinitis and intermittent asthma and at least as much or even more than psoriasis, acne or atopic dermatitis [4-7]. A large cross-sectional survey of 176,000 adults reflecting health in 5 European Union countries (France, Germany, Italy, United Kingdom and Spain) confirmed these observations. It revealed a 0.5% point prevalence of CU (1:200 adults; 40% using a prescription treatment). In these patients CU caused high levels of health-related impairment (work and private life QoL) and self-reported depression, anxiety and sleep disorders compared to the individuals without CU [3].

The delay in diagnosis and cost of treatment are substantial. ASSURE-CSU, a multinational real-world study, examined 673 patients who were symptomatic despite treatment. They reported average disease duration of 5 years and a delay of 2 years between onset of symptoms and diagnosis. Angio-oedema was present in 59% of patients (mean 19 episodes of angioedema per year) [8]. A decade ago, the mean annual direct and indirect costs of CSU in the US were estimated to be \$244 million: medication accounted for 62.5% and income loss due to travel to hospital appointments/absences from work for 15.7% [9]. The recent ASSURE study confirmed that CSU is associated with high annual direct healthcare costs ranging from a mean of £733 per patient in the UK to €2,443 in France [10].

II. Current UK guideline-driven approach:

1. standard dose H1AH
2. higher dose of H1AH up to 4x recommended dose or add in second H1AH
3. consider a 2 nd line agent, antileukotriene or tranexamic acid for angio-oedema without weals
4. consider omalizumab or ciclosporin

nsH1AH - non-sedating H1 antihistamine

Table 1. British Society of Allergy and Clinical Immunology (BSACI) treatment algorithm for chronic urticaria [1]

The guidelines published by the British Society for Allergy and Clinical Immunology (BSACI) outline the principles of treatment (Tbl 1) [1]. The recommendations of the European Academy of Allergy and Clinical Immunology, British Association of Dermatologists and the US Joint Task Force on Practice Parameters follow a similar approach with subtle differences only [2, 11, 12]. In the UK, H1 antihistamines (H1AH) were the only licensed treatment until omalizumab (OMA; Xolair®, Novartis Pharmaceuticals Ltd, Frimley) was approved by the European Medicines Agency in April 2014 as add-on therapy for the treatment of chronic spontaneous urticaria (CSU) in adults and children over 12 years of age with inadequate response to H1AH. The National Institute for Health and Care Excellence (NICE) subsequently approved National Health Service (NHS) funding of omalizumab for severe CSU unresponsive to H1AH and montelukast in June 2015 [13]. The availability of this drug has transformed the management of most severe and treatment-refractory CSU patients but current UK guidance on use in CSU does not address the needs of those with less severe disease (UAS7 <28), inducible urticarias or provide a recommendation for treatment of idiopathic angio-oedema without weals as a presentation of CSU. For them NHS-funded OMA is

currently not available in the UK, despite emerging evidence of efficacy for most of these urticaria subtypes [14, 15]. Moreover, there is also an emerging unmet need for CSU OMA non-responders (10-15% of those treated). Historically, a wide variety of drugs have been used off-licence for CU including CSU and CIndU. The evidence is based mainly on clinical experience or small/uncontrolled studies so most of them are not highlighted in current treatment algorithms but may, nevertheless, provide valuable options [1, 2, 11, 12]

III. BEYOND H1 ANTIHISTAMINES

The purpose of this practical review is to highlight treatments that aim to target specific subtypes (phenotypes) of CU based on clinical experience but limited evidence. They may be of value to patient groups for whom approved treatments are not available or unfunded. Our suggested algorithm incorporates currently licensed and unlicensed (targeted) treatment options (Fig. 2).

The initial pathway aimed at symptom control with anti-mast cell mediator drugs is applicable to all patterns of CU and is appropriate for primary and secondary care. A recent meta-analysis confirmed that 38.6% of patients with CSU responded to standard doses of H1AH and up to 63% to updosing. It is noteworthy that updosing improved mainly pruritus but not weal numbers [16]. More complex treatments should generally be initiated in secondary care and maintained with shared care in the community. We have used this approach successfully for many years in our tertiary Difficult Urticaria Clinic. Despite the recent evidence-based guidelines there is a real gap between the guidelines-recommended approach and real life clinical practice. Our algorithm and a summary of the evidence to support its principles is intended to offer guidance and a more systematic targeted approach to using agents off-label for specific phenotypes of CU.

1. INITIAL TREATMENT OF CU IN PRIMARY AND SECONDARY CARE

Anti-mast cell mediator drugs

The national and international guidelines recommend initial treatment with standard doses of non sedating H1AH. The dose can be increased up to fourfold if necessary with the addition of an H2AH and a leukotriene receptor antagonist (montelukast) [1, 2, 11, 12].

Oral corticosteroids (OCS) for CSU

It is common practice to prescribe 'rescue' prednisolone treatment for acute exacerbations of CSU at 0.5mg/kg for 3 days in addition to standard anti-mast cell mediator drugs. If used sparingly, this safe option empowers patients to self-manage the unpredictable flare ups of CSU, especially angio-oedema. The literature on OCS is surprisingly scarce despite their availability, low cost and widespread use worldwide.

The use of short courses of OCS for severe CSU is supported by an Italian study in which 40 of 86 (47%) CSU patients refractory to standard doses of H1AH responded fully to 10 days of prednisone (25 mg and 12.5 mg daily, 3 days each; 6.25 mg for 4 days) then became controlled on H1AH only (full responders). 35/86 (30%) patients responded initially but relapsed after stopping steroids (temporary responders). Twenty three of the 35 temporary responders benefited from a second 10-day course of prednisolone (identical protocol); 8 of them became full responders [17]. The evidence for topical steroids however is weak and mainly confined to a study of two weeks of clobetasol propionate cream applied daily to the body for 6 h under occlusion and a DBPCRT of clobetasone foam for delayed pressure urticaria [18, 19].

2. BEYOND INITIAL TREATMENTS FOR CSU (SPECIALIST CARE OR SHARED CARE)

A. Omalizumab

Omalizumab (OMA), a recombinant humanized monoclonal IgG antibody to free IgE is the most extensively studied drug used in the treatment of CU. **Its mode of action in CU is not entirely understood. It might reduce mast cell releasability, by reducing high affinity receptors for IgE (FcεRI) and IgE, as well as IgE against autoantigens (20). It seems to decrease *in vitro* coagulation abnormalities that mirror disease activity (20, 21).** In the UK, OMA is licensed only for CSU as add-on treatment to H1AH [13]. Three double-blind placebo-controlled randomized (DBPCRT) phase III trials: ASTERIA I, II and GLACIAL confirm the safety and efficacy of a 300 mg dose administered every 4 weeks [22-24]. OMA reduced weekly itch scores by 62-71%, induced good urticaria control (UAS7 < 6) in 55-62% and complete remission (UAS7 = 0) in 34-44% of patients [22-24]. A recent meta-analysis of 7 DBPCRT, which included 1,312 patients treated with OMA, lends further support to using this drug and confirms its safety and efficacy [25]. Interestingly, the published real life data and our experience in a cohort of 130 patients treated with OMA in our Clinic to date confirm an even higher rate of 77- 90% of good control/complete resolution [26-28].

A review of the aforementioned DBPCRTs suggests that treatment with 300 mg of omalizumab is efficacious in reducing patient-reported angio-oedema [29]. Further evidence from a recent DPBCRT X-ACT confirms its role as a viable therapeutic option for patients with CSU with difficult to control angio-oedema [15]

In the UK, OMA is not licensed for CIndU but multiple case reports and case series support its efficacy in different phenotypes [14]. Many DBPCRT are ongoing or will be reporting soon: CUTEX: cold contact urticaria, UFO: symptomatic dermographism; XOLUS: solar urticaria; CUN-OMAL-UCOL: cholinergic urticaria [14].

According to NICE guidance OMA should be given in dermatology, allergy or immunology clinics. However preliminary UK experience of self-administration is a potential future option in the correct healthcare context [30].

B. Immunosuppressives

There is evidence that about a third of CSU patients have functional IgG autoantibodies that release histamine from healthy donor basophils and mast cells (chronic autoimmune urticaria, CAU) [31].

The specificity of these autoantibodies for the high affinity IgE receptor (FcεRI) and IgE has been established. Autoreactivity can be demonstrated in about 50% of CSU patients using autologous serum skin test (a red weal response to intradermal injection of autologous serum into nonlesional skin), which provides further indirect evidence of functional factors in patients with active disease [31]. An increased prevalence of thyroid autoimmunity (up to 30% in patients with a positive BHRA) and other autoimmune diseases in CSU provides further indirect evidence of an autoimmune aetiology in these patients [32-34]. Ongoing studies are looking at the phenotypes of CSU that may predict an autoimmune cause for clinicians without access to BHRA or basophil activation test (BAT). There is emerging evidence for 2 endotypes of CAU which are IgE and IgG/IgM mediated, respectively [35]. This evidence should inform the choice of treatment: immunosuppression to inhibit the normal immune response or immunomodulation to 'regulate' the immune system.

- **Ciclosporin**

Ciclosporin (CS) has the best evidence base of the immunosuppressive drugs used for CSU and is recommended as 3rd or 4th line treatment in current guidelines [1, 2, 11, 12]. Open and DBPCRT confirm its efficacy in 67% of patients and long term improvement in 25- 40% patients (remission 9 months after stopping treatment) [36-40]. We start at 4mg/kg/day for 4 weeks, reducing by 1 mg/kg every 6 weeks to zero although longer treatment duration is an option. Adverse reactions are rare in

our practice but they can be dose limiting and treatment protocols need defining. Patients with a positive BHRA have a good clinical response to CS by contrast with those with a negative BHRA who generally respond to 4 mg/kg/d but relapse as the dose is reduced [41]. Histamine releasing activity of positive sera falls within a month of starting CS [36]. There was an overall complete response in 81% of CSU patients treated with CS for 4-8 weeks, which was in keeping with the reduction of serum histamine releasing activity and a direct inhibitory effect on mast cell histamine release. *In vitro* and clinical evidence raises the possibility that CS may have a disease-modifying effect on CAU but comparative studies with symptom controlling therapies alone or OMA have not been done to date.

- **Mycophenolate and methotrexate**

These agents may be considered if CS is contraindicated, for instance, due to hypertension, renal impairment or intolerance. In the US, Shahar et al treated 9 patients with CSU nonresponsive to H1AH, H2AH and prednisone with 12 weeks of mycophenolate. The UAS significantly improved at the end of the treatment period

($p < 0.001$). There was a statistically significant decrease in the mean weekly oral prednisone dose after 4 weeks and all patients successfully discontinued prednisone at the end of the study. There was no rebound six months after concluding the study [42]. Moreover a 90% response and safety of mycophenolate was reported in 19 CSU patients in a retrospective chart review [43]. Methotrexate led to improvement in 75% of 16 CU patients (including 4 patients with urticarial vasculitis) in a retrospective chart review. There was a pronounced steroid-sparing effect but only 2 patients managed to discontinue prednisolone [44]. In an Israeli study oral/intramuscular methotrexate was safe and efficacious in 7 of 8 steroid-dependent CSU patients who successfully discontinued prednisolone [45].

C. Immunomodulators

- **Hydroxychloroquine**

In 21 patients with CSU, hydroxychloroquine improved the global symptom severity score and the LAMY-7, a quality of life index designed by Lamy, at 12 weeks

($p < 0.01$ and $p < 0.05$, respectively). There was no significant change in medication requirement or urticaria score but differences between treatment groups approached statistical significance ($0.05 < p < 0.10$). Hydroxychloroquine was well tolerated [46].

D. Antifibrinolytics

Angio-oedema without weals may be broadly categorized into histaminergic or bradykininergic.

Histaminergic angio-oedema falls within the spectrum of chronic spontaneous urticaria (see introduction). Most cases are idiopathic [1]. Treatment with mast cell mediator antagonists should be offered but may be unsuccessful. Around 10% of patients presenting with recurrent angio-oedema without weals can be surmised to be bradykininergic by demonstrating C1 inhibitor deficiency or lack of response to conventional anti-mast cell mediator therapies.

- **Tranexamic acid**

It inhibits activation of the kallikrein-kininogen-kinin pathway. There is no evidence of effectiveness for CU weals alone but clinical experience indicates that it can serve as a targeted treatment for idiopathic non-histaminergic angio-edema [47, 48]. It is therefore included in the BSACI guidelines as a 3rd line option for CU if angio-oedema is present [1].

E. Other options for CSU

- **Psychotherapy and tricyclic antidepressants**

CSU often coexists with anxiety and depression [49, 50]. It can be exacerbated by psychological comorbidities but can also induce them [51]. Moreover, QoL impairment in CSU patients with psychiatric comorbidity e.g. depression and/or anxiety appears greater than in those without a psychiatric diagnosis [52].

There is emerging evidence of benefits of psychological therapy in CSU. Relaxation therapies seemed more effective in hypnotizable than non-hypnotizable subjects [53]. A recent pilot study of a 'whole person treatment' approach utilizing psychotherapy listening skills led to improvement in UAS and a 12 question Urticaria Severity Score [54].

- **Doxepin**

Doxepin has the most potent anti- H1, H2, muscarinic, serotonergic and adrenergic properties. It was effective in small placebo-controlled and active comparator (diphenhydramine) studies [55, 56].

3. INDUCIBLE URTICARIAS

H1AH are the primary management for most patients but may be unhelpful in a minority. Addition of other anti-mast cell mediator drugs tends to be ineffective.

A. Narrow-band ultraviolet B phototherapy (NB-UVB)

In a small study eight H1AH-unresponsive patients with symptomatic dermographism showed a mean 52% reduction in itch and 71% wealing after 18 exposures over 6 weeks. NB-UVB improved both itch and wealing for up to 12 weeks after finishing the course [57]. Two open series of H1AH-unresponsive CSU reported clearance in 40% and 45% after a median of 22 and 31 exposures [58, 59]. A randomized trial of NB-UVB with H1AH versus H1AH alone led to a reduction of mean UAS

after 20 exposures: 17.4 vs 20.73 [60]. Clinical experience shows that the benefit can be maintained by reducing the frequency of treatment from three times a week to once every fortnight in most patients with an appropriate dose reduction. **We usually recommend a 6-week course of NB treatment to minimise the risk of adverse skin reactions.** In a small DBPCRT there was no difference in outcomes of CSU between psoralen ultraviolet A (PUVA) and UVA over 2/12 [61]. A study by Khefagy et al confirmed that NB-UVB and PUVA showed comparable efficacy in the treatment of CU with minimal side effects [62]. Finally, a recent randomized prospective observer blinded study confirmed the efficacy of PUVA and NB-UVB in steroid-dependent CSU. NB-UVB fared statistically better than PUVA at different time points. Adverse events were rare and did not warrant treatment discontinuation [63].

B. Sulphone anti-inflammatories

Delayed pressure urticaria is a chronic, often disabling, condition with the average duration of 9 years. Isolated DPU is rare but it co-exists with CSU in up to 40% of patients (mixed phenotype) [64-66]. It typically presents as erythematous, painful rather than pruritic weals, usually hours after the initial stimulus (pressure due to standing up, kneeling, tight clothes) and can persist up to 48 hrs. At times, there are systemic symptoms: fatigue, myalgia, arthralgia etc. OCS are often required to control the symptoms when anti-mast cell mediator treatments are ineffective. In the UK, OMA is not licensed for this indication [13, 14]. Dapsone and sulphasalazine can be useful targeted therapies with steroid-sparing effects.

- **Dapsone (diaminodiphenyl sulphone)**

It is a sulphone antibiotic with anti-inflammatory properties that inhibits myeloperoxidase in neutrophils and the formation of leukotrienes and prostaglandins. Side effects include dose-dependent haemolysis and methaemoglobinaemia; glucose-6-phosphate dehydrogenase (G6PD) deficiency must be ruled out before treatment. In a recent retrospective study 75% of patients with DPU reported good or very good response measured using an 11-point numeric scale (NRS-11) to 25 mg dapsone

increased to 100 mg on a weekly basis with 1g vitamin C supplementation [65]. Dapsone has been also found to be efficacious for H1AH-refractory CSU /urticarial vasculitis in many case reports, an open study and a non-blinded study [67, 68]. A recent DBPCRT confirmed the efficacy of dapsone 100 mg daily with a predictable but asymptomatic decrease in hemoglobin level by 1.8 mg/dL [69].

- **Sulphasalazine (sulphapyridine + 5-aminosalicylate)**

Clinical experience indicates that it is especially useful as a targeted treatment for patients with predominant DPU. This anti-inflammatory agent was also beneficial in a retrospective series for CU at 0.5-4.0 g/day [70]. It might exacerbate associated urticaria in Aspirin-sensitive patients [64].

C. Anabolic steroids

Cholinergic urticaria is usually intensely pruritic and often affects QoL severely by reducing exercise tolerance and preventing work in hot or stressful conditions. Its pathogenesis is not clear but sweat hypersensitivity, α 1-antichymotrypsin deficiency and increased parasympathetic tone with high acetylcholine levels might be relevant [71, 72]. It is often difficult to treat and standard guideline-driven approaches might fail. There is very limited evidence for beta-blockers (propranolol) and anticholinergic agents (scopolamine or oxybutynin) [73, 74]. In the UK, OMA is not licensed although there are encouraging data from case series [13, 14].

- **Danazol**

This anabolic steroid, a synthetic derivative of testosterone, increases hepatic production of protease inhibitors, especially C1 inhibitor, and is mainly used in HAE. A small DBPCRT of cholinergic urticaria patients showed reduced wealing and increased blood protease inhibitors, including α 1-antichymotrypsin [71]. It is usually well tolerated but androgenic effects may be dose-limiting in women. Patients need to continue H1AH throughout treatment and after stopping. An older study reported improvement in 78% (7/8) CSU patients with DPU [75].

IV. Real world data and safety aspects of using alternative agents:

Many of the alternative agents are not included in the recent CU guidelines because the evidence for using them is low. Nevertheless, they are commonly and successfully used by physicians managing difficult urticaria. A recent Canadian survey confirmed that although H1AH, LRTA and OCS played the main role in the management of CSU, other agents commonly used included CS (38% of surveyed practitioners), OMA (28%), hydroxychloroquine (19%), dapsone (14%), mycophenolate (13%) and sulphasalazine (9.5%). Moreover, in H1AH-refractory CU the next step, in addition to OMA or/and OCS, often involved CS (19%), hydroxychloroquine and dapsone [76]. It is noteworthy that in this study 60% of dermatologists were not familiar with the European CU guidelines and did not follow any other guideline. A recent Italian survey of 160 allergists and 160 dermatologists confirmed that 56% were familiar with the guidelines but only 27% used them regularly. Compared with dermatologists, allergy specialists were more aware of the guidelines (73% vs. 43%) and twice more likely to adhere to them (36% vs. 18%). However, 36% of all responders would still use oral corticosteroids as 3rd line treatment (after H1AH and high dose H1AH) and 31% as 4th line (after H1AH, high dose H1AH and LRTA). 55% opted for CS as next line treatment. The study was performed before the approval of OMA in 2014 [77]. Amin et al reviewed retrospectively 221 patients: 33% achieved completed control when CS, OMA or other nonstandard agents were added to H1AH and LRTA regimen [78].

The relative safety of the alternative agents with mild and/or reversible side effects is supported by all studies cited in this review. A recent US retrospective case series reported that very few of 127 patients on alternative CU agents discontinued the drugs due to side effects. The rate of discontinuation was: 1.7% for tacrolimus, 5.5% dapsone, 6.7% hydroxychloroquine, 7.4% mycophenolate and 17% sulphasalazine. Of note, no one stopped OMA or CS due to side effects. Moreover, all adverse reactions resolved after dose reduction or on discontinuation of treatment [79]. Finally, the safety of the alternative agents has been observed in our day-to-day practice in a large tertiary level Urticaria Clinic.

The choice of the *right drug* for the *right patient* must consider phenotypical and endotypical differences between different forms of CU. Patients are encouraged to persevere with ineffective CU treatment far too often because of a common misconception that there is ‘nothing else out there’. However, compliance with medication is variable. A recent study employed the Morisky 8 Item Medication Adherence Score in 103 patients with CSU and found 72% to have poor adherence to medication. It could be explained by real or perceived lack of efficacy and/or concerns about side effects as well as forgetfulness [80]. Keneko et al reviewed 751 patients with urticaria also confirming low adherence to mainly oral treatment. Reported reasons included fluctuating severity and non-life threatening nature of CU symptoms and the ease of stopping medication with no tapering required [81]. Therefore, it is imperative to review CU treatment on a regular basis and explore patients’ concerns and expectations. **Patient reported outcome measures (PROM) embody patient-centred healthcare and should be routinely used in all CU patients. They help assess CU activity (Urticaria Activity Score, Angio-oedema Activity Score), control (Urticaria Control Test) and its impact on health-related quality of life (Dermatology Life Quality Index, Chronic Urticaria Quality of Life Questionnaire and Angio-oedema Quality of Life Questionnaire). These validated and reliable tools help physicians adjust treatment depending on its efficacy and tolerability. Finally, they are obligatory to justify the use of more expensive treatment options [82].** When treatment with guideline-recommended mast cell mediator antagonists does not provide symptom control and using OMA is unfunded, ineffective or not practical, a range of options is available.

References:

1. Powell RJ, Leech SC, Till S et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2015;45:547-65.
2. Zuberbier T, Aberer W, Asero R et al. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69:868-87.
3. Balp MM, Vietri J, Tian H, Isherwood G. The Impact of Chronic Urticaria from the Patient's Perspective: A Survey in Five European Countries. *Patient* 2015;8:551-8
4. Grob JJ, Revuz J, Ortonne JP, Auquier P, Lorette G. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol* 2005;152:289–295.
5. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. *Br J Dermatol* 1999;140:667–671.
6. Baiardini I, Giardini A, Pasquali M et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;58:621–623.
7. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;136:197–201.
8. Weller K, Maurer M, Grattan C et al. ASSURE-CSU: a real-world study of burden of disease in patients with symptomatic chronic spontaneous urticaria. *Clin Transl Allergy* 2015;5:29.
9. Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 non-immunosuppressed patients. *Arch Dermatol* 2008;144:35–39.
10. Balp MM, Abuzakouk M, Berard F et al. Comparison of direct healthcare costs associated with chronic spontaneous/idiopathic urticaria in 7 countries – results from the ASSURE-CSU study. Abstract presented at the 19th Annual Congress of the International Society for Pharmacoeconomics and Outcomes Research, Vienna 2016

11. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Br J Dermatol. 2007;157:1116-23.
12. Bernstein JA, Lang DM, Khan DA et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7.
13. National Institute for Health and Care Excellence, United Kingdom Omalizumab for previously treated chronic spontaneous urticaria. Technology appraisal guidance 339. Published 08 June 2015. www.nice.org.uk/guidance/TA339 [Accessed: 19/01/2017]
14. Chicharro P, Rodríguez P, de Argila D. Omalizumab in the treatment of chronic inducible urticaria. Actas Dermosifiliogr 2016 Oct 5. doi: 10.1016/j.ad.2016.07.018. [Epub ahead of print]
15. Staubach P, Metz M, Chapman-Rothe N et al. Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: results from X-ACT, a randomized controlled trial. Allergy 2016;71:1135-44.
16. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol 2016; 175:1153-65.
17. Asero R, Tedeschi A. Usefulness of a short course of oral prednisone in antihistamine-resistant chronic urticaria: a retrospective analysis. J Investig Allergol Clin Immunol 2010;20:386-90.
18. Ellingsen AR, Thestrup-Pedersen K. Treatment of chronic idiopathic urticaria with topical steroids. An open trial. Acta Derm Venereol. 1996;76:43-4.
19. Vena G, Cassano N, D'Argento V, Milani M. Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized double-blind, placebo-controlled trial. Br J Dermatol 2006; 154: 353–6.
- 20. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy 2017;72:519-533.**
- 21. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. Int Arch Allergy Immunol 2017;172:40-44.**

22. Kaplan A, Ledford D, Ashby M et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;132:101–109.
23. Maurer M, Rosen K, Hsieh HJ et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924–935.
24. Saini SS, Bindslev-Jensen C, Maurer M et al. Efficacy and safety of omalizumab in patients with chronic idiopathic urticaria/chronic spontaneous urticaria who remain symptomatic on H1-antihistamines: a randomized placebo-controlled study. *J Invest Dermatol* 2015;135:67–75.
25. Zhao ZT, Ji CM, Yu WJ et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016;137:1742-1750.
26. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci* 2014;73:57–62.
27. Rottem M, Segal R, Kivity S et al. Omalizumab therapy for chronic spontaneous urticaria: the Israeli experience. *Isr Med Assoc J* 2014;16:487–490.
28. Sussman G, Hebert J, Barron C et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol* 2014;112:170–174.
29. Zazzali JL, Kaplan A, Maurer M et al. Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies. *Ann Allergy Asthma Immunol* 2016;117:370-377
30. Denman S, Ford K, Toolan J et al. Home self-administration of omalizumab for chronic spontaneous urticaria. *Br J Dermatol* 2016; 175:1405-1407.
31. Konstantinou GN, Asero R, Ferrer M et al. EAACI taskforce position paper: evidence for autoimmune urticaria and proposal for defining diagnostic criteria. *Allergy* 2013;68:27-36.
32. O'Donnell BF, Francis DM, Swana GT et al. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 2005;153:331-335.
33. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001;107:1056-62.

34. Confino-Cohen R, Chodick G, Shalev V et al. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129:1307-13
35. Kolkhir P, Church MK, Weller K et al. Autoimmune chronic spontaneous urticaria: what we know and what we don't know. *J Allergy Clin Immunol* 2016 Oct 21. doi: 10.1016/j.jaci.2016.08.050 [Epub ahead of print]
36. Grattan CE, O'Donnell BF, Francis DM et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000;143:365-72.
37. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006;55:705-9.
38. Di Gioacchino M, Di Stefano F, Cavallucci E et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc* 2003;24:285-90.
39. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997;52:312-6.
40. Baskan EB, Tunali S, Turker T, Saricaoglu H. Comparison of short- and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatolog Treat* 2004;15:164-8.
41. Iqbal K, Bhargava K, Skov PS, Falkencrone S, Grattan CEH. A positive serum basophil histamine release assay is a marker for cyclosporin-responsiveness in patients with chronic spontaneous urticaria. *Clin Transl Allergy* 2012 2:19
42. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006;45:1224-7.
43. Zimmerman AB, Berger EM, Elmariah SB, Soter NA. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. *J Am Acad Dermatol* 2012 ;66:767-70.
44. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. *Br J Dermatol* 2010;162:191-4

45. Sagi L, Solomon M, Baum S et al. Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. *Acta Derm Venereol*. 2011;91:303-6.
46. Reeves GE, Boyle MJ, Bonfield J, Dobson P, Loewenthal M. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J* 2004;34:182-6.
47. Munch EP, Weeke B. Non-hereditary angioedema treated with tranexamic acid. A 6-month placebo controlled trial with follow-up 4 years later. *Allergy* 1985;40:92-7.
48. Laurberg G. Tranexamic acid (Cyklokapron) in chronic urticaria: a double-blind study. *Acta Derm Venereol* 1977;57:369-70.
49. Staubach P, Dechene M, Metz M et al. M. High prevalence of mental disorders and emotional distress in patients with chronic spontaneous urticaria. *Acta Derm Venereol* 2011;91:557-61.
50. Berrino AM, Voltolini S, Fiaschi D et al. Chronic urticaria: importance of a medical-psychological approach. *Eur Ann Allergy Clin Immunol* 2006;38:149-52.
51. Staubach P, Eckhardt-Henn A, Dechene M et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006 Feb;154:294-8.
52. Engin B, Uguz F, Yilmaz E, Ozdemir M, Mevlitoglu I. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008;22:36–40.
53. Schertzer, CL, Lookingbill, DP. Effects of relaxation therapy and hypnotizability in chronic urticaria. *Arch Dermatol* 1987;123:913–916.
54. Lindsay K, Goulding J, Solomon M, Broom B. Treating chronic spontaneous urticaria using a brief 'whole person' treatment approach: a proof-of-concept study. *Clin Transl Allergy* 2015; 5:40
55. Greene SL, Reed CE, Schroeter AL. Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985;12:669-75.
56. Goldsobel AB, Rohr AS, Siegel SC et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986;78:867-73.

57. Borzova E, Rutherford A, Konstantinou GN, Leslie KS, Grattan CE. Narrowband ultraviolet B phototherapy is beneficial in antihistamine-resistant symptomatic dermographism: a pilot study. *J Am Acad Dermatol* 2008;59:752-7.
58. Berroeta L, Clark C, Ibbotson SH, Ferguson J, Dawe RS. Narrow-band [TL-01] ultraviolet B phototherapy for chronic urticaria. *Clin Exp Dermatol* 2004;29:97-8.
59. Aydogan K, Karadogan SK, Tunalı S, Saricaoglu H. Narrowband ultraviolet B [311 nm, TL01] phototherapy in chronic ordinary urticaria. *Int J Dermatol* 2012;51:98-103.
60. Engin B, Ozdemir M, Balevi A, Mevlitoglu I. Treatment of chronic urticaria with narrowband ultraviolet B phototherapy: a randomized controlled trial. *Acta Derm Venereol* 2008;88:247-51.
61. Olafsson JH, Larko O, Roupe G, Granerus G, Bengtsson U. Treatment of chronic urticaria with PUVA or UVA plus placebo: a double-blind study. *Arch Dermatol Res* 1986;278:228-31.
62. Khafagy NH, Salem SA, Ghaly EG. Comparative study of systemic psoralen and ultraviolet A and narrowband ultraviolet B in treatment of chronic urticaria. *Photodermatol Photoimmunol Photomed* 2013;29:12-7.
63. Bishnoi A, Parsad D, Vinay K, Kumaran MS. Phototherapy using NB-UVB and PUVA is beneficial in steroid dependent antihistamine refractory chronic urticaria: A randomized prospective observer blinded comparative study. *Br J Dermatol* 2017; 176: 62-70.
64. Swerlick RA, Puar N. Delayed pressure urticaria: response to treatment with sulfasalazine in a case series of seventeen patients. *Dermatol Ther* 2015; 28:318-22.
65. Grundmann SA, Kiefer S, Luger TA, Brehler R. Delayed pressure urticaria - dapsone heading for first-line therapy? *J Dtsch Dermatol Ges* 2011;9:908-12
66. Barlow RJ, Warburton F, Watson K, Black AK, Greaves MW. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. *J Am Acad Dermatol*. 1993;29:954-8.
67. Cassano N, D'Argento V, Filotico R, Vena GA. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. *Acta Derm Venereol* 2005;85:254-5.
68. Engin B, Ozdemir M. Prospective randomized non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008;22:481-6.

69. Morgan M, Cooke A, Rogers L, Adams-Huet B, Khan DA. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract* 2014;2:601-6
70. McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. *Arch Dermatol* 2006;142:1337-42.
71. Wong E, Eftekhari N, Greaves MW, Ward AM. Beneficial effects of danazol on symptoms and laboratory changes in cholinergic urticaria. *Br J Dermatol* 1987;116:553-6.
72. Altrichter S, Wosny K, Maurer M. Successful treatment of cholinergic urticaria with methantheliniumbromide. *J Dermatol* 2015;42:422-424
73. Amman P, Surber E, Bertel O. Beta blockers therapy in cholinergic urticaria. *Am J Med* 1999;107:191.
74. Tsunemi Y, Ihn H, Saeki H, Tamaki K. Cholinergic urticaria successfully treated with scopolamine butylbromide. *Int J Dermatol* 2003;42:850
75. Ceuppens JL, Stevens E, Rijon M. Danazol treatment in chronic urticaria and delayed pressure urticaria: effect on protease inhibitors. *Allergie und Immunologie*. 1985;17:46-51.
76. Cheung LY, Lynde CW. Chronic Spontaneous Urticaria: Canadian Dermatologists' Perspective. *J Cutan Med Surg* 2016;20:308-12
77. Rimoldi M, Rossi O, Rota N. State of the art of chronic spontaneous urticaria in Italy: a multicentre survey to evaluate physicians' and patients' perspectives. *BMJ Open* 2016;6:e012378
78. Amin P, Levin L, Holmes SJ, Picard J, Bernstein JA. Investigation of patient-specific characteristics associated with treatment outcomes for chronic urticaria. *J Allergy Clin Immunol Pract* 2015;3:400-7.
79. Seth S, Khan DA. The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients. *J Allergy Clin Immunol Pract*. 2017;5:165-170.e2.
80. Heng JK, Koh LJ, Toh MP, Aw DC. A study of treatment adherence and quality of life among adults with chronic urticaria in Singapore. *Asia Pac Allergy* 2015;5:197-202
81. Kaneko S, Masuda K, Hiragun T et al. Transient improvement of urticaria induces poor adherence as assessed by Morisky Medication Adherence Scale-8. *J Dermatol* 2015;42:1078-82

82. Weller K, Zuberbier T, Maurer M. Clinically relevant outcome measures for assessing disease activity, disease control and quality of life impairment in patients with chronic spontaneous urticaria and recurrent angioedema. *Curr Opin Allergy Clin Immunol*. 2015;15:220-226.

Conflict of interest:

KR and CEHG declare no conflict of interest

Figure legends:

Figure 1 Classification of chronic urticaria [1, 2].

Figure 2 Chronic urticaria management pathway.

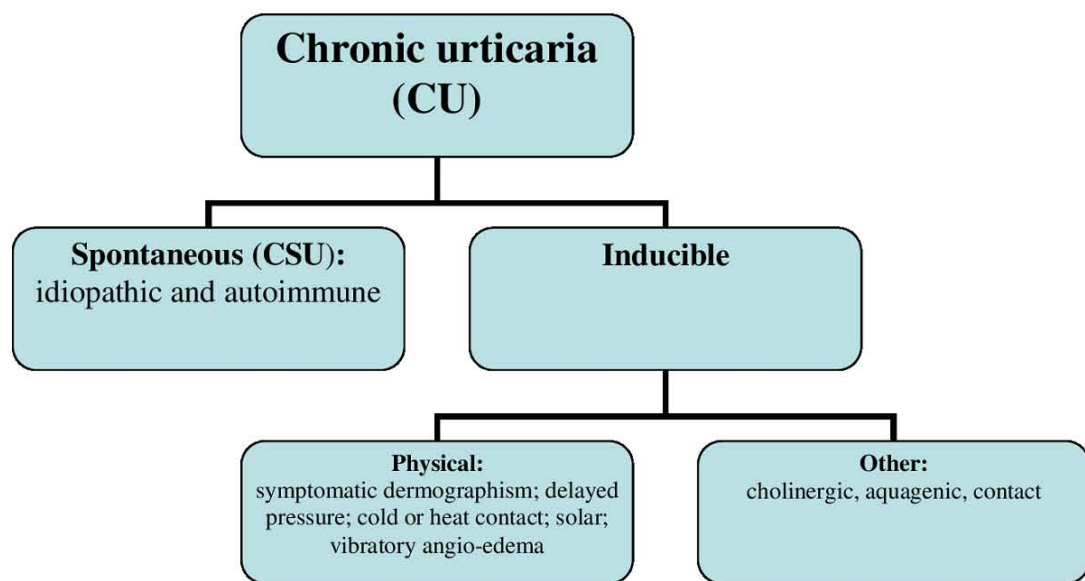


Figure 1 Classification of chronic urticaria [1, 2].

CHRONIC URTICARIA MANAGEMENT PATHWAY

