Chronic Spontaneous Urticaria (CSU)

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Abbreviations used in this document

AE	adverse event
ASST	autologous serum skin test
BD	bis die (twice daily)
CAPS	cryopyrin-associated periodic syndromes
CIU	chronic idiopathic urticaria
CSU	chronic spontaneous urticaria
CU-Q2oL	chronic urticaria quality-of-life questionnaire
DLQI	dermatology life quality index
DPU	delayed pressure urticaria
DQOLS	dermatology quality of life scales
DSQL	dermatology specific quality of life
FACS	familial cold autoinflammatory syndrome
Ga2len	Global Allergy and Asthma European Network
GIT	gastrointestinal
H1RA	histamine 1 receptor antagonist
H2RA	histamine 2 receptor antagonist
IgE	Immunoglobulin E
IL	interleukin
ISS	Itch severity score
IVIg	intravenous immunoglobulin
LTRA	leukotriene receptor antagonists
MIID	minimum important difference
MTX	methotrexate
NOMID	neonatal onset multisystem inflammatory disease
nsAH	non-sedating antihistamines
NSAIDs	non-steroidal anti-inflammatory drugs
QOL	quality of life
SLE	systemic lupus erythematous
TNF	tumour necrosis factor
UAS	urticaria activity score
UAS7	urticaria activity score over 7 days
USS	urticarial severity score
UV	urticarial vasculitis
VAS	visual analogue score
WAO	World Allergy Organisation

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Introduction

Urticaria is a disabling skin condition characterised by recurrent, raised, pruritic lesions, lasting between one hour and several days that settle without disruption of the epidermal barrier. Angioedema often coexists with urticaria but can also occur independently. It is timely to review current evidence for various treatments and their potential role in management of this troublesome condition given recent advances in research and availability of new medications.

Definitions

Urticaria is caused by mast cell degranulation in superficial layers of the dermis. Angioedema is swelling in deeper dermal layers, triggered by mast cells or bradykinin.

The diagnosis of urticaria and angioedema is made based on clinical symptoms. For consistency, we refer to the EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update (1) for the characteristics of urticaria, namely:

1. Central swelling (wheal) of variable size, almost invariably surrounded by erythema.
2. Associated itching or, sometimes, burning sensation
3. A fleeting nature with the skin returning to normal appearance, usually within 1-24 hours.

And angioedema:

1. A sudden, pronounced swelling of the deeper dermis and subcutis.
2. Sometimes pain rather than itching
3. Frequent involvement of mucous membranes
4. Resolution is slower than for wheals, can take up to 72 hours.

Acute urticaria defines recurrent lesions for a period of less than 6 weeks. There are multiple possible causes including allergies and infection, although it is often idiopathic. Discussion of acute urticaria is beyond the scope of this document.

Chronic spontaneous urticaria (CSU) refers to urticarial lesions arising spontaneously, occurring on most days of the week for six weeks or more. The term “spontaneous” is used to distinguish CSU from the inducible (physical) urticarias, where lesions are induced by physical stimuli such as scratching (dermographism), cold (cold urticaria), sunlight (solar urticaria), increased body heat (cholinergic urticaria), pressure (delayed pressure urticaria) or vibration. These forms of urticaria are not considered further, although it should be noted that physical forms of urticaria can coexist with CSU. Often the management for both will overlap and the coexistence of physical urticaria with CSU should not exclude the patient from usual CSU therapies. The term “chronic idiopathic urticaria” is no longer used because the current understanding is that many cases of CSU have an autoimmune basis, although this cannot be determined routinely in individual cases.

Other conditions may mimic CSU but are entirely distinct and represent different pathophysiological entities. Urticarial vasculitis differs from CSU in that lesions tend to last longer than 24 hours, are painful rather than pruritic and often bruise. The pathology shows leucocytoclastic vasculitis. This type of urticaria is more likely to be associated with systemic autoimmune conditions such as systemic lupus erythematosis (SLE) (2). Urticarial dermatitis is a condition characterised by pruritic urticarial plaques caused by superficial dermal inflammation which persist for weeks and settle with scale. It is usually idiopathic (3).

Epidemiology and natural history

CSU is a common condition that has a life time prevalence rate of around 1.8% of the general population, (4) with a point prevalence rate in adults of 0.6-0.8% (5,4) and affects females more often than males (4,5).

The prevalence of urticaria in children has been reported at between 2% and 7% (6) and that of chronic urticaria at between 0.1% and 3% (7-9). Most (80 – 90%) infants and young children presenting with urticaria have acute urticaria while fewer than 10% develop chronic urticaria (10-14). Recurrent acute urticaria is reported in between 10% and 30% of young children (10-12). Chronic urticaria is more common among adolescents and older children (10-14). CSU is by far the commonest subgroup of chronic urticaria in children (15) while physical urticaria (most commonly dermographism) accounts for the next most common subgroup (8).

CSU is accompanied by angioedema in approximately 40% of cases (16, 17). Recurrent angioedema may also occur in the absence of urticaria; in general this should be considered a separate disorder. Chronic recurrent angioedema may be histamine-mediated (prevented by regular prophylactic antihistamines) or bradykinin-mediated. Further discussion of angioedema in the absence of urticaria is beyond the scope of this document.

CSU is usually self-limited. In a population based study of 5003 adults, 147 (2.9%) had current or previous CSU. In 52.3% it had resolved within 12 weeks, however it lasted for more than 1 year in 20% of patients, and more than 5 years in 11.3% of patients (5). The presence of angioedema or anti-thyroid antibodies was associated with increased duration of disease in one study of 139 patients (18). Fifty-two percent of patients with anti-thyroid antibodies still had urticaria after 5 years, compared to 16% of those without.

In children CSU may also persist for months to years (7-9). Sahiner (15) reported resolution rates for CSU in children of 16.5%, 38.8% and 50% at 12, 36 and 60 months of follow up respectively. Female sex and age over 10 carried a worse prognosis. Chansakulporn (19) reported slightly more optimistic resolution rates of 18.5%, 54% and 67% at the same time points. There was no significant difference in resolution rates comparing those children with proven autoimmune CSU and those without.

Differential diagnosis and investigations

CSU is diagnosed by history and examination - there is no single investigation to confirm this diagnosis. There is no underlying or associated disease in the vast majority of cases. Guidelines and position papers from Europe, the United Kingdom and The United States agree that extensive routine investigations are not required or recommended for CSU (1,20,21), unless concomitant disorders are suggested by the history.

In a retrospective study of 356 adults (22), 1872 tests were ordered and 319 (17%) were abnormal. However most abnormal results were trivial and only one subject had an improvement in urticaria as a result of management changes implemented because of testing. Therefore in the majority of cases of CSU, routine tests appear unnecessary and unhelpful.

The following conditions should be distinguished from CSU by history and examination and require more extensive investigation:

- Urticarial vasculitis
- Urticaria pigmentosa
- Autoinflammatory disorders/Cryopyrin-associated periodic syndromes

Further discussion of these conditions is beyond the scope of this document.

Pathogenesis

CSU is caused principally by activation of cutaneous mast cells, and possibly also extravasated basophils (23). Intradermal injection of autologous serum was found to cause a wheal and flare reaction in some patients with CSU, indicating the presence of serum histamine-releasing factors (HRF) (24). Subsequent studies demonstrated the presence of circulating antibodies directed against the alpha chain of the high-affinity IgE receptor (FcεR1) in 30-50% of patients with CSU (25), with a smaller proportion of patients with an autoantibody directed against the low-affinity IgE receptor (26) and some to the IgE molecule itself.

Antibodies to FcεR1 can be detected by enzyme linked immunoassay (ELISA) however these are not specific to autoimmune urticaria and therefore ELISA is not used routinely for diagnosis (27). Not all patients with a positive intradermal serum test have autoantibodies, implying the presence of other serum HRF. Many patients with CSU have a negative intradermal serum test, therefore there are other pathways to cutaneous mast cell activation as yet unknown.

There is a strong association between CSU and other autoimmune disorders, in particular thyroid autoimmune disease. Thyroid (anti-thyroperoxidase) autoantibodies are the most common laboratory abnormality associated with CSU, being present in 20% of patients, compared to 1.8% of controls (28), although the incidence of clinical hyper- or hypothyroidism was only present in 5% of patients, and 1.4% of controls tested (28).

Assessment of activity and quality of life (QoL) in CSU

Quantitative measurement of CSU activity is useful to monitor disease and the effects of medications and other interventions. In the absence of biochemical markers or objective parameters, patient reported outcomes (PRO) are used. Parameters such as extent of rash, severity of symptoms, and quality of life (QOL) impact are recorded.

The UAS7 is a measure of the extent and severity of urticaria. This scores wheals and itch separately from 0-3 (therefore a total of 0-6 daily) for seven days, giving a maximum score of 42. The UAS7 has been shown to correlate weakly with other measures of quality of life if the data obtained for periods of 4 days or more are averaged (29). UAS7 scores of less than 6 are considered a marker of well controlled symptoms and UAS7 scores of 0 a complete response (30). In the Asteria 1 study (30) comparing omalizumab and placebo, itch alone was used as the primary endpoint, the maximum weekly score being 21, with the minimally important difference a decrease of greater or equal to 5.

Mathias et al (31) defined the minimally important difference in the UAS7 as 9.5-10.5.

Table 1: The UAS7 for assessing disease activity in CSU

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

Sum of score: 0-6 for each day is summarised over 1 week (maximum 42).

Another measurement of disease activity used in CSU efficacy studies is the urticaria severity score (USS). This questionnaire assesses the extent of urticaria present in the week prior, and assesses comfort, duration of urticaria, body parts affected, medication required, effect on sleep, work and school, as well as the presence of angioedema (32) giving a maximum score of 93. Again a weak correlation was shown between this score and the Dermatology Life Quality Index (DLQI) but was shown to be more sensitive to changes in the urticaria (32).

A number of measures of quality of life have been applied to assessment of CSU including generic questionnaires for quality of life (SF-36, SF-12, NHP, SAT-P, Euro-QOL, WHOQOL-BREF, WPA-AS, PRISM) as well as those that assess quality of life particularly for dermatological diseases (Dermatology Quality of Life Index (DQLI), Children's DQLI, Dermatology Quality of Life Scales (DQOLS), Dermatology specific Quality of Life (DSQL), Skindex-29, Skindex-16, VQ-Dermato). Two specific quality of life scores are available specifically for assessment of CSU - CU-Q2oL and the previously described, urticaria severity score (USS) (33-35).

Baiardini et al (34) in a GA2LEN position paper recommended the use of the urticaria specific quality of life assessment CU-Q2oL due to its availability in a number of languages, and due to an urticaria specific QOL assessment being more sensitive to changes in symptoms but no references were given. Further support for using both a severity score and a quality of life score come from Koti et al (36) who found that there was only a moderate correlation between the quality of life scores determined from CU-Q2OL translated into Greek, and a generic QOL score as well as the UAS.

We recommend the UAS7 and CU-Q2oL in clinical practice for the assessment of CSU and monitoring response to therapy.

Treatment

Drug treatments

CSU has a high rate of spontaneous remission (5); 80% of patients settle within 12 months without intervention. This leaves a significant minority of patients with a long term condition. Whilst induction of remission, or cure, would be the optimal therapeutic goal, there is no evidence that any of the currently available agents have any effect on the natural history of the disease. It is possible that, by analogy with other autoimmune or inflammatory diseases, some immunomodulatory medications might have "disease modifying" effects but this remains to be proven.

Therefore currently the goal of management is to control or suppress symptoms. This should be emphasised at the outset in managing patients with CSU. Treatment will need to be continued until remission occurs. Because of this, it is important that medications used are well tolerated and do not have significant long-term morbidity. Symptom control includes suppression of itch, suppression of visible rash, and prevention of angioedema episodes. Optimal adherence to medications will result in optimal symptom control. There is no evidence that adherence to medications (for example, regular compared with on-demand antihistamines) has any influence on the natural history of CSU but it has been shown to result in improved QOL (37).

Antihistamines

First generation (sedating) H1 antihistamines

First generation sedating antihistamines (diphenhydramine, hydroxyzine, promethazine, chlorpheniramine, dexchlorpheniramine) have been shown to be effective in patients with CSU (38-42). There is no evidence that their efficacy is superior to second generation antihistamines despite carrying a higher degree of sedation, anticholinergic effects and cognitive impairment (38-43). Randomised controlled trials comparing loratadine vs hydroxyzine (not available in Australia)

(39,40) and cetirizine vs hydroxyzine (41,42) did not demonstrate any significant difference in efficacy. A single randomised controlled trial evaluating the addition of nocturnal sedating H1 antihistamine (hydroxyzine), to standard dose levocetirizine monotherapy, also reported no additional benefit despite higher degree of daytime sedation (44). First generation antihistamines are not recommended as first line treatment for patients with CSU because of their significant side effects.

Second generation (non-sedating) H1 antihistamines

Second generation H1 antihistamines (cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine) all have proven efficacy in CSU in a vast number of randomised controlled trials including a total of nearly 4000 patients (37,39-42,45-62).

Cetirizine has been investigated in five randomised controlled trials, at daily doses of 10mg and 20mg, including a total of 595 participants (41,42,45-47). Loratadine has been evaluated in three randomised controlled trials including a total of 375 patients (39,40,48). Fexofenadine has been extensively investigated in a variety of doses (20-240mg BD) with seven double blind placebo controlled trials, including a total of 1917 patients (49-55). Five randomised controlled trials have evaluated desloratadine (5-20mg) including a total of 796 patients (37,56-60) and two randomised double blind placebo controlled trials, including a total of 272 patients have demonstrated levocetirizine efficacy in CSU (61,62).

All have demonstrated safety and efficacy with no significant adverse effects (37,39-42,45,62). Levels of somnolence and sedation are consistently comparable to placebo-treated patients (36,39-42,45-62) and significant improvements in health related QOL, work performance and daily activities have also been reported (37,54,55,59). Minor adverse events only have been noted in a minority of patients (headache, drowsiness, constipation, abdominal pain) (37,39-42,45-62).

Second generation H1 antihistamine comparisons

Comparative studies suggest that second generation antihistamines (histamine-1 receptor antagonists, H1RA) may not be equally effective, however there is insufficient evidence currently to make strong recommendations. Cetirizine has been compared with loratadine, fexofenadine and levocetirizine in two randomised controlled trials and one open label study (63-65). These studies suggest superiority of cetirizine over fexofenadine (64) but no greater efficacy when compared to loratadine or levocetirizine (63,65). There are two randomised controlled comparison studies of levocetirizine and desloratadine both suggesting greater symptom control in the levocetirizine group (66,67) although no significant difference in health related quality of life scores was reported (66). Levocetrizine has also been compared to loratadine in a small open label randomised study with minimal statistically significant improvement in symptom score in the levocetirizine group (68). Evidence for combinations of H1 antihistamines is currently lacking.

Second Generation H1 antihistamines: Updosing

A number of small randomised controlled trials have investigated treatment with H1-antihistamines at up to four fold higher than standard dose suggesting improved efficacy (cetirizine, levocetirizine, desloratadine) without compromising safety. However, other studies have failed to demonstrate additional benefit (cetirizine, fexofenadine) and long term data is lacking (49,50,67,69-72).

Cetirizine has been evaluated at dosage range 20-30 mg. Two small studies have demonstrated increased efficacy at double standard dose without increased side effects (69,70). Another study demonstrated improvement in only 1 /21 patients with higher 30mg doses (71). Two large double blind placebo controlled studies of fexofenadine updosing in CIU have failed to demonstrate greater efficacy above the standard 60mg BD dose (49,50). All dosages were more efficacious than placebo and the 60mg BD dose was more efficacious than the 20mg BD dose, however, there was no additional improved efficacy above the 60mg BD dosage (49). This was confirmed with a subsequent study (50) again demonstrating no additional benefit above a 60mg BD dose (trials

totalling 857 patients). Levocetirizine and desloratadine have both been investigated at doses up to 20mg daily with improved symptom control in approximately three quarters of patients with no reports of increased somnolence (67,72).

Doxepin

Tricyclic antidepressants are also potent blockers of histamine H1 and H2 receptors. Doxepin is among the tricyclic antidepressants with the most potent anthistamine activity, old studies indicating that is approximately 56 times more potent than hydroxyzine as a H1 blocker and six times more potent than cimetidine as an H2 blocker (73,74). A single, double-blind placebo controlled crossover trial of 16 adults with CSU of more than 3 months duration and refractory to antihistamines, demonstrated improved itch, urticaria and angioedema in doxepin treated subjects (25mg TDS) compared to placebo (75). Doxepin treated patients also required less concomitant antihistamine use and had significantly suppressed histamine and codeine induced cutaneous wheal responses. Drowsiness was reported in twelve of the sixteen patients, resolving within 3-4 days in half of these. One patient ceased therapy due to degree of lethargy. Dry mouth and constipation were also commonly observed (75).

In clinical practice, doxepin may provide additional relief for some patients with CSU and generally, smaller doses (10-50mg), are often used. All patients should be appropriately counseled regarding drowsiness and anticholinergic side effects and doxepin should only be considered in patients able to safely tolerate this. Doxepin should be avoided in high risk occupations such as commercial drivers (e.g. bus, taxi, aircraft) or any work involving operation of heavy machinery.

H2 Antagonists

Limited low level evidence based on relatively small trials suggests the addition of histamine-2 receptor antagonists (H2RA) to H1RA provides incremental efficacy in CSU (76-81). Early studies demonstrated improved itch, wheal size and intensity despite no significant greater overall improvement in symptoms of urticaria (76,77). Others have demonstrated no clinically significant benefit (78,79). More recently a small randomised controlled trial reported greatest treatment efficacy of combination H1 and H2 receptor antagonist therapy in CSU, when compared to: placebo, H1sedating/H1 non-sedating antihistamine, and LRTA/H1 antihistamine combination therapies (80). A subsequent follow up trial again demonstrates further improvement with montelukast/H1 antihistamine/H2 antihistamine combination therapy (cetirizine/famotidine/montelukast) in CSU cases refractory to LTRA/H1 antihistamine and H1/H2 antihistamine combination therapy (81). Follow up did not extend beyond four weeks and long term data is lacking.

Current evidence for the use of H2 receptor blockers in CSU is low. Nonetheless, evidence supports possible additional benefit in some patients, and in view of their excellent tolerability and low cost, a short trial may be considered.

Leukotriene receptor antagonists (LTRAs)

There is limited evidence regarding the use of LTRAs in CSU. One small placebo-controlled trial of zafirlukast monotherapy showed no benefit (82). Two randomised controlled trials with montelukast reported reduction in number of hives compared to placebo, but no significant benefit in other outcomes (83,84). A number of head to head studies comparing montelukast with antihistamines favour antihistamines (83,86-88). However some studies have demonstrated efficacy of LTRAs in particular patient groups, notably; delayed pressure-urticaria, cold urticaria, positive ASST and intolerance to aspirin or food additives (85,88,89).

Combination LTRA and antihistamine therapy appears more promising with three randomised trials demonstrating increased efficacy with combined therapy compared with H1RA alone (80,89,90). A subsequent randomised controlled trial also demonstrated additional improved efficacy of

LRTA/H1/H2 antihistamine combination therapy in refractory CSU patients failing therapy with either LRTA/H1 or H1/H2 combination therapy (81). All demonstrated improved VAS, itch and urticaria scores at follow up ranging from three to six weeks (80,81,89,90). Long term data is lacking. Two further contradictory trials have, however, failed to demonstrate additional efficacy of combined therapy, in all but a small minority of patients, particularly when patients with positive ASST and intolerance to aspirin or food additives were excluded (83,91). All trials have, however, consistently reported excellent tolerability and side effect profile (80-91).

Omalizumab

Omalizumab is a recombinant humanised monoclonal antibody engineered to bind to the CH3 domain of the ε chain of IgE, close to the binding site of IgE for both the high affinity (FcεRI) and low affinity (CD23) IgE receptors (92,93). This binding target means that Omalizumab may only bind circulating IgE and cannot bind cell bound IgE to cause receptor cross-linking. Omalizumab has been has been shown to reduce the levels of both free IgE and the high-affinity IgE receptor (FcεRI) (94,95), both of which are essential in mast-cell and basophil activation. Omalizumab has been approved as add-on therapy in the IgE-mediated disease of moderate-to-severe persistent allergic asthma (96).

Proof-of concept (97,98) and early phase II studies (99,100) suggested that omalizumab may be effective in controlling symptoms, with acceptable safety profile in patients with CSU, who remained symptomatic despite antihistamine treatment. Phase III trial data is now available in 735 Omalizumab-treated patients at doses of 75, 150 or 300mg (30,101) or standard 300mg dosing (102) for 12-24 weeks. Recruited patients had persistent symptoms despite standard dose antihistamines (30,101) or high dose antihistamines (up to fourfold nsAH dosing) plus the use of either H2 antihistamines or leukotriene receptor antagonists (102). Patients treated with 300mg of Omalizumab in all three trials had consistent, superior and significant suppression of the primary outcome Itch Severity Score (ISS) with onset of protection commencing 1-2 weeks following commencement and decaying over 12 weeks from the final dose. Benefit was also consistently noted with reduction in UAS7 and improvement in quality of life. Minor adverse events were common (headache, upper respiratory tract infection and arthralgia) and matched between placebo and omalizumab treated patients and no anaphylaxis or treatment related adverse events were reported. No long-term treatment data is available yet.

Real life studies examining open label responses to omalizumab at 150mg on a monthly basis have tended to support trial data (103,104). These studies have suggested complete remission rates of 70-79% and provide some suggestion of further flexibility in relation to both dose and dose interval.

Cyclosporin

In the first randomised controlled trial of cyclosporin for CSU (29 subjects) (105), two thirds experienced short term complete resolution of urticaria, but a long term remission (where urticaria did not recur after cyclosporin was ceased) was seen in only 5 subjects.

In a double blind randomised placebo controlled trial with 99 antihistamine-refractory patients (106), cyclosporin (in conjunction with cetirizine 10mg/day) was given at a dose of 5mg/kg/day for the first 2 weeks, 4mg/kg/day for the next 2 weeks, and then 3mg/kg/day. Patients were treated for 16 weeks, and reviewed 8 weeks after study conclusion. Although adverse events were common (60%), these led to discontinuation of treatment in only 6%. Cyclosporin was shown to be significantly more effective than placebo and cetirizine. There was a 52.9% improvement in the mean urticaria severity score at week 16, compared to 25% in the placebo group ($p<0.01$). At week 24, there was 41.7% improvement in the mean severity score for the cyclosporin group, versus 30.2% in the placebo group.

More prolonged courses of low dose cyclosporin treatment has been shown to be safe and effective in an observational study involving 120 patients with severe CSU (107). At a dose of 3mg/kg/day for three months of treatment, 20 patients discontinued because of side effects. Cyclosporin was not effective for 18 patients. Thirty patients had complete resolution, whilst 32 had a moderate response and needed ongoing antihistamine treatment. A further 20 patients found cyclosporin beneficial, but required much longer periods of treatment. In this group of cyclosporin dependent patients, dosage was reduced to 1–2mg/kg/day after 3 months of treatment. Eight patients were given cyclosporin at this dosage for 8–14 months of follow-up, and 12 patients were given cyclosporin for 60–120 months.

For the treatment of CSU, the dosage for cyclosporin ranges from 1 to 5 mg/kg per day. Patients taking cyclosporin need to have blood pressure and renal function closely monitored during treatment. From 1st of May, 2015, cyclosporin has become exempt from the Pharmaceutical Benefits Scheme Statutory Price Reductions, and is available on a private prescription.

Dapsone

Dapsone was evaluated in a randomised (non-blinded) controlled trial involving 65 subjects (108). Thirty-eight subjects received dapsone 50mg/day in conjunction with desloratadine 10mg/day for three months. There was a significant reduction in UAS and VAS in the dapsone group but it was not different to the placebo group. Within the dapsone group, nine patients had a complete response, 27 had a partial response, and two had no response. No complete response was found in the control group. Five of nine complete responders were still clear at six months. Five of 38 patients in the dapsone group experienced nausea, and this led to two of these patients discontinuing the study.

In another study using dapsone at a low dose of 25mg daily (109), nine of eleven patients had a complete response within three months of treatment. The remaining two patients were unresponsive to dapsone at four weeks. One of these two patients had complete response when the dose was increased to 50mg/day, and the other had a partial response.

Recently the first double-blinded controlled study of dapsone in CSU was published (110). Twenty-two subjects received dapsone 100mg daily or placebo for six weeks in a 14-week crossover trial. Dapsone resulted in significant improvements in UAS, itch score and VAS compared to placebo. After the full trial (all 22 subjects had received dapsone for six weeks), three subjects were completely symptom free, and 30% had >50% improvement. No subject had achieved >50% improvement during the placebo arm. Dapsone-treated subjects had a mean decline in Hb level of 1.8g/L.

It is recommended to check patients for glucose-6-phosphate dehydrogenase deficiency prior to commencing dapsone. It is recommended to commence at 50mg daily and increase to 100mg if tolerated, monitoring haemoglobin weekly for the first 6 weeks. A 4-week trial should be adequate to detect response.

Hydroxychloroquine

Hydroxychloroquine was shown to improve quality of life in a randomised controlled trial involving 21 patients with CSU (111). The dose was not stated. However, no significant effect was found in medication requirements or urticaria score.

Hydroxychloroquine continues to be widely used despite a limited evidence base. Six case series published only in abstract form (conference presentations) (112-117) report clinical experience in a cumulative total of 227 patients and claim remission of CSU in 164 (72%) cases. Doses were 400mg or 200mg daily. There are reports of cessation of hydroxychloroquine in 13 patients, of whom seven relapsed but were controlled by resumption of treatment.
A small (39 subjects) randomised placebo-controlled trial of hydroxychloroquine 400mg/day for three months was reported in abstract form in 2013 (118); the result was a significant reduction of the

urticaria symptom score and DLQI in the active group compared with placebo.

Overall, the published evidence for hydroxychloroquine is limited, however it does reflect a considerable interest in, and use of, hydroxychloroquine for CSU in clinical practice, and is consistent with local clinical experience.

Long term hydroxychloroquine requires regular monitoring for ocular toxicity and patients should be cautioned about photosensitivity and drug induced hyperpigmentation.

Corticosteroids

Systemic corticosteroid use for CSU, although widely accepted, has not been extensively studied. There are no randomised controlled trials and quality evidence regarding systemic corticosteroids is lacking. Current evidence is limited to a single retrospective study evaluating a short course of moderate dose prednisone (25mg tapered over 10 days) in 86 patients not responding to standard dose antihistamines (119). All patients responded well, evident as early as 24 hours after the first 25mg dose. Half the patients achieved a maintained response one month after the initial course and the remaining 50% relapsed when dose was tapered or ceased. In almost one third of these, a second ten day tapering course, induced and maintained remission at one month. There has been no followup beyond four weeks and long term data is lacking.

Systemic corticosteroids have a role in short term rescue therapy only, and long term, or frequent short term use, should be avoided. Patients suffering diabetes, hypertension or significant cardiovascular disease are at high risk of significant steroid related morbidity and systemic corticosteroid use would not be recommended.

Anticoagulants

Case reports of CSU and angioedema responding to treatment with warfarin first appeared in the literature in the 1980s (120,121) and a small case series was reported in 2000 in which 3/8 patients had an excellent response to anticoagulation with warfarin, proven by placebo crossover for those patients (122). This was shown to be a coumarin class effect (123). Heparin has been shown to inhibit the wheal and flare reaction of the ASST (124) and a case has been reported with complete response of urticaria to heparin but not to warfarin (125). Recently Asero has proposed that heparin and tranexamic acid therapy may be effective in CSU with elevated D-dimer, and report improvement in five of eight patients in an uncontrolled series (126).

Thyroxine

Thyroid autoantibodies are present in a higher proportion of CSU patients than in the population. An early case series (127) reports 90 of 624 (14%) patients had thyroid autoimmunity, usually associated with severe antihistamine-unresponsive disease. Forty- six of these patients were treated with thyroxine; eight patients had remission of urticaria within four weeks. In four cases, urticaria relapsed when thyroxine was stopped and remitted when it was restarted. A series of ten patients with antihistamine-unresponsive urticaria was reported (128) of whom seven were euthyroid but had thyroid autoantibodies. All received thyroxine treatment (50-250mcg). The autoantibody-positive patients reported resolution of urticaria within four weeks, whereas there was no effect in those without thyroid autoantibodies. A further group of 20 patients were reported in whom 16 improved after treatment with thyroxine (129). In a retrospective study of a total of 749 CIU patients, 44 were found to have thyroid autoantibodies and biochemical hypothyroidism (130). Correction of hypothyroidism with thyroxine resulted in improvement of urticaria, but a control group of 44 euthyroid patients without thyroid autoantibodies showed similar improvement. Finally, in perhaps the most directly relevant (albeit small) study of 15 euthyroid CSU patients with thyroid autoantibodies, eight received thyroxine plus desloratidine and seven desloratidine alone; aggregate scores were no different.

Taken together this literature suggests that a minority of individuals with CSU who are euthyroid yet have thyroid autoantibodies may respond to thyroxine therapy, and a trial of thyroxine could be considered at 100-200mcg per day for 4 weeks.

Sulfasalazine

Sulfasalazine was first reported to be effective in a small series of three cases of corticosteroid-dependent CSU in 1991 (131). Since then three case series comprising a total of 70 patients have been reported (132-134). Complete or near-complete remission was reported in 37 cases (53%) and partial response in 12, with 19 (27%) treatment failures. Two patients experienced serious adverse reactions (leukopenia, rhabdomyolysis) necessitating cessation. Eleven patients were reported to have remained in complete remission after cessation of sulfasalazine (134), albeit after more than a year of treatment. A small randomised controlled crossover trial was reported in abstract form but has not been published (135); of 15 patients, six had complete remission, three partial and six failed to respond. Doses were 2-3g daily; response was reported to take up to three months, but some patients responded in one to two weeks.

Tacrolimus

In a pilot study (136) of low dose tacrolimus, nineteen patients with severe CSU were treated with tacrolimus for 12 weeks. For the first four weeks, patients were given 0.1mg/kg/day to 0.14mg/kg/day, and this was reduced to 0.025mg/kg/day to 0.035mg/kg/day thereafter. Two patients dropped out after one week of treatment because of severe diarrhoea and headaches. Following three months of treatment, nine were able to discontinue antihistamines, and three had moderate improvement. Three months after discontinuation of tacrolimus, three had maintained a complete resolution of their urticaria, and three had mild deterioration controlled by antihistamines alone. One of the patients who had a full remission had previously not shown a response to three weeks of low dose cyclosporin (3mg/kg/day).

Methotrexate

There is limited evidence of the effectiveness and safety of methotrexate in CSU. One placebo-controlled trial of MTX 15mg weekly in addition to levocitirizine has been published (137) but of the 29 patients randomised, 12 failed to complete the study (eight in the placebo and four in the MTX arms, respectively) and no difference was noted between the MTX and placebo groups. A number of positive retrospective case series have been published (138-140) with Perez et al (139), reporting 12/16 patients who had previously failed to respond to other medications improving with MTX doses of 10-15mg weekly, and Sagi et al (140), reporting improvement in 7/8 patients with steroid dependent urticaria. However, not all patients in these cohorts had CSU, with some patients noted to have urticarial vasculitis.

Mycophenolate

Mycophenolate is an anti-proliferative immunosuppressant targeting B and T cells. Its use has been described in CSU. The only prospective study has been an open label study (141) in which nine patients (all with positive autologous serum skin tests) requiring steroids for disease control were given standard doses (1 gram twice a day) with a statistically significant decrease in symptom scores and all patients were able to cease their steroids. A retrospective case series (142) has shown improvement in symptom control describing 19 patients, 17 of whom had improvement in their symptoms with the use of mycophenolate and of those 10 had complete resolution of their symptoms. A separate case report also reported improvement in symptoms (143).

Azathioprine

There is very limited published evidence on the efficacy of azathioprine in CSU with Tal et al (144) reporting positive results for two patients prescribed 150mg of azathioprine, after failure of other treatments and Tedeschi (145) showing improvement after the use of 100mg of azathioprine in a patient with a positive autologous serum skin test but an unusual reaction to antihistamines.

IVIg

Use of intravenous immunoglobulin (IVIg) for CSU has been described in both prospective and retrospective studies. O'Donnell et al (146) reported improvement in nine of ten patients treated with a total of 2g/kg of IVIg and followed prospectively. A number of retrospective case series (147-149) have described improvements in some patients. CSU is not an indication for IVIg under the current Australian Criteria for the Clinical Use of Immunoglobulin.

TNF antagonists and other biologicals

Biological agents have been trialled in antihistamine-unresponsive patients who have failed to respond to numerous other immunosuppressive drugs. Three small case series have been published describing the use of anti-TNF agents in the management of CSU. A response to infliximab was reported in three of four patients treated (150), etanercept, infliximab or adalimumab were effective in six of six patients with severe recalcitrant urticaria (151), and etanercept or adalimumab achieved a response in 12 of 20 patients treated (152). There was no evidence of disease-modifying effect since in the majority of cases, urticaria flared following withdrawal of treatment. Rituximab was reported to be effective in two individual case reports (153,154) and one report of two cases (155), but ineffective in another reported case (156).

Treatment in paediatric populations

Second generation H1-antihistamines remain the mainstay of CSU treatment in children. These non-sedating drugs are safe and usually very effective at controlling urticaria in infants and children (157-159). Second generation H1 antihistamines are preferred to first generation H1-antihistamines, which have a higher incidence of adverse effects, including central nervous system depression and anti-muscarinic effects (158). Although up-dosing of second generation H1-antihistamines, to up to four times the recommended dose, is effective in adults and often trialled in children in clinical practice, there have been no studies undertaken in paediatric populations to support its use. Overall there is a paucity of evidence to support the use of most second line treatments in children with CSU. The strongest evidence exists for omalizumab, which has been shown to be safe and effective in treating CSU in patients from seven years of age (17,29,102,104). Adolescents aged ≥ 12 were included in three large randomised control phase III studies (ASTERIA I, ASTERIA II, GLACIAL), which clearly demonstrated the efficacy of omalizumab over placebo (29,102,104). In Canada, a prospective open label trial demonstrated a good response to omalizumab in children as young as 7 years (104). In addition a single case series found cyclosporin to be effective at controlling symptoms in seven children with CSU (160). However, there are no controlled trials to support the use of cyclosporin or other second line agents, such as leukotriene receptor antagonists, H2 receptor antagonists, hydroxychloroquine, azathioprine or methotrexate, in treating children with CSU (157,158). The rationale for the use of these medications in paediatric patients with CSU is based on their safety and tolerability treating other conditions in children and extrapolation of data from trials in adults with CSU.

Non-drug management

The role of diet manipulation in CSU in adults

Dietary factors have long been suspected of influencing the manifestation of urticaria (161-163). Trials in dietary modification designed to restrict exposure to pseudoallergens including food additives, preservatives, dyes, vasoactive and aromatic compounds have been reported with varied results (166-174), and pseudoallergen challenges have been shown to exacerbate urticarial reactions (164,165).

Magerl *et al* reported that pseudoallergen restriction resulted in a strong or moderate reduction in itch and rash in 34% of subjects (167). Responders were significantly less likely to have a positive autologous serum skin test. A second, open, 4-week trial of pseudoallergen avoidance has suggested a 41% response rate in CIU with the additional finding of a reduction in urinary leukotriene levels in responders but not non-responders (168). Zuberbier *et al* (166) reported cessation or greatly reduced symptoms in 73% of patients treated with 2-week stringent pseudo-allergen free diet. Subsequent blinded pseudoallergen challenges however found that only 19% of diet responders had urticarial reactions in response to pseudoallergen challenge.

Taken together these results tend to suggest the use of a pseudoallergen-restricted diet may provide additional benefit in chronic urticaria as an add-on to standard therapy in 34-73% of subjects. There is no clear guidance available however on the use of history or pseudoallergen challenges to identify likely responders (164,171). There is also significant uncertainty about the tolerability and nutritional sufficiency of stringent pseudoallergen-restricted diets.

A 12 week trial of high dose vitamin D supplementation (4000iu per day) in chronic urticaria patients treated with H1 and H2 antihistamines in addition to montelukast, suggested a reduction in Urticaria Symptom Score which was not seen in subjects treated with low dose vitamin D (600iu/day) (175). This suggests a possible useful benefit as add on therapy.

The role of diet in the management of CSU in children

CSU is not caused by IgE-mediated food allergy, but allergy to a commonly ingested food may cause frequent recurrent episodes of urticaria which might be mistaken for CSU. It is a common misconception that food allergy is a likely cause of CU.

Hsu et al (176) studied 494 Chinese adults and children (2-82yrs). At study entry, a third of patients were avoiding certain foods even though the majority found this avoidance to be ineffective. 341 patients were tested for IgE to foods, with 75 (22%) showing a positive result. Of these, 9 patients (2.8% of those tested) were positive on challenge with the relevant foods. In a further study on 94 Thai children aged 4 to 15 years with CU (177), skin prick test (SPT) was performed with a panel of 12 commonly allergenic foods. Thirty-three (35%) had positive SPT to foods (most commonly shrimp). Eight children had a positive oral food challenge to a SPT-positive food and of those, four had remission of CU when the food was eliminated. Thus overall 4% of those who presented with CU were found to have food allergy (shellfish in all cases) as the cause; in all cases, food allergy was evident on the history. SPT or blood testing for food-specific IgE is not recommended in those who present with CU unless food allergy is suggested by the history.

There are no studies of pseudoallergen-free diets for CSU in paediatric populations. Taking into account that these diets are restrictive, difficult to follow, and may have adverse outcomes (178), pseudoallergen-free diets are not recommended for routine use in children with CSU.

Management of CSU in pregnancy and lactation

Urticaria commencing during pregnancy must be distinguished from other pruritic conditions of pregnancy such as pruritic urticarial papules and plaques of pregnancy (PUPPS); pemphigoid gestationis; prurigo of pregnancy; cholestasis of pregnancy and autoimmune progesterone dermatitis of pregnancy.

Pregnant women with CSU should be treated with the least amount of medication possible to control symptoms, particularly pruritus. Most women can be treated with a second generation H1 antihistamine. Occasional short courses of corticosteroids may be required for severe flares. There is no data available on the advisability of escalating the currently recommended doses of antihistamines in pregnancy. The physician should undertake a careful discussion with the pregnant woman regarding the risks and benefits of available treatments.

The table below lists the medications used in CSU by their pregnancy and lactation categories.

Medication	Pregnancy category (MIMS)	Lactation category*
First generation H1:		
Promethazine	C	L2
Diphenhydramine	A	L2
Dexchlorpheniramine	A	L3
Second generation H1:		
Loratadine	B1	L1
Desloratadine	B1	L2
Cetirizine	B2	L2
Levocetirizine	B2	L3
H2:		
Ranitidine	B1	L2
Others		
Montelukast	B1	L3
Prednisone/Prednisolone	A	L2
Hydroxychloroquine	D	L2
Cyclosporin	C	L3
Dapsone	B2	L4
Tacrolimus	C	L3
Methotrexate	D	L3
Mycophenolate	D	L4
Azathioprine	D	L3
Omalizumab	B1	L3

*Lactation categories as per Medications and Mothers Milk 2012, by Thomas W Hall, 15th Edition
L1 – safest
L2 – safer
L3- probably safe
L4: probably hazardous
L5: hazardous

Drug availability in New Zealand

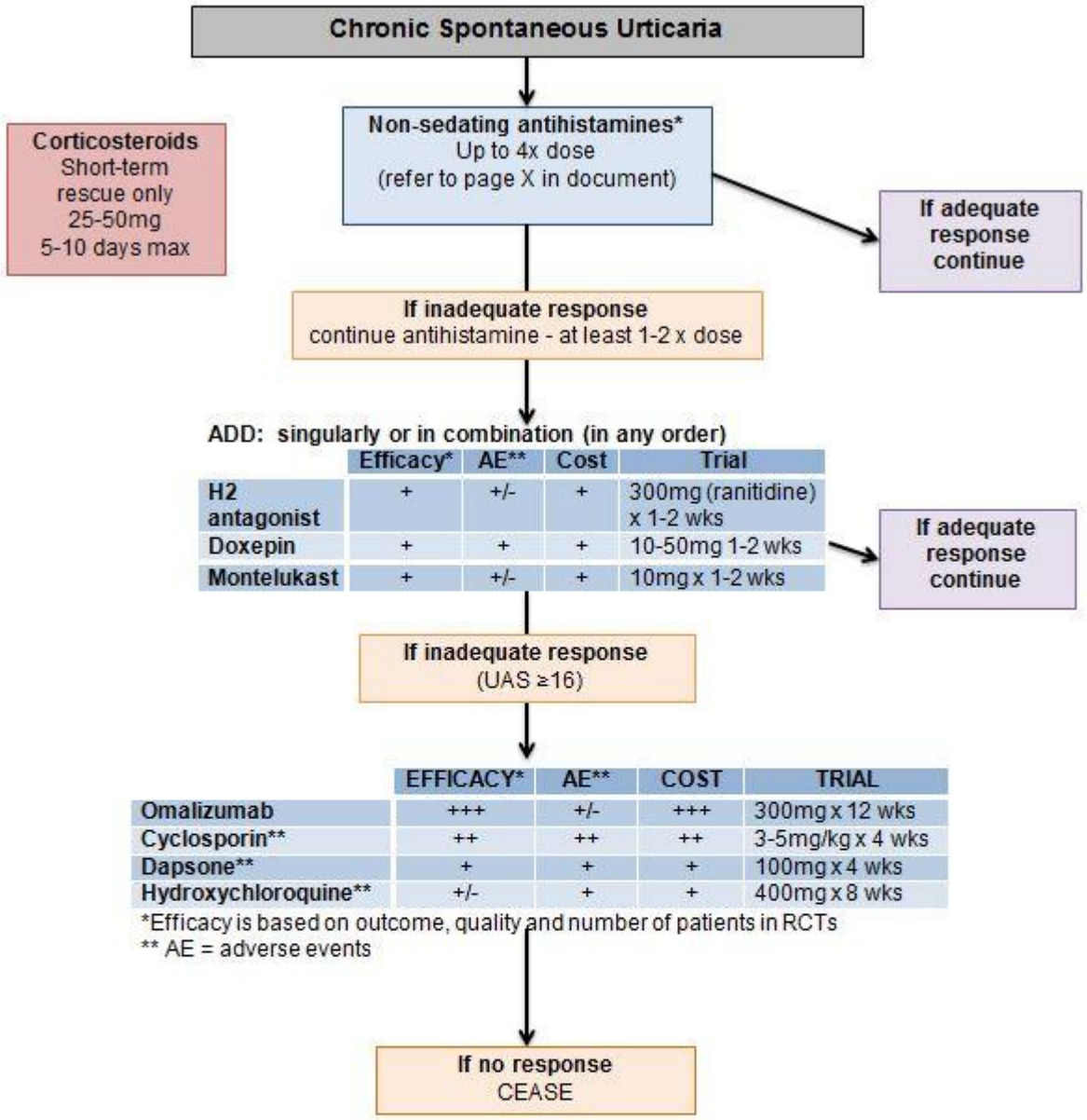
For antihistamines, loratadine, cetirizine and ranitidine are available fully subsidised on prescription. Fexofenidene and levocetirizine are available but at full cost to the patient, except for a part funding for fexofenidene 120mg.

Montelukast is available but not funded for CSU or angioedema.

Doxepin, hydroxychloroquine, cyclosporin, Dapsone, methotrexate, azathioprine are all available fully subsidised on prescription.

Omalizumab is only available via an NPPA application justifying exceptional circumstances.

Treatment algorithm - Adult



If responding:

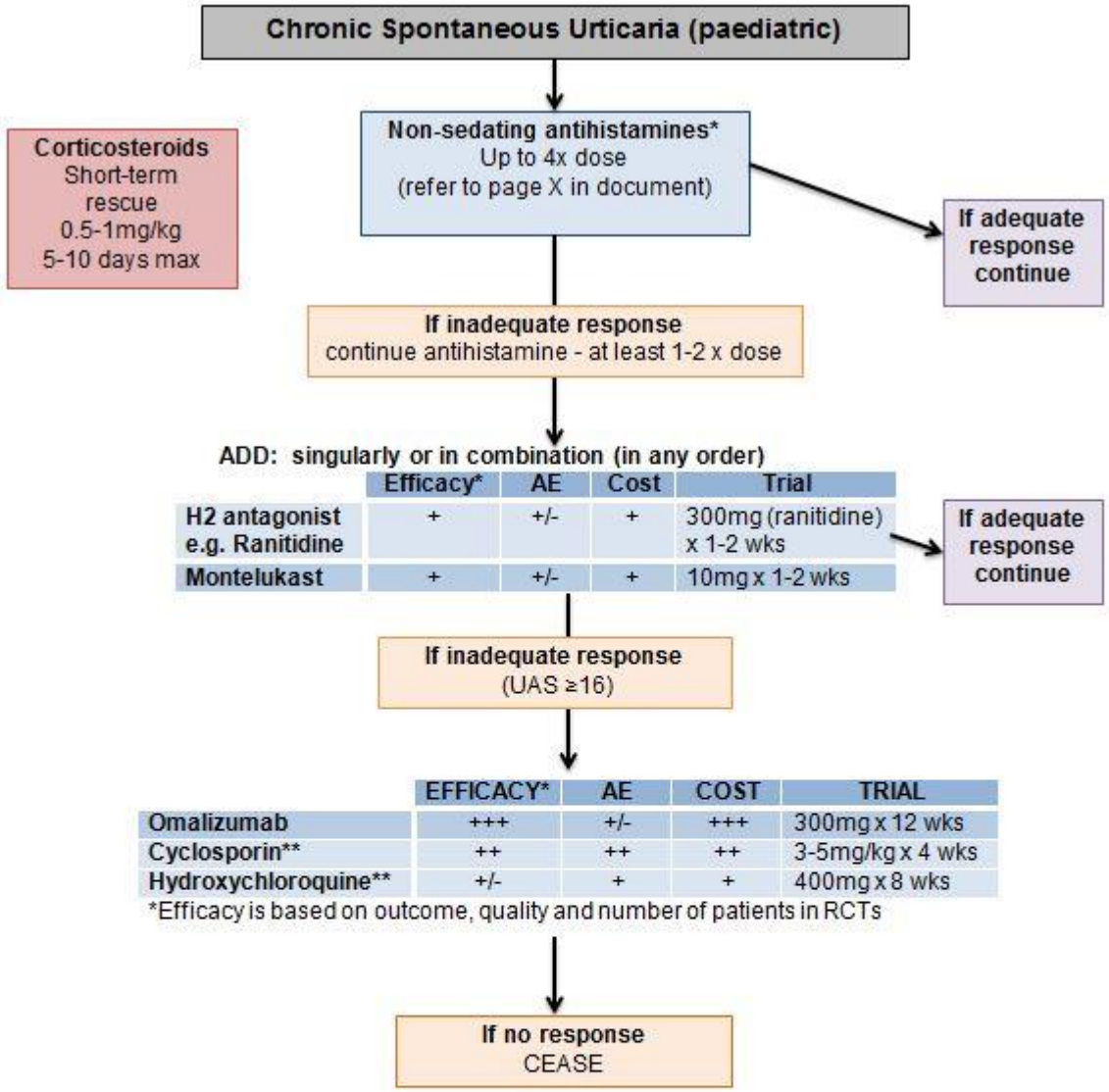
Omalizumab
Consider reducing the dose if there is a response after 3 months

- 3 month trial 300mg
- 3 month trial 150mg
- trial cessation; provision to recommence if recurrence (UAS >16)

Other drugs
Consider back titration of cyclosporine, dapsone, hydroxychloroquine

**Chronic urticaria is not a registered indication however, these drugs are commonly used for this indication in Australia

Treatment algorithm - Paediatric



If responding:

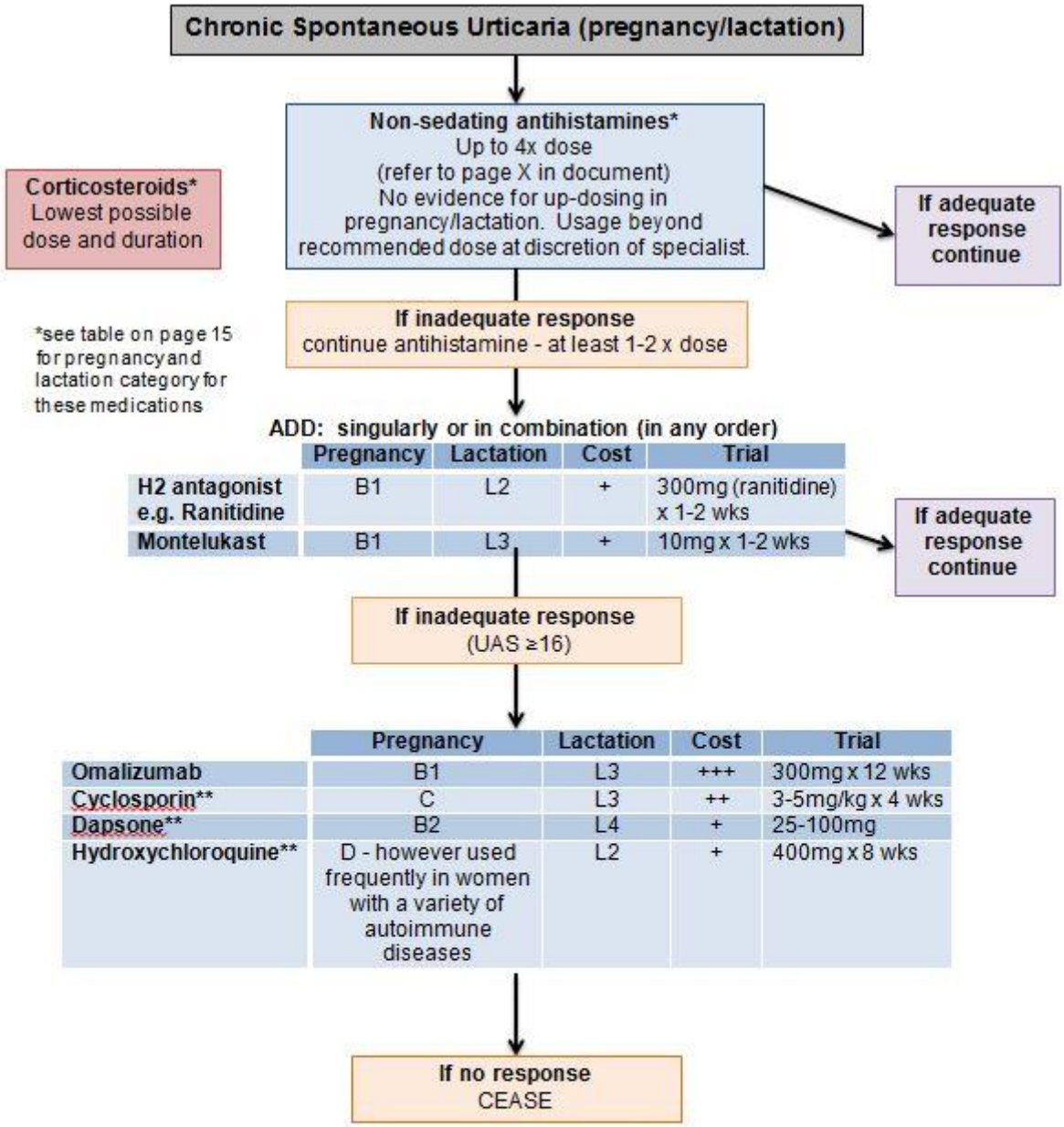
Omalizumab
Consider reducing the dose if there is a response after 3 months

- 3 month trial 300mg
- 3 month trial 150mg
- trial cessation; provision to recommence if recurrence (UAS >16)

Other drugs
Consider back titration of cyclosporine, hydroxychloroquine

**Chronic urticaria is not a registered indication however, these drugs are commonly used for this indication in Australia

Treatment algorithm – Pregnancy/Lactation



**Chronic urticaria is not a registered indication however, these drugs are commonly used for this indication in Australia

Appendix: References

1. Zuberbier T, Asero R, Bindslev-Jensen G, et al. EAACI/GA^{2}LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allerty 2009; 1417-1426.
2. Brown NA, Carter. Urticarial Vasculitis. Curr Rheumatol Rep 2007; 9:312-9
3. Aust J Derm 55,137
4. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of Urticaria; a representive cross-sectional population survey. Clin Exp Dermatol 2010; 869-73.
5. Gaig P, Olona M, Munoz Lejarazu D, et al. Epidemiology of urticaria in Spain. J Investig Alergol Clin Immunol, 2004; 14:214-20.
6. Greaves MW. Chronic urticaria in childhood. Allergy. 2000; **55**: 309-20.
7. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. The New England journal of medicine. 2002; **346**: 175-9.
8. Khakoo G, Sofianou-Katsoulis A, Perkin MR, Lack G. Clinical features and natural history of physical urticaria in children. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2008; **19**: 363-6.
9. Zitelli KB, Cordoro KM. Evidence-based evaluation and management of chronic urticaria in children. Pediatric dermatology. 2011; **28**: 629-39.
10. Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. Pediatric dermatology. 1990; **7**: 101-7.
11. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria in infancy and early childhood: a prospective study. Archives of dermatology. 1998; **134**: 319-23.
12. Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. Pediatric dermatology. 2004; **21**: 102-8.
13. Konstantinou GN, Papadopoulos NG, Tavladaki T, Tsekoura T, Tsilimigaki A, Grattan CE. Childhood acute urticaria in northern and southern Europe shows a similar epidemiological pattern and significant meteorological influences. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2011; **22**: 36-42.
14. Liu TH, Lin YR, Yang KC, et al. Significant factors associated with severity and outcome of an initial episode of acute urticaria in children. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2010; **21**: 1043-51.
15. Sahiner UM, Civelek E, Tuncer A, et al. Chronic urticaria: etiology and natural course in children. International archives of allergy and immunology. 2011; **156**: 224-30.
16. Kaplan JACI 2004;114:465
17. Maurer M, Rosen K, Hsieh HJ et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticarial. N Engl J Med 2013; 368: 924-35
18. Toubi E, Kessel A, Avshovich N, Bamber E, Sabo E, Nusem D, Panasoff J. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. Allergy 2004; 59:869-73
19. Chansakulporn S, Pongpreuksa S, Sangacharoenkit P, et al. The natural history of chronic urticaria in childhood: a prospective study. Journal of the American Academy of Dermatology. 2014; **71**: 663-8.
20. Bernstein JA, Lang DM, Khan DA*, et al.* The diagnosis and management of acute and chronic urticaria: 2014 update. *The Journal of allergy and clinical immunology*. 2014; **133**: 1270-7.
21. Powell RJ, Du Toit GL, Siddique N*, et al.* BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2007; **37**: 631-50.
22. Tarbox JA, Gutta RC, Radojicic C, Lang DM. Utility of routine laboratory testing in management of chronic urticaria/angioedema. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2011; **107**: 239-43.
23. Grattan CE, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. Clin Exp Allergy. 2003 Mar;33(3):337-41.
24. Grattan CEH, Wallington TB, Warin RP, Kennedy CTC, Bradfield JW. A serological mediator in chronic idiopathic urticaria- a clinical, immunological and histological evaluation. British J Derm 1986, 114; 583-590.
25. Hide M, Francis DM, Grattan CEH et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993; 328:1599–604
26. Puccetti A, Bason C, Simeoni S, Millo E, Tinazzi E, Beri R, Peterlana D, Zanoni G, Senna G, Corrocher R, Lundari C. In chronic idiopathic urticaria autoantibodies against Fc epsilonRII/CD23 induce histamine release via eosinophil activation. Clin Exp Allergy 2005; 35:1599-607
27. Sabroe RA, Greaves MW. Chronic idiopathic urticaria with functional autoantibodies: 12 years on. Br J Dermatol. 2006 May;154(5):813-9
28. Diaz-Angulo S, Lopez-Hoyos M, Munoz Casho P, Fernandez M, Lopez-Escobar M, Rodriguez F, Gonzalez-Lopez MA. Prevalence of thyroid autoimmunity in Spanish patients with chronic idiopathic urticaria: a case-control study involving 343 subjects. J Eur Acad Dermatol Venereol 2015; Jan 28.doi: 10.111/jdv.12979. [epub ahead of print]
29. Mlynek, A., Zalewska-Janowska, A., Martus, P., Staubach, P., Zuberbier, T., and Maurer, M. (2008). How to assess disease activity in patients with chronic urticaria? Allergy 63, 777-780).
30. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of

omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75.
31. Mathias, S.D., Crosby, R.D., Zazzali, J.L., Maurer, M., and Saini, S.S. (2012). Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology *108*, 20-24.
32. Jariwala et al, 2009
33. Jauregui, I., Ortiz de Frutos, F.J., Ferrer, M., Gimenez-Arnau, A., Sastre, J., Bartra, J., Labrador, M., Silvestre, J.F., and Valero, A. (2014). Assessment of severity and quality of life in chronic urticaria. Journal of investigational allergology & clinical immunology 24, 80-86.
34. Baiardini, I., Braido, F., Bindslev-Jensen, C., Bousquet, P.J., Brzoza, Z., Canonica, G.W., Compalati, E., Fiocchi, A., Fokkens, W., Gerth van Wijk, R., et al. (2011). Recommendations for assessing patient-reported outcomes and health-related quality of life in patients with urticaria: a GA(2) LEN taskforce position paper. Allergy 66, 840-844.
35. Tondury, B., Muehleisen, B., Ballmer-Weber, B.K., Hofbauer, G., Schmid-Grendelmeier, P., French, L., and Buchi, S. (2011). The Pictorial Representation of Illness and Self Measure (PRISM) instrument reveals a high burden of suffering in patients with chronic urticaria. Journal of investigational allergology & clinical immunology 21, 93-100.
36. Koti, I., Weller, K., Makris, M., Tiligada, E., Psaltopoulou, T., Papageorgiou, C., Baiardini, I., Panagiotakos, D., Braido, F., and Maurer, M. (2013). Disease activity only moderately correlates with quality of life impairment in patients with chronic spontaneous urticaria. Dermatology 226, 371-379.
37. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. Allergy. 2009 Apr;64(4):605-12.
38. Grant JA, Bernstein DI, Buckley CE, et al. Double-blind comparison of terfenadine, chlorpheniramine and placebo in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol 1998:81:574-9.
39. Monroe EW, Bernstein DI, Fox RW et al. Relative efficacy and safety of loratadine, hydroxyzine and placebo in chronic idiopathic urticaria. Arzneimittelforschung 1992 ; 42:9 1119-21
40. Monroe EW. Relative efficacy and safety of loratadine, hydroxyzine, and placebo in chronic idiopathic urticaria and atopic dermatitis. Clin Ther. 1992;14:1:17-21.
41. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. Ann Pahramcother 1996 30:10; 1075-9.
42. Kalivas J, Breneman D, Tharp M et al. urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. J Allergy Clin Immunol 1990 86; 6pt 2:1014-8.
43. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. Hum Psychopharmacol 200;15(s1):s3-30.
44. Staevska M, Gugutkova M, Lazarova C et al. Night-time sedating H1-antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomized controlled trial. British Journal of Dermatology 2014 (171); 148-154.
45. Juhlin L. Cetirizine in the treatment of chronic urticaria. Clin Ther 1991 Jan-Fe; 13 (1). 81-6.
46. Goh CL, Wong WK, Lim J. Cetirizine vs placebo in chronic idiopathic urticaria: a double blind randomized cross-over study. Ann Acad Med Singapore 1991 May; 20(3):328-30.
47. Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydorchloride a non-sedating antihistaimine. Br J Dermatol 1988:119:67-72.
48. Monroe EW, Fox RW, Green AW, et al. Efficacy and safety of loratadine (10mg once daily) in the management of idiopathic chronic urticaria. J Am Acad Dermatol 1988 Jul;19(1pt1):138-9.
49. Finn Jr AF, Kaplan AP, Fretwell R, et al. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol 1999;104;5:1071-8.
50. Nelson HS, Raynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2000;84:5:517-22.
51. Thompson AK, Finn AF, Schoenwetter WF. Effect of 60mg twice-daily fexofenadine HCl on quality of life work and classroom productivity, and regular activity in patietns with chronic idiopathic urticaria. J Am Acad Dermatol 2000;43:1pt:24-30.
52. Kulthanan K, Gritiyarangsan P, Sitakalin C, et al. Multicenter study of the efficacy and safety of fexofenadine 60mg twice daily in 108 Thai patients with chronic idiopathic urticaria. J Med Assoc Thai 2001;84:2:153-9.
53. Kawashima M, Harada M. Efficacy and safety of fexofenadine HCl in Japanese patients with chronic idiopathic urticaria. Int Arch Allergy Immunol 2001;124:343-5.
54. Kaplan AP, Spector SL, Meeves S, et al. Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind placebo-controlled study. Ann Allergy Asthma Immunol 2005;94:6:662-9.
55. Spector SL, Shikiar R, Harding G, et al. The effect of fexofenadine hydrochloride on productivity and quality of life in patients with chronic idiopathic urticaria. Cutis 2007;79:2:157-62.
56. Ring J, Hein R, Gauger A, et al. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind placebo-controlled study. Int J Dermatol 2001. 40;1:72-6.
57. Monroe E, Finn A, Patel P, et al. Efficacy and safety of desloratadine 5mg once daily in the treatment of chronic idiopathic urticaria: a double-blind , randomized, placebo-controlled tria. J Am Acad Dermatol 2003;48:4:535-41.
58. Ortonne JP, Grob JJ, Auquier P, et al. Efficacy and safety of desloratadine 5mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, placebo-controlled, multicenter trial. Am J Clin Dermatol 2007;8:1:37-42.
59. Grob JJ, Auquier P, Dreyfus I, et al. Quality of life in adults with chronic idiopathic urticaria receiving desloratadine: a randomized, double-blind, multicenter, placebo-controlled study. J Eur Acad Dermatol Venereol 2008:22:1:87-93.

60. Augustin M, Ehrle S. Safety and efficacy of desloratadine in chronic idiopathic urticaria in clinical practice: an observational study of 9246 patients. J Eur Acad Dermatol Venereol 2009:23(3):292-9
61. Nettis E, Clolanardi MC, Barra L, et al. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2006;154:533-8.
62. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, pacebo-controlled, parallel, multicenter study. Int J Dermatol 2006;45:4:469-74.
63. Guerra L, Vinceni C, Marchesi E, et al. Loratadine and cetirizine in the treatment of chronic urticaria. J Eur Acad Dermatol Venereol 1994;3:2:148-52.
64. Handa S Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J Dermatolog Treat 2004: 15:1:55-7.
65. Garg G, Thami GP. Comparative efficacy of cetirizine and levocetirizine in chronic idiopathic urticaria. J Dermatolog Treat 2007:18;1:23-4.
66. Potter PC, Kapp A, Maurer M, et al. Comparison of the efficacy of levocetirizine 5mg and desloratadine 5mg in chronic idiopathic urticaria patients. Allergy 2009. 64;4;596-604.
67. 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. J Allergy Clin Immunol 2010;125:3:676-82.
68. Anuradha P, Maiti R, Jyothirmai J, et al. Loratadine versus levocetirizine in chronic idiopathic urticaria: a comparative study of the efficacy and safety. Indian J Pharacol 2010:42:1:12-6.
69. Zuberbier T, Munzberger C, Haustein U, et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. Dermatology 1996:193:4:324-7.
70. 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. Br J Dermatol 2007:157:4:803-4.
71. Asero R. Chornic unremitting urticaria: is the use of antihistamines above the licensed dose effective. A preliminary study of cetirizine at licensed and above-licensed doses. Clin Exp Dermatol 2007:32:1:34-8.
72. Siebenhaar F, Degener F, Zuberbier T, et al. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard dose treatment in patients with acquired cold urticaria: a randomized, placebo controlled crossover study J Allergy Clin Immunol 2009;123(3):672-9.
73. Richelson E: Tricyclic antidepressants and histamine H1 receptors. Mayo Clin Proc. 54:669.1979.
74. Green JP, Masayani S; Tricyclic antidepressant drugs block histamine H2 receptors in brain. Nature 269:163,1977.
75. Goldsobel AB, Rohr AS, Siegel SC et al. Efficacy of doxepin in the treatment of chronic idiopathic urticarial. J Allergy Clin Immunol. 198678(5):867-873.
76. Bleehan SS, Thomas SE, Greaves MW, et al. Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: a multi-centre randomized double-blind study. Br J Dermatol 1987;117:404-7.
77. Monroe EW, Cohen SH, Kalbfleisch J, et al. Combined H1 and H2 antihistamine therapy in chronic urticaria. Arch Dermatol 1981;117:404-7.
78. Paul E, Bodeker RH. Treatment of chronic urticaria with terfenadine and ranitidine. A randomized double-blind study in 45 patients. Eur J Clin Pharmacol. 1986;31:277-80.
79. Sharpe GR, Shuster R. In dermographic urticaria H2 receptor antagonists have a small but therapeutically irrelevant additional effect compared with H1 antagoniss alone. Br J Dermatol 1993;129:575-9.
80. Wan KS. Efficacy of leukotriene receptor antagonist with an anti-H1 receptor antagonist for treatment of chronic idiopathic urticaria. J Dermatolog Treat. 2009;20:194-197
81. Wan KS, Yung-sen Chang. Efficacy of leukotriene receptor antagonist with anti-H1 receptor antagonist plus anti-H2 receptor antagonist for treatment of refractory chronic idiopathic urticaria. J Dermatolog treat. 2014;25:6:459-461.
82. Reimers A, Pichler C, Helbling A, et al. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. Clin Exp Allergy 2002;32:1763-8.
83. Di Lorenzo G, Pacor ML, Mansueto P. et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. J Allergy Clin Immunol 2004;114:619-25.
84. Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled crossover clinical study. J Allergy Clin Immunol 2002;110:484-8.
85. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. Clin Exp Allergy 2001;31:1607-14.
86. Godse KV: Oral monelukast monotherapy is ineffective in chronic idiopathic urticaria: a comparison with oral cetirizine. Indian J Dermatol Venereol Leprol 2006, 72 (4):312-314.
87. Nettis E, Dambra P, D'Oronzio L, Loria MP, Ferrannini A, Tursi A; Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. Arch Dermatol. 2001, 137(1) 99-100.
88. Nettis E, Pannofino A, Cavallo E, Ferrannini A, Tursi A; Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. J Allergy Clin Immunol 2003,112(1):212-213.
89. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. J Allergy Clin Immunol 2004;113:134-40.
90. Nettis E, Colanardi MC, Paradiso MT et al. Desloratadine in combination with montelukast in the treatment of chronic urticaria: a randomized, double-blind, placebo-controlled study. Clin Exp Allergy 2004;34(9):1401-1407.
91. Kosnik M, Subi T: Add-on montelukast in antihistaimine-resistant chronic idiopathic urticaria. Respir Med 2011,105 (Suppl1): S84-S88.
92. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol 2005;115:459-65.

93. Babu KS, Arshad SH, Holgate ST. Omalizumab, a novel anti-IgE therapy in allergic disorders. Expert Opin Biol Ther 2001;1:1049-58.
94. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. J Allergy Clin Immunol 2004;114:527-30.
95. Saini SS, MacGlashan D. How IgE upregulates the allergic response. Curr Opin Immunol 2002;14:694-7.
96. European Medicines Agency. Xolair summary of product characteristics (http://www. ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/ human/000606/WC500057298.pdf).
97. Kaplan AP, Joseph K, Maykut RJ, Geba GP, Zeldin RK. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol. 2008;122(3):569-73.
98. Groffik A, Mitzel-Kaoukhov H, Magerl M, Maurer M, Staubach P. Omalizumab-an effective and safe treatment of therapy-resistant chronic spontaneous urticaria. Allergy. 2011;66(2):303-5.
99. Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol. 2011;128(3):567-73.e1.
100. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. J Allergy Clin Immunol 2011; 128:202e205–209e205.
101. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368(10):924-35.
102. Kaplan AP. Treatment of chronic spontaneous urticaria. Allergy Asthma Immunol Res. 2012;4(6):326-31.
103. 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 Jan;73(1):57-62.
104. Sussman G, Hébert J, Barron C, Bian J, Caron-Guay RM, Laflamme S, Stern S. Real-life experiences with omalizumab for the treatment of chronic urticaria. Ann Allergy Asthma Immunol. 2014 Feb;112(2):170-4.
105. Grattan C, O'Donnell B, Francis D, Nimi N, Barlow R, Seed P, et al. Randomized double blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000;143:365–72.
106. Vena G, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: A double-blind, randomised, placebo-controlled trial. J Am Acad Dermatol 2006;55:705–9
107. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long term therapy. Allergy 2010;65:1478–1482.
108. Engin B, Ozdemir M. Prospective randomised non-blinded clinical trial on the use of dapsone plus antihistamine vs. antihistamine in patients with chronic idiopathic urticaria. JEADV 2008;22:481–486.
109. Cassano N, D'Argento V, Filotico R, Vena G. Low dose dapsone in chronic idiopathic urticaria: Preliminary results of an open study. Acta Derm Venereol 2005; 85:254–255.
110. 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 Sep-Oct;2(5):601-6.
111. Reeves G, Boyle M, Bonfield J, Dobson P, Loewenthal M. Impact of hydroxycholoroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. Internal Medicine Journal 2004; 34:182–186.
112. Lammert JK, Robinson DM. Hydroxychloroquine (HCQ) in corticosteroid-dependent chronic urticaria (CDCU). Journal Of Allergy And Clinical Immunology, 1996 Jan, Vol.97(1), pp.730-730
113. Baumgart K; Mullins R. Use of hydroxychloroquine in refractory urticaria. The Journal of Allergy and Clinical Immunology, 2000, Vol.105(1), pp.S268-S269
114. Ditto, Am. Hydroxychloroquine in the treatment of 12 patients with severe chronic idiopathic urticaria; A case series. Journal Of Allergy And Clinical Immunology, 2007 Jan, Vol.119(1) Suppl S, pp.S199-S199
115. Pongonis RM, Fahrenholz JM. Efficacy of Hydroxychloroquine in the Treatment of 19 Patients with Antihistamine-refractory Chronic Urticaria. Journal Of Allergy And Clinical Immunology, 2012 Feb, Vol.129(2) Suppl S, pp.AB224-AB224
116. Hall A, Marshall GD. A Retrospective review of hydroxychloroquine use in patients with chronic idiopathic urticaria (CIU). Annals Of Allergy Asthma & Immunology, 2013 Nov, Vol.111(5) Suppl 1, pp.A18-A19
117. Eastman J, Wilde N, Jerath MR. Outcomes Of Chronic Urticaria Patients Treated With Hydroxychloroquine. Journal Of Allergy And Clinical Immunology, 2014 Feb, Vol.133(2) Suppl S, pp.AB119-AB119
118. Boonpiyathad S, Fuengthong R, Sangasapaviriya A. Effect of hydroxychloroquine treatment in the patients with anti-histamine refractory chronic spontaneous urticaria, randomised controlled trial. Allergy, 2013 Sep, Vol.68 Suppl 97, pp.62-62
119. 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
120. Duvall LA, Boackle RJ, King RG. Warfarin sodium therapy for chronic urticaria and angioedema. South Med J. 1986 Mar;79(3):389.
121. Berth-Jones J, Hutchinson PE, Wicks AC, Mitchell VE. Chronic urticaria with angio-oedema controlled by warfarin. BMJ. 1988 Nov 26;297(6660):1382-3.
122. Parslew R, Pryce D, Ashworth J, Friedmann PS. Warfarin treatment of chronic idiopathic urticaria and angio-oedema. Clin Exp Allergy. 2000 Aug;30(8):1161-5.
123. Samarasinghe V, Marsland AM. Class action of oral coumarins in the treatment of a patient with chronic spontaneous urticaria and delayed-pressure urticaria. Clin Exp Dermatol. 2012 Oct;37(7):741-3.
124. Fagiolo U, Cancian M, Bertollo L, Peserico A, Amadori A. Inhibitory effect of heparin on skin reactivity to autologous serum in chronic idiopathic urticaria. J Allergy Clin Immunol. 1999 Jun;103(6):1143-7.
125. Chua SL, Gibbs S. Chronic urticaria responding to subcutaneous heparin sodium. Br J Dermatol. 2005 Jul;153(1):216-7.

126. Asero R, Tedeschi A, Cugno M. Heparin and Tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria with elevated d-dimer: a pilot study. Int Arch Allergy Immunol. 2010;152(4):384-9.
127. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol. 1989 Jul;84(1):66-71.
128. Rumbyrt JS1, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. J Allergy Clin Immunol. 1995 Dec;96(6 Pt 1):901-5.
129. Aversano M, Caiazzo P, Iorio G, Ponticiello L, Laganá B, Leccese F. Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response? Allergy. 2005 Apr;60(4):489-93.
130. Magen E, Mishal J. The effect of L-thyroxine treatment on chronic idiopathic urticaria and autoimmune thyroiditis. Int J Dermatol. 2012 Jan;51(1):94-7.
131. Jaffer AM. Sulfasalazine in the treatment of corticosteroid-dependent chronic idiopathic urticaria. J Allergy Clin Immunol. 1991 Dec;88(6):964-5.
132. McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. Arch Dermatol. 2006 Oct;142(10):1337-42.
133. Pitt T, Warrington R, Kalicinsky C. Adjunctive treatment of chronic idiopathic urticaria and angioedema with sulfasalazine. Allergy, Asthma & Clinical Immunology 2010, 6(Suppl 1):P25
134. Orden RA, Timble H, Saini SS. Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria. Ann Allergy Asthma Immunol. 2014 Jan;112(1):64-70.
135. Jaffer AM, Reid RT. Sulfasalazine in the treatment of chronic urticaria. J Allergy Clin Immunol. 2002 109(1):S127.
136. Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: An open-label prospective study. J Am Acad Dermatol 2005;52:145–8.
137. Sharma, V.K., Singh, S., Ramam, M., Kumawat, M., and Kumar, R. (2014). A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria. Indian journal of dermatology, venereology and leprology 80, 122-128.
138. Gach, J.E., Sabroe, R.A., Greaves, M.W., and Black, A.K. (2001). Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. The British journal of dermatology 145, 340-343.
139. Perez, A., Woods, A., and Grattan, C.E. (2010). Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. The British journal of dermatology 162, 191-194.
140. Sagi, L., Solomon, M., Baum, S., Lyakhovitsky, A., Trau, H., and Barzilai, A. (2011). Evidence for methotrexate as a useful treatment for steroid-dependent chronic urticaria. Acta dermato-venereologica 91, 303-306
141. Shahar, E., Bergman, R., Guttman-Yassky, E., and Pollack, S. (2006). Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. International journal of dermatology 45, 1224-1227.
142. Zimmerman, A.B., Berger, E.M., Elmariah, S.B., and Soter, N.A. (2012). The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. Journal of the American Academy of Dermatology 66, 767-770.
143. Raghavendran, R.R., Humphreys, F., and Kaur, M.R. (2014). Successful use of mycophenolate mofetil to treat severe chronic urticaria in a patient intolerant to cyclosporin. Clinical and experimental dermatology 39, 68-69.
144. Tal, Y., Toker, O., Agmon-Levin, N., and Shalit, M. (2014). Azathioprine as a therapeutic alternative for refractory chronic urticaria. International journal of dermatology.
145. Tedeschi, A. (2009). Paradoxical exacerbation of chronic urticaria by H1-antihistamines and montelukast. European annals of allergy and clinical immunology 41, 187-189.
146. O'Donnell, B.F., Barr, R.M., Black, A.K., Francis, D.M., Kermani, F., Niimi, N., Barlow, R.J., Winkelmann, R.K., and Greaves, M.W. (1998). Intravenous immunoglobulin in autoimmune chronic urticaria. The British journal of dermatology 138, 101-106.
147. Hrabak, T., and Calabria, C.W. (2010). Multiple treatment cycles of high-dose intravenous immunoglobulin for chronic spontaneous rticarial. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 105, 245;
148. Mitzel-Kaoukhov, H., Staubach, P., and Muller-Brenne, T. (2010). Effect of high-dose intravenous immunoglobulin treatment in therapy-resistant chronic spontaneous urticaria. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 104, 253-258
149. Wetter, D.A., Davis, M.D., Yiannias, J.A., Gibson, L.E., Dahl, M.V., el-Azhary, R.A., Bruce, A.J., Lookingbill, D.P., Ahmed, I., Schroeter, A.L., and Pittelkow, M.R. (2005). Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. Mayo Clinic proceedings 80, 41-47.
150. Reider N, Egger C. Infliximab in the treatment of refractory chronic urticaria. J Am Acad Dermatol. 2009 60(3): AB39
151. Wilson LH, Eliason MJ, Leiferman KM, Hull CM, Powell DL. Treatment of refractory chronic urticaria with tumor necrosis factor alfa inhibitors. J Am Acad Dermatol. 2011 Jun;64(6):1221-2.
152. Sand FL, Thomsen SF. TNF-Alpha Inhibitors for Chronic Urticaria: Experience in 20 Patients. J Allergy (Cairo). 2013;2013:130905.
153. Arkwright PD. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. J Allergy Clin Immunol. 2009 Feb;123(2):510-1;.
154. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. J Allergy Clin Immunol. 2011 Dec;128(6):1354-5.
155. Bingham CO, Jones PE, Gober LM, Eckman JA, Sterba PM, Saini SS. Targeted B-cell Depletion using Rituximab (Anti-CD20) in Recalcitrant Autoimmune Urticaria. J Allergy Clin Immunol. 121:S172

156. Mallipeddi R, Grattan CE. Lack of response of severe steroid-dependent chronic urticaria to rituximab. Clin Exp Dermatol. 2007 May;32(3):333-4.
157. Asero R, Tedeschi A, Cugno M. Treatment of Refractory Chronic Urticaria: Current and Future Therapeutic Options. Am J Clin Dermatol (2013) 14:481-488
158. Church M, Weller C, Stock P, Maurer M. Chronic spontaenous urticaria in children: Itching for insight. Paediatric Allergy and Immunology 22 (2011): 1-8
159. Simons FE. Prevention of acute urticarial in young children with atopic dermatitis. J Allergy Clin Immunol 2001;107: 703-706
160. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticarial. Pediatr Dermatol 2009; 26: 409-13
161. Rudzki E, Czubalski K, Grzywa Z. Dermatologica. 1980;161(1):57-62. Detection of urticaria with food additives intolerance by means of diet.
162. Henz BM, Zuberbier T. Exp Dermatol. 1998 Aug;7(4):139-42. Most chronic urticaria is food-dependent, and not idiopathic.
163. Zuberbier T. J Investig Dermatol Symp Proc. 2001 Nov;6(2):132-4. The role of allergens and pseudoallergens in urticaria.
164. Reese I, Zuberbier T, Bunselmeyer B, Erdmann S, Henzgen M, Fuchs T, Jäger L, Kleine-Tebbe J, Lepp U, Niggemann B, Raithel M, Saloga J, Vieths S, Werfel T. J Dtsch Dermatol Ges. 2009 Jan;7(1):70-7. Diagnostic approach for suspected pseudoallergic reaction to food ingredients.
165. Ehlers I, Niggemann B, Binder C, Zuberbier T. Allergy. 1998 Nov;53(11):1074-7. Role of nonallergic hypersensitivity reactions in children with chronic urticaria.
166. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Acta Derm Venereol. 1995 Nov;75(6):484-7 Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study.
167. Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M. Allergy. 2010 Jan;65(1):78-83 Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial.
168. Akoglu G, Atakan N, Cakır B, Kalayci O, Hayran M. Arch Dermatol Res. 2012 May;304(4):257-62 Effects of low pseudoallergen diet on urticarial activity and leukotriene levels in chronic urticaria.
169. Malanin G, Kalimo K. Clin Exp Allergy. 1989 Sep;19(5):539-43. The results of skin testing with food additives and the effect of an elimination diet in chronic and recurrent urticaria and recurrent angioedema.
170. King W, McCargar L, Joneja JM, Barr SI. Can J Diet Pract Res. 2000 Spring;61(1):24-26. Benefits of a Histamine-Reducing Diet for Some Patients with Chronic Urticaria and Angioedema.
171. Bunselmeyer B, Laubach HJ, Schiller M, Stanke M, Luger TA, Brehler R. Clin Exp Allergy. 2009 Jan;39(1):116-26. Incremental build-up food challenge - a new diagnostic approach to evaluate pseudoallergic reactions in chronic urticaria: a pilot study: stepwise food challenge in chronic urticaria.
172. Guida B, De Martino CD, De Martino SD, Tritto G, Patella V, Trio R, D'Agostino C, Pecoraro P, D'Agostino L. Eur J Clin Nutr. 2000 Feb;54(2):155-8. Histamine plasma levels and elimination diet in chronic idiopathic urticaria.
173. Verschave A, Stevens E, Degreef H. Dermatologica. 1983;167(5):256-9. Pseudo-allergen-free diet in chronic urticaria.
174. Doeglas HM. Dermatologica. 1977;154(5):308-10 Dietary treatment of patients with chronic urticaria and intolerance to aspirin and food additives.
175. Rorie A, Goldner WS, Lyden E, Poole JA. Ann Allergy Asthma Immunol. 2014 Apr;112(4):376-82. Beneficial role for supplemental vitamin D3 treatment in chronic urticaria: a randomized study.
176. Hsu ML, Li LF. Prevalence of food avoidance and food allergy in Chinese patients with chronic urticaria. *The British journal of dermatology*. 2012; **166**: 747-52.
177. Jirapongsananuruk O, Pongpreuksa S, Sangacharoenkit P, Visitsunthorn N, Vichyanond P. Identification of the etiologies of chronic urticaria in children: a prospective study of 94 patients. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*. 2010; **21**: 508-14.
178. Gray PE, Mehr S, Katelaris CH, Wainstein BK, Star A, Campbell D, Joshi P, Wong M, Frankum B, Keat K, Dunne G, Dennison B, Kakakios A, Ziegler JB. Salicylate elimination diets in children: is food restriction supported by the evidence? Med J Aust. 2013 Jun 17;198(11):600-2.