Position Paper - Chronic Spontaneous Urticaria (CSU)

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Abbreviations used in this document

ASST	autologous serum skin test
CIndU	chronic inducible urticaria
CSU	chronic spontaneous urticaria
CU-Q2oL	chronic urticaria quality of life questionnaire
DLQI	dermatology life quality index
EAACI	European Academy of Allergology and Clinical Immunology
EDF	European Dermatology Forum
GA^{2}LEN	Global Allergy and Asthma European Network
IgE	Immunoglobulin E
IVIg	Intravenous immunoglobulin
LTRA	leukotriene receptor antagonists
QoL	quality of life
TNF	tumour necrosis factor
UAS	urticaria activity score
UAS7	urticaria activity score over 7 days
WAO	World Allergy Organisation

Contents

1. Introduction

Urticaria is a skin condition characterised by recurrent transient raised pruritic lesions (wheals), which last for between one hour and several days, and resolve without disruption of the epidermis. Angioedema is localised subcutaneous swelling, and often coexists with urticaria but can also occur independently. Urticaria may be acute, with lesions recurring over a period of hours, days or weeks, or chronic, lasting for more than 6 weeks. There have been recent advances in research and availability of new medications to treat chronic urticaria.

Definitions

Urticaria is defined by pruritic wheals, caused by mast cell degranulation in the superficial dermis. Angioedema is swelling arising in deeper dermal layers, triggered either by mast cell-derived histamine or by bradykinin.

The diagnosis of urticaria and angioedema is made based on clinical features. For consistency, we refer to the EAACI/GA^{2}LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria: The 2017 Revision and Update (Zuberbier et al., 2018).

Urticaria is characterized by:

1. wheals of variable size, surrounded by erythema.
2. pruritus of variable severity, or sometimes a burning sensation.
3. a transient nature with the skin returning to normal, usually within 30 minutes to 24 hours.

Angioedema is characterised by:

1. a sudden, pronounced swelling of the deeper dermis or mucus membranes.
2. painful or uncomfortable, rather than pruritic.
3. resolution slower than for urticaria, may take up to 72 hours.

Acute urticaria is urticaria (recurrent wheals) lasting for a period of less than 6 weeks. Acute urticaria may be caused by allergy, in which case it usually lasts for 24-48 hours or less. Urticaria lasting for days or weeks can be caused by infection. However, in many cases no cause can be found. Discussion of acute urticaria is beyond the scope of this document.

Chronic spontaneous urticaria (CSU) (known autoimmune + unknown) refers to wheals arising spontaneously 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 or friction (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 inducible urticaria can coexist with CSU. Often the management for both will overlap and the coexistence of inducible 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 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) (Brown & Carter, 2007). Urticarial dermatitis (urticarial eczema) is a condition characterised by pruritic urticarial plaques caused by superficial dermal inflammation that persists for weeks and settles with scale. It is usually idiopathic (Banan, Butler & Wu, 2014). Urticaria (either

spontaneous or cold-induced) may occur in the context of rare autoinflammatory/periodic fever syndromes. Urticaria pigmentosa is a form of cutaneous mastocytosis that manifests as fixed pigmented lesions that may urticate with friction (Darier's sign) but it has a different appearance to CSU.

Epidemiology and natural history

In adults, CSU is a common condition with a life time prevalence rate of around 1.8% of the general population, (Zuberbier, Balke, Worm, Edenharter, & Maurer, 2010) and a point prevalence rate in adults of 0.1-0.8%. It affects females more often than males (females 68-80% of cases). (Broder, Raimundo, Antonova, & Chang, 2015; Gaig et al., 2004; Zuberbier et al., 2010).

In children, the life time prevalence of urticaria has been reported at 22.5% (Bruske et al., 2013; Shin & Lee, 2017). Acute urticaria occurs more commonly in paediatric populations, with prevalence rates of between 2% and 14%, compared with chronic urticaria which has a reported prevalence of 0.1 and 3% (Greaves, 2000; Kaplan, 2002; Khakoo, Sofianou-Katsoulis, Perkin, & Lack, 2008; Shin & Lee, 2017; Zitelli & Cardoro, 2011). Most (80-90%) infants and young children presenting with urticaria have acute urticaria, while fewer than 10% develop chronic urticaria (Konstantinou et al., 2011; Legrain, et al., 1990; Liu, Lin, & Yang, 2010; Mortureaux et al., 1998; Sakesen et al., 2004) Recurrent acute urticaria is reported in between 10% and 30% of young children (Legrain, Taieb, Sage, & Maleville,1990; Mortureaux et al., 1998; Sakesen et al., 2004). Chronic urticaria is more common among adolescents and older children (Konstantinou et al, 2011; Legrain, et al., 1990; Liu, Lin, & Yang, 2010; Mortureaux et al., 1998; Sakesen et al., 2004). CSU is by far the most common subgroup of chronic urticaria in children (Sahiner, Civelek, & Tuncer, 2011). Chronic inducible urticaria (most commonly dermographism) accounts for the next most common subgroup (Khakoo et al., 2008).

CSU is accompanied by angioedema in approximately 40% of cases (Kaplan, 2004; Maurer, Rosen, & Hsieh, 2013). Recurrent angioedema may also occur in the absence of urticaria, and may be histamine-mediated (prevented by regular prophylactic antihistamines) or bradykinin-mediated (anti-histamine resistant). 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 (Gaig et al., 2004). The presence of angioedema or anti-thyroid antibodies was associated with increased duration of disease in one study of 139 patients (Toubi et al., 2004). 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 with an estimated resolution rate of 10% per year (Kaplan, 2002; Khakoo et al., 2008; Netchiporouk et al., 2017; Zitelli & Cordoro, 2011). In terms of prognosis, children with detectable basophils on a blood count showed slower resolution compared to those with undetectable basophils (Netchiporouk et al., 2017) Also, surprisingly, children with a positive result on a Basophil Activation Test (BAT; > 1.8% CD63 positive basophils) which correlates with the presence of mast cell auto antibodies and higher disease activity, also showed faster resolution of their disease compared to children with a negative BAT result. (Netchiporouk et al., 2017; Sahiner et al., 2011) 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 years carried a worse prognosis. Chansakulporn et al. (2014) 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. Skin biopsy will provide confirmation but is seldom necessary unless an alternative diagnosis (usually vasculitis) is suspected. 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 (Bernstein et al., 2018; Powell et al., 2007; Zuberbier et al., 2009), unless concomitant disorders are suggested by the history or physical examination.

In a retrospective study of 356 adults (Tarbox, Gutta, Radojicic, & Lang, 2011), 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 (Grattan, Dawn, Gibbs & Francis, 2003). 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) (Grattan, Wallington, Kennedy, & Bradfield, 1986). 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 (Hide, Francis, Hakimi, Kochan & Greaves, 1993), with a smaller proportion of patients with an autoantibody directed against the low-affinity IgE receptor (Puccetti et al., 2005) and some to the IgE molecule itself. Therefore in these cases, CSU would appear to be an autoimmune disorder.

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 (Sabroe & Greaves, 2006). 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 (Diaz-Angulo et al., 2016), although clinical hyper- or hypothyroidism was only present in 5% of patients, and 1.4% of controls tested (Diaz-Angulo et al., 2016). The rates of thyroid antibodies associated with CSU in children seem to be lower at around 2% of cases.

Whereas IgG autoantibodies have been designated type II autoimmunity, type I autoimmunity (autoallergy), in which IgE against soluble autoantigens (particularly demonstrated for thyroglobulin), has also been proposed as a mechanism for CSU (Kolkhir et al., 2017).

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 validated tool and is the sum of scores for wheals and itch over seven days. (Hawro et al., 2017; Mlynek et al., 2008). It is now used extensively in clinical practice and clinical trials as a measure of disease activity. It is a required measure in the assessment of patient suitability for omalizumab prescription in Australia. CSU is a variable condition so a measure of overall disease activity over several days is most useful. This is a patient –recorded score on a daily basis, reflecting on activity over the previous 24 hours. Over a 7 day period the maximum score is 42. UAS7 scores of less than 6 are considered a marker of well controlled symptoms and UAS7 scores of 0 a complete response (Saini et al., 2015). In the ASTERIA I study 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, Crosby, Zazzali, Maurer & Saini (2012) 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).

Two other measures, QoL and disease control, are used in clinical trials and are useful measures to apply in clinical practice as well. While generic measures (such as SF-36 and SF-12) and dermatological disease-specific questionnaires (such as DLQI) have been used, an urticaria-specific QoL tool has been developed and validated. The CU-Q2oL has been developed specifically for assessment of CSU.

Baiardini et al. (2011), in a GA^{2}LEN 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. (2013) 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.

Another score, the Urticaria Control Test (UCT) is used in the assessment of patients' disease status and is useful in assisting in treatment decisions (Ohanyan et al., 2017; Weller et al., 2014). The UCT was developed and validated to determine the level of disease control in all forms of CU (CSU and

CIndU). The UCT has only four items and a clearly defined cut off for patients with “well-controlled” vs. “poorly controlled” disease, and it is thus suited for the management of patients in routine clinical practice. The cut-off value for well-controlled disease is 12 of 16 possible points. This helps to guide treatment decisions.

For patients with angioedema, a novel activity score, the Angioedema Activity Score (AAS) has been developed and validated (Weller et al., 2013).

A validated angioedema-specific QoL tool, the AE-QoL may be used for assessing and monitoring quality of life impairment in those with angioedema without wheals. The recently published International Guidelines for CSU recommend that patients with chronic urticaria be assessed for disease activity, impact, and control at every visit and that the UAS7 and AAS be utilised for assessing disease activity. In the same guideline, the CU-Q2oL and the AE-QoL are recommended for assessing quality of life impairment in patients with chronic spontaneous urticaria.

2. Treatment

Drug treatments

CSU has a high rate of spontaneous remission (Gaig et al., 2004); 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 (Grob, Auquier, Dreyfus & Ortonne, 2009).

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 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 (Breneman, 1996; Grant et al., 1998; Kalivas et al., 1990; Monroe et al., 1992; Monroe, 1992; Shamsi & Hindmarch, 2000).

Randomised controlled trials comparing loratadine vs hydroxyzine (not available in Australia) (Monroe et al., 1992; Monroe, 1992) and cetirizine vs hydroxyzine (Breneman, 1996; Kalivas et al., 1990) 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 (Staevska et al., 2014). 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 in Australia and New Zealand include cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine. All have proven efficacy in CSU in a vast number of randomised controlled trials, including a total of nearly 4,000 patients. All have demonstrated safety and efficacy with no significant adverse effects. Levels of somnolence and sedation are consistently comparable to placebo-treated patients and significant improvements in health-related QoL, work performance and daily activities have also been reported. Minor adverse events only have been noted in a minority of patients, including headache, drowsiness, constipation and abdominal pain. (Augustin & Ehrle, 2009; Breneman, 1996; Finn et al.,1999; Goh, Wong & Lim, 1991; Grob et al., 2008; Grob, Auquier, Dreyfus & Ortonne, 2009; Juhlin & Arendt, 1988; Juglin,1991; Kalivas et al., 1990; Kaplan et al., 2005; Kapp & Pichler, 2006; Kawashima & Harada, 2001; Koti et al., 2013; Kulthanan et al, 2001; Monroe et al., 1992; Monroe, 1992; Monroe et al., 2003; Nettis, 2006; Monroe et al., 1988; Nelson, Ortonne et al., 2007; Raynolds & Mason, 2000; Ring et al., 2001; Spector et al., 2007; Thompson, Finn & Schoenwetter, 2000).

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 and antihistamine choice for CSU is usually dependent on clinician preference. Cetirizine has been compared with loratadine, fexofenadine and levocetirizine in two randomised controlled trials and one open label study (Garg & Tharmi, 2007; Guerra et al., 1994; Handa, Dogra & Kumar, 2004). These studies suggest superiority of cetirizine over fexofenadine (Handa, Dogra & Kumar, 2004) but no greater efficacy when compared to loratadine or levocetirizine (Garg & Tharmi, 2007; Guerra et al.,1994). There are two randomised controlled comparison studies of levocetirizine and desloratadine both suggesting greater symptom control in the levocetirizine group (Potter et al., 2009; Staevska et al., 2010) although no significant difference in health related quality of life scores was reported (Potter et al., 2009). 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 (Anuradha et al., 2010).

Second generation H1 antihistamines: updosing

Standard treatment protocols recommend increasing the dose of second-generation H1 antihistamines up to 4 times the standard dose, if standard doses are ineffective (Zuberbier et al., 2018). While there are no large, double blind placebo controlled studies to support this, a recent systematic review and meta-analysis did find that while the studies did not show an improvement in wheal number at higher doses there are improvements in pruritus scores (Guillén-Aguinaga, Jáuregui Presa, Aguinaga-Ontoso, Guillén-Grima, & Ferrer, 2016), and also that a larger number of patients responded to treatment with higher doses of antihistamines than to standard doses, however there was heterogeneity amongst these studies (Guillen-Aguinaga et al., 2016). Interestingly, in the meta-analysis fexofenadine was the drug most likely to have increased response rates at higher doses, in contrast to previous studies that had not shown an improvement with up-dosing this medication (Finn et al., 1999; Nelson et al., 2000).

A recent study has looked at data from one centre in which antihistamines have been up-dosed at doses greater than 4 times the standard dose and found an additional number of patients achieved symptom relief (van den Elzen et al., 2017) with a 10% rate of side effects. However, given this is a single study, a recommendation to increase to greater than 4 times the current dose cannot be made at this time.

Doxepin

Doxepin is a tricyclic antidepressant that is approximately 56 times more potent than hydroxyzine as a H1 blocker and six times more potent than cimetidine as an H2 blocker (Green & Masayani, 1977; Richelson, 1979). A 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 (Goldsobel et al.,1986). Although drowsiness, dry mouth, and constipation were commonly observed, only one patient ceased therapy because of lethargy (Goldsobel et al., 1986).

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 the drug 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

Current evidence for the use of H2 receptor blockers in CSU is lacking and are now difficult to source. Early studies demonstrated improved itch, wheal size and intensity despite no significant greater overall improvement in symptoms of urticaria (Bleehan et al., 1987; Monroe et al.,1981). Others have demonstrated no clinically significant benefit (Paul & Bodeker, 1986; Sharpe & Shuster, 1993). Small randomised trials have reported treatment efficacy of combination H1 and H2 receptor antagonist/ Montelukast therapy, however, follow up did not extend beyond four weeks and long term data is lacking (Wan, 2009; Wan & Chang, 2014).

Leukotriene receptor antagonists (LTRAs)

There is limited low level evidence regarding the use of LTRAs in CSU. One small placebo-controlled trial of zafirlukast monotherapy showed no benefit (Reimers et al, 2002). Two randomised controlled trials with montelukast reported reduction in number of hives compared to placebo, but no significant benefit in other outcomes (Erbagci, 2002; Di Lorenzo et al., 2004).

A number of head to head studies comparing montelukast with antihistamines favour antihistamines (Di Lorenzo et al., 2004; Godse, 2006; Nettis et al., 2001; Nettis et al., 2003). 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 (Bagenstose, Levin & Bernstein, 2004; Pacor, Di Lorenzo & Corrocher, 2001)

Combination LTRA and antihistamine therapy studies have demonstrated variable improvement in VAS, itch and urticarial scores at follow up ranging from three to six weeks (Bagenstose et al., 2004; Nettis et al., 2004 Wan, 2009; Wan & Chang, 2014). 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 (Di Lorenzo et al., 2004; Nosik & Subi, 2011). All trials have, however, consistently reported excellent tolerability and side effect profile (Bagenstose et al., 2004; Di Lorenzo et al., 2004; Erbagci, 2002; Godse, 2006; Kosnik & Subi, 2011; Nettis et al., 2001; Nettis et al., 2003, Nettis et al., 2004; Pacor et al., 2001; Reimers et al., 2002; Wan, 2009; Wan & Chang, 2014).

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 (Babu, Arshad & Holgate, 2001; Holgate et al., 2005). 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 shown to reduce the levels of both free IgE and the high-affinity IgE receptor (FcεRI) (Beck, Marcotte, MacGlashan, Togias & Saini, 2004; Saini & MacGlashan, 2002), 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 (European Medicines Agency Assessment Report for Paediatric Studies 2017).

The use of Omalizumab (Xolair® - Novartis Pharmaceuticals Australia Pty Ltd) was added to the Pharmaceutical Benefits Scheme (PBS) on 1st September 2017 for the treatment of patients with severe chronic spontaneous urticaria (CSU).

Post marketing research has consistently shown benefit, similar to the original studies at 300mg/month with around 63% of patients well controlled, and an additional 25% with fair to weak response with 12% labelled as non-responders. While a lower dose of 150mg/4 weeks has been beneficial in some (Vadasz et al., 2017), in patients with a poor response, studies have shown improvement in some, but not all, with either increasing the frequency of injections to 2 weekly, (Clarke et al., 2016), or increasing the dose to 450mg (Curto 2018; Vadasz et al., 2017;) and 600mg 4 weekly (Valdas 2017). Obesity, age >57 years and prior ciclosporin therapy predicts treatment failures at standard doses (Curto et al,2018).

The common side effects include headache, fatigue and injection site reactions (Bernstein et al., 2018). More unusual reported side effects include serum sickness in a 12 year old girl (Eapen & Kloepfer, 2018) and transient hair loss (Konstantinou, Chioti & Daniilidis, 2016; Noshela & Thomsen, 2017).

As use becomes more widespread, experience is growing with serious adverse events. The most concerning immediate reaction is the potential for anaphylaxis. Post marketing data encompassing 819,018 patient years, including patients receiving omalizumab for both chronic spontaneous urticaria and asthma, demonstrated a 0.20% reported rate of anaphylaxis. (Australian Public Assessment Report for Omalizumab, 2016). In the most recent study of 96 episodes of anaphylaxis, 80% where it was given for asthma, 72% of episodes occurred within the first 3 doses. (Lieberman, Umetsu, Carrigan & Rahmaoui, 2016).

There are reports of increased risk of cardiovascular and cerebrovascular events in a cohort of 5007 severe asthmatic patients treated with omalizumab, compared to 2829 moderately severe asthmatic controls. The omalizumab treated group had 13.4 events per 1000 person years, compared to the non-omalizumab treated group with 8.1 events per 1000 person years. (Iribarren et al., 2017). It should be noted however, that there is a higher risk of these events in patients with chronic, severe asthma (Iribarren, Tolstykh, Miller, Sobel & Eisner, 2012), which is not present in patients with chronic urticaria (Egeberg, 2016). No study has been performed on patients with CSU treated with omalizumab. Fortunately, there does not appear to be an increased risk of malignancy in the same cohort of patients with severe asthma treated with omalizumab. (Long et al., 2014).

Although there has been reported resistance with retreatment with other biologic therapies, this has not been the case with omalizumab where if treatment is stopped, retreatment appears equally effective. (Metz, 2014).

Unmet needs and unknowns with omalizumab use

There are now ample data available to support the efficacy and safety of omalizumab in patients with CSU. However, there remain many unanswered questions regarding this treatment. Knowledge gaps include efficacy of omalizumab in patients with angioedema, but no hives; mode of action; safety of long-term use (greater than 12 months) in this population; efficacy and safety in children with CSU.

Very practical questions for the treating physician include:

- How to determine if a CSU patient is likely to respond to omalizumab?
- How to measure response to omalizumab for a CSU patient?
- When should a CSU patient be classified as a non-responder to omalizumab and on what basis?
- Omalizumab dose and frequency for a CSU patient from the point that they have been determined to be a responder?
- Whether there should be a trial of omalizumab cessation and if so, when?
- Whether patients no longer on omalizumab should be re-treated with it upon CSU recurrence and if yes, with what dose and frequency?

What is the response to omalizumab?

Response patterns to omalizumab in CSU are dose dependent. Commencing with 300mg monthly ensures the largest percentage of patients gain complete (UAS 7=0) or good (UAS 7 ≤6) control with half the patients achieving this after the second dose. This finding has been confirmed in the OPTIMA study (Lynde et al., 2017). While real-life studies of omalizumab in CSU reveal a response rate of 77%-83% (UAS 7 ≤6), some patients do not achieve good control at the recommended dose of 300mg every 4 weeks. Curto-Barredo et al. (2018) showed that 21% of CSU patients required a higher dose of omalizumab to achieve UAS 7 ≤6; 15% did with 450mg monthly, while 6% required 600mg monthly.

Predictors of partial response to 300mg and good response with the updosing were previous treatment with ciclosporin, obesity and age >57 years old. Previous use of ciclosporin could alter responsiveness to omalizumab by modifying patients' immune status or may reflect severity of the disease itself. Long-term efficacy of biologics in other inflammatory cutaneous diseases such as psoriasis is influenced by body mass index (BMI), so this may also be the case for omalizumab in CSU (Curto–Baredo et al., 2018).

Late responders to omalizumab

Patients should be treated for at least 6 months before being regarded as non-responsive to omalizumab treatment (Kaplan et al., 2016). At this point, omalizumab should be discontinued and alternative treatments may be considered. In the ASTERIA I study (Saini et al., 2011) the median time to complete response was observed between 8-10 weeks at 300mg monthly. 58% of patients in the omalizumab group who had not responded with a UAS7 ≤6 by week 12 did so during weeks 13-24. Results were similar in both GLACIAL and ASTERIA I studies. Three doses of omalizumab may therefore miss the opportunity to bring symptoms under control. (Kaplan et al., 2016). Further research is needed to understand mechanisms responsible for early and late patterns of responses.

Outcomes after cessation of omalizumab treatment

Further unanswered questions regarding omalizumab treatment in CSU relate to whether there should be a trial of omalizumab cessation after a good response to treatment, and if so, at what point should this be attempted. If there is recurrence of CSU, should patients be re-treated, with what dose and frequency and will re-treatment be as effective as initial treatment?

In the OPTIMA study (Lynde et al., 2017), after being well controlled (UAS7 ≤ 6), 44.5% of CSU patients on omalizumab 150 mg and 50% of patients on omalizumab 300 mg relapsed (UAS7 ≥ 16) upon withdrawal of treatment. Within the allocated 8-week treatment withdrawal period as per protocol, the overall time to relapse in both dosages was 4.7 weeks. Re-introduction of treatment with both dosages was effective. Overall, 87.8% of patients regained symptom control upon re-treatment, after being previously well controlled and relapsing. Quality of life worsens considerably after drug withdrawal. It is unknown whether stepping down rather than cessation of treatment would allow continued symptom control.

Angioedema component – omalizumab responsiveness

The effect of omalizumab on the angioedema component of CSU had not been studied until recently. (Staubach et al., 2016). The X-ACT study was a phase III, randomised, double-blind study conducted in 24 German centres which selectively included CSU patients with angioedema and wheals. Patients were randomised (1:1) to omalizumab 300 mg or placebo (every 4 weeks up to week 24). The primary objective was to evaluate the efficacy of omalizumab vs placebo at week 28 using the Chronic Urticaria Quality of Life (CU-Q2oL) questionnaire.

Omalizumab was superior to placebo in reducing the CU-Q2oL total score from week 4 onwards over the 28 weeks of treatment ($P < 0.001$ at all measurement points). There was a threefold improvement in angioedema-burdened days/week with omalizumab (0.3) vs placebo (1.1). The median time to first recurrence of angioedema was 57–63 days with omalizumab and <5 days with placebo. Omalizumab significantly improved angioedema-specific QoL ($P < 0.001$). The adverse events reported were in line with the established safety profile of omalizumab.

Ciclosporin

In the first randomised controlled trial of ciclosporin for CSU in 29 subjects (Zuberbier et al., 2009), two thirds experienced short term complete resolution of urticaria. Long term remission (where urticaria did not recur after ciclosporin was ceased) was seen in only 5 subjects.

In the largest, double blind randomised placebo controlled trial with 99 antihistamine-refractory patients (Brown, 2007), ciclosporin (5mg/kg/day in conjunction with cetirizine 10mg/day) was given 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%. Ciclosporin 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 ciclosporin group, versus 30.2% in the placebo group.

More prolonged courses of low dose ciclosporin treatment have been shown to be safe and effective in an observational study involving 120 patients with severe CSU (Banan et al., 2014). At a dose of 3mg/kg/day for three months of treatment, 20 patients discontinued because of side effects. Ciclosporin was not effective for 18 patients. Thirty patients had complete resolution, while 32 had a moderate response and needed ongoing antihistamine treatment. A further 20 patients found ciclosporin beneficial, but required much longer periods of treatment. In this group of ciclosporin dependent patients, dosage was reduced to 1–2mg/kg/day after 3 months of treatment. Eight patients were given ciclosporin at this dosage for 8–14 months of follow-up, and 12 patients were given ciclosporin for 60–120 months.

Short term (5-month) use of ciclosporin in CSU with positive autologous serum skin test (ASST) has been suggested from an open label study of 23/30 subjects completing a 5-month trial of ciclosporin (receiving mean dose of 2.16 mg/kg for the first month and 0.55 mg/kg for the fifth month) with 3 non responders and 4 dropouts due to adverse events (Zuberbier et al., 2014). At 1 year follow up 87% remained symptom free and repeat ASST was negative in 78% suggesting a possible role for short term, low dose treatment benefit in some.

Recently, a systematic review and meta-analysis of ciclosporin CSU identified 18 studies (909 participants) receiving very low (<2 mg/kg/d), low (from 2 to< 4 mg/kg/d), and moderate (4-5 mg/kg/d) doses of ciclosporin, respectively (Gaig et al., 2004). Of concern only 3 studies were available to assess impact on UAS7 of which only a single RCT was included. After 4 weeks of ciclosporin treatment, the pooled statistical estimate of mean relative UAS7 changes from baseline was -17.89 (95% CI, -21.95 to -13.83), and significantly different ($p<0.001$) to placebo -2.3 (1 study; 95% CI, -3.72 to -0.88). After 12 weeks of treatment, the pooled response rate appeared dose responsive, for low-dose ciclosporin 69.9% (95% CI, 63.1%-75.9%) and 84.3% for moderate-dose ciclosporin (95% CI, 69.3%-92.8%).

At least one adverse event was reported following ciclosporin treatment in patients treated with very low 6.2% (95% CI, 1.0%-29.8%), low 23.4% (95% CI, 14.4%- 35.6%), and moderate doses of ciclosporin 57.9% (95% CI, 32.3%-79.8%). Adverse events that led to the discontinuation of CsA included hypertension, severe gastrointestinal adverse events, precordialgia, persistent peripheral neuropathy, and severe headaches. These limited findings suggest that ciclosporin is effective in CSU in low (from 2 - <4 mg/kg/d) to moderate doses (4-5 mg/kg/d) although adverse events appeared dose dependent and at least one adverse event was experienced by more than half of patients treated at moderate doses. A previous EAACI/GA²LEN/EDF/WAO Guideline (Greaves, 2000) suggested that ciclosporin may have a role in CSU unresponsive to high dose H1-antihistamines. However, with the availability of omalizumab,a trial of ciclosprin should follow failure of omalizumab to bring about control, given its off

label status and increased adverse event profile, this should follow a trial of omalizumab. For the treatment of CSU, the dosage for ciclosporin ranges from 1 to 5 mg/kg per day. Patients taking ciclosporin need to have blood pressure and renal function closely monitored during treatment. From 1st of May, 2015, ciclosporin has become exempt from the Pharmaceutical Benefits Scheme (PBS) statutory price reductions, and is available on a private prescription.

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 (Asero & Tedeschi, 2010). 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 follow up 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. In a retrospective cohort study of 12647 patients with CSU analysing a commercial claims data base, those who were treated with oral corticosteroids had an increased risk of side effects and higher total health care costs. Patients suffering diabetes, hypertension or significant cardiovascular disease are especially at high risk of significant steroid related morbidity.

Anticoagulants

There have been several small case series reporting **warfarin or heparin** to be effective for CSU (Berth-Jones, Hutchinson, Wicks & Mitchell, 1988; Duvall, Boackle & King, 1986; Fagiolo, Cancian, Bertollo, Pesetico & Amadori,1999; Parslew, Pryce, Ashworth & Friedman, 2000; Samarasinghe & Marsland, 2012; Chua & Gibbs, 2005). Recently Asero, Tedeschi & Cugno (2010) 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.

Thyroxine

There have been several case series showing mixed results for **thyroxine** given to euthyroid patients with CSU, whether they had thyroid autoantibodies or not (Averssano et al., 2005; Leznoff & Sussman, 1989; Magen & Mishal, 2012; Rumbyrt, Katz & Schocket, 1995). On balance, there is probably a minority of euthyroid CSU patients who have thyroid autoantibodies and may respond to thyroxine therapy, and a trial of thyroxine could be considered at 100-200mcg per day for four weeks.

Other treatments

Studies on small numbers of patients have suggested some benefit from the use of **dapsone** in CSU (Engin & Ozdemir, 2008; Morgan et al., 2014). Glucose-6-phosphate dehydrogenase (G6PD) deficiency should be checked for prior to commencing dapsone.

Hydroxychloroquine Overall, the published evidence for hydroxychloroquine is limited (Boonpiyathad et al., 2013; Lammert & Robinson, 1996).

There is only limited evidence showing possible efficacy in CSU for:

- **Sulfasalazine** (Jaffer,1991; McGirt, Pitt, Warrington & Kalicinsky, 2010; Orden, Timble & Saini, 2014; Vasagar, Gobar, Saini & Beck, 2006).
- **Tacrolimus** (Kessel, Bamberger & Toubi, 2005).
- **Methotrexate** (Gach, Sabroe, Greaves & Black, 2001; Perez, Woods & Grattan, 2010; Sagi et al., 2011; Sharma et al., 2014).

- **Mycophenolate** (Shahar, Bergamn, Guttman-Yassky & Pollack, 2006; Zimmerman, Berger, Elmariah & Soter, 2012).
- **Azathioprine** (Tal, Toker, Agmon-Levin & Shalit, 2014; Tedeschi, 2009).
- **Intravenous immunoglobulin** (Hrabak & Calabria, 2010; Mitzel-Kaoukhov, Staubach & Muller-Brenne, 2010; Wetter et al., 2005).
- **TNF antagonists** (Reider & Egger, 2009; Wilson, Eliason, Leiferman, Hull & Powell, 2011; Sand & Thomsen, 2013).
- **Rituximab** (Arkwright, 2009; Bingham et al., 2008; Chakravarty, Yee & Paget, 2011;).

Other medications with more evidence for treatment efficacy are therefore recommended.

Drug treatment in paediatric populations

Although further studies of CSU are needed in paediatric populations, evidence to date suggest that the prevalence and causes are similar to that in adults (Caffarelli et al., 2013; Maurer, Church & Weller, 2017; Zuberbier et al., 2010).

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 (Asero et al., 2013; Church, Weller, Stock, & Maurer, 2011; Simons, 2001). 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 (Church et al, 2011). 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 (Kaplan, 2012; Maurer et al., 2013; Mlynek et al., 2008; Sussman et al., 2014). Adolescents aged ≥ 12 were included in three large randomised control phase III studies (ASTERIA I, ASTERIA II, and GLACIAL) which clearly demonstrated the efficacy of omalizumab over placebo (Kaplan, 2012; Mlynek et al., 2008; Sussman et al., 2014). In Canada, a prospective open label trial demonstrated a good response to omalizumab in children as young as seven years (Sussman et al., 2014).

In addition, a single case series found ciclosporin to be effective at controlling symptoms in seven children with CSU (Doshi & Weinberger, 2009). However, there are no controlled trials to support the use of ciclosporin or other second line agents, (e.g. leukotriene receptor antagonists, H2 receptor antagonists, hydroxychloroquine, azathioprine or methotrexate), in treating children with CSU (Asero et al., 2013; Church et al., 2011). 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.

Drug availability in New Zealand

The second-generation antihistamines loratadine and cetirizine are available and fully subsidised on prescription. There is a partial subsidy for fexofenadine 60mg and 120mg. Fexofenadine 180mg, levocetirizine and desloratadine are available but at full cost to the patient.

Montelukast is fully funded and used off license for CSU and angioedema.

Ciclosporin is fully subsidised (off license indication) on prescription.

Omalizumab is Pharmac funded by application for subsidy by special authority. Applications must be made by a clinical immunologist or dermatologist.

Doxepin, ciclosporin, dapsone, hydroxychloroquine, methotrexate and azathioprine are fully subsidised (off-licence indication) on prescription.

PBS requirements in Australia

In Australia, PBS requirements for omalizumab prescription require:

- a UAS7 of ≥ 28;
- a trial of high dose non-sedation antihistamines in combination with any two of H2 antagonist, montelukast or doxepin.
- In addition, the first PBS prescription is for three months only with demonstration of benefit required for further prescriptions.

Recent international guidelines and this updated guideline provides evidence that some patients may take longer than three months to gain a response and an evidence-based argument can be made to allow a six month trial before accepting treatment failure.

Furthermore, H2 antagonists are now difficult to source and the evidence base for efficacy in CSU is weak, so these should no longer be required as a step before allowing prescription of omalizumab.

There is also limited evidence for the use of montelukast, so while a treatment trial may be attempted, this should no longer be required as a step before allowing prescription of omalizumab.

Finally, most clinicians believe that setting the UAS7 criteria at ≥ 28 ignores the very significant burden of disease that occurs with lower scores. For these reasons the algorithm in this document proposes modified criteria.

Non-drug management

Dietary management

Dietary manipulations are not recommended for the majority of patients with CSU (Banan et al., 2014; Brown & Carter, 2007; Zuberbier et al., 2009). Although dietary factors have long been suspected of influencing the manifestations of urticaria it is extremely rare for IgE-mediated food allergy to be causative in CSU (Juhlin,1981; Zuberbier et al., 2010). IgE-independent pseudoallergens including food additives, preservatives, dyes, vasoactive and aromatic compounds have been reported to induce and/or aggravate urticaria in CSU patients (Henz & Zuberbier,1998; Juhlin,1982; Zuberbier,1995) but with varied results (Bunselmeyer et al., 2009; Zuberbier et al., 2010; Zuberbier et al., 2009). No reliable laboratory or skin tests can currently identify those patients who may benefit from a pseudoallergen-free diet (Reese et al., 2009). There is a lack of supportive quality evidence and these diets remain controversial (Banan et al., 2014). For the majority of patients with CSU, dietary manipulations are not recommended (Bernstein et al., 2014; Rajan, Zuberbier & Bosso, 2014; Zuberbier et al., 2018)

Supervised pseudoallergen-free diets may improve symptoms in strongly motivated adult patients with CSU, if maintained for 3-4 weeks (Greaves, 2000; Zitelli & Cordoro, 2011; Legrain et al., 1990; Magerl, Pisarevskaja, Scheufele, Zuberbier, & Maurer, 2010; Wagner et al., 2017; Zuberbier et al., 1995). The risk of adverse outcomes, including nutritional deficiencies, food aversion and development or exacerbation of eating disorders should be considered by the treating physician prior to recommending dietary restriction.

Pseudoallergen-free diets in the paediatric population may have adverse outcomes (Gray et al., 2013) and are not recommended for use in children with CSU (Mortureaux et al.,1998).

A small RCT found supplementation with high dose vitamin D (4000iu per day) as add on therapy to antihistamines and montelukast was of possible benefit in reducing the symptoms of urticaria (Rorie, Goldner, Lyden, & Poole, 2014). However, further studies are required on appropriate dosage and duration of vitamin D supplementation.

Reduction of emotional stress

Emotional factors and physical stress are recognised to correlate with CSU severity and activity (Konstantinou et al., 2011; Verghese et al., 2016), although the mechanisms are not well understood. Stress reduction techniques, screening for comorbid mental health problems and a whole person treatment approach may be of benefit in managing CSU (Ben-Shoshan, Blinderman & Raz, 2013; Kaplan, 2004; Lindsay, Goulding, Solomon & Broom, 2013; Liu et al., 2010; Sahiner et al., 2011; Staubach et al., 2011).

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. Omalizumab in pregnancy has not been associated with increased risks to the mother or foetus but more data is needed (EXPECT). 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
Ciclosporin	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

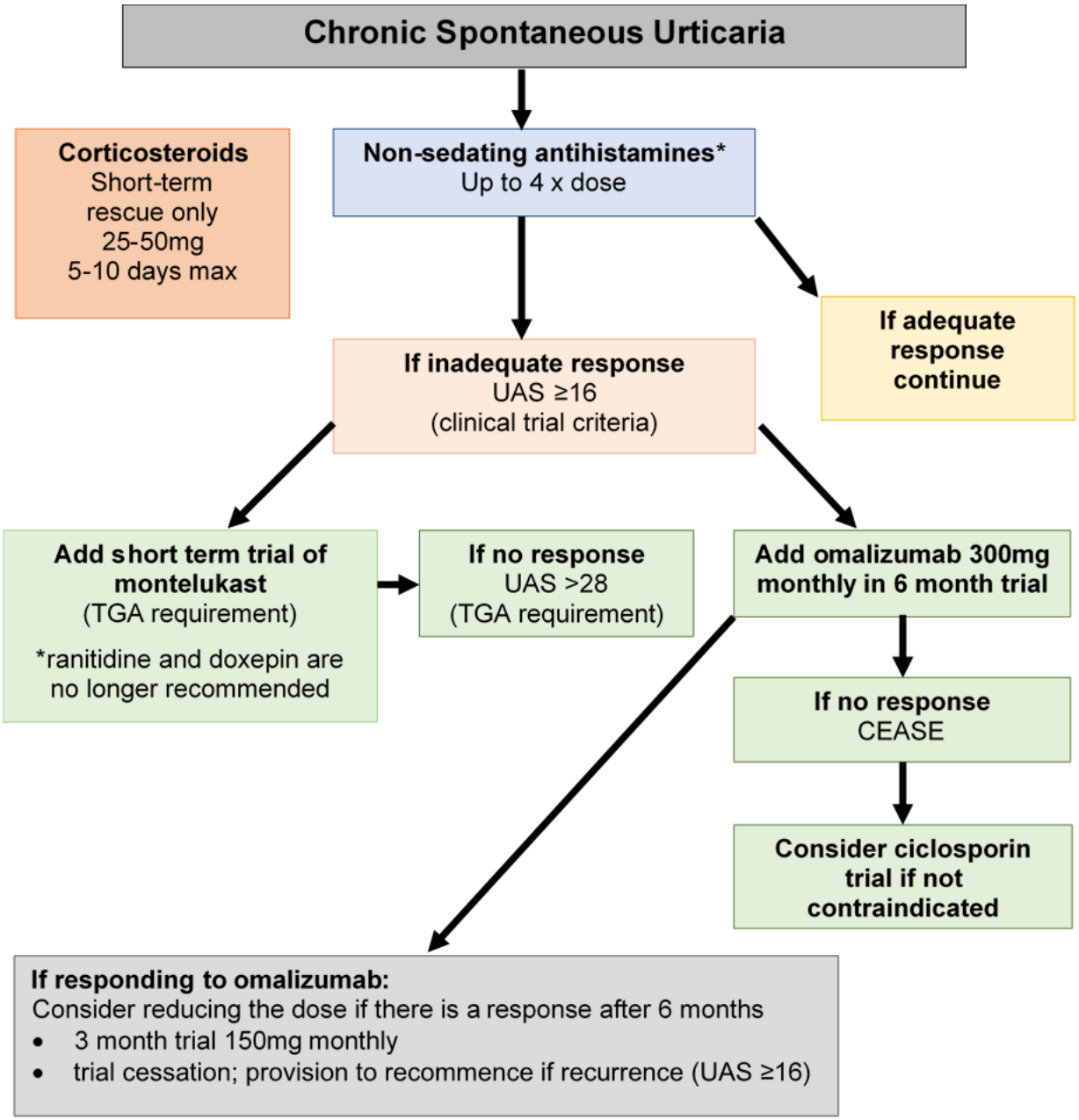
L1 – safest
L2 – safer
L3- probably safe
L4: probably hazardous
L5: hazardous

3.Treatment Algorithms

ASCIA treatment guideline for chronic spontaneous urticaria (Australia)

Whilst the pathway shaded in green is approved by TGA/PBS, ASCIA recommends that some patients may benefit from omalizumab who have a lower UAS, as supported by clinical trial data.

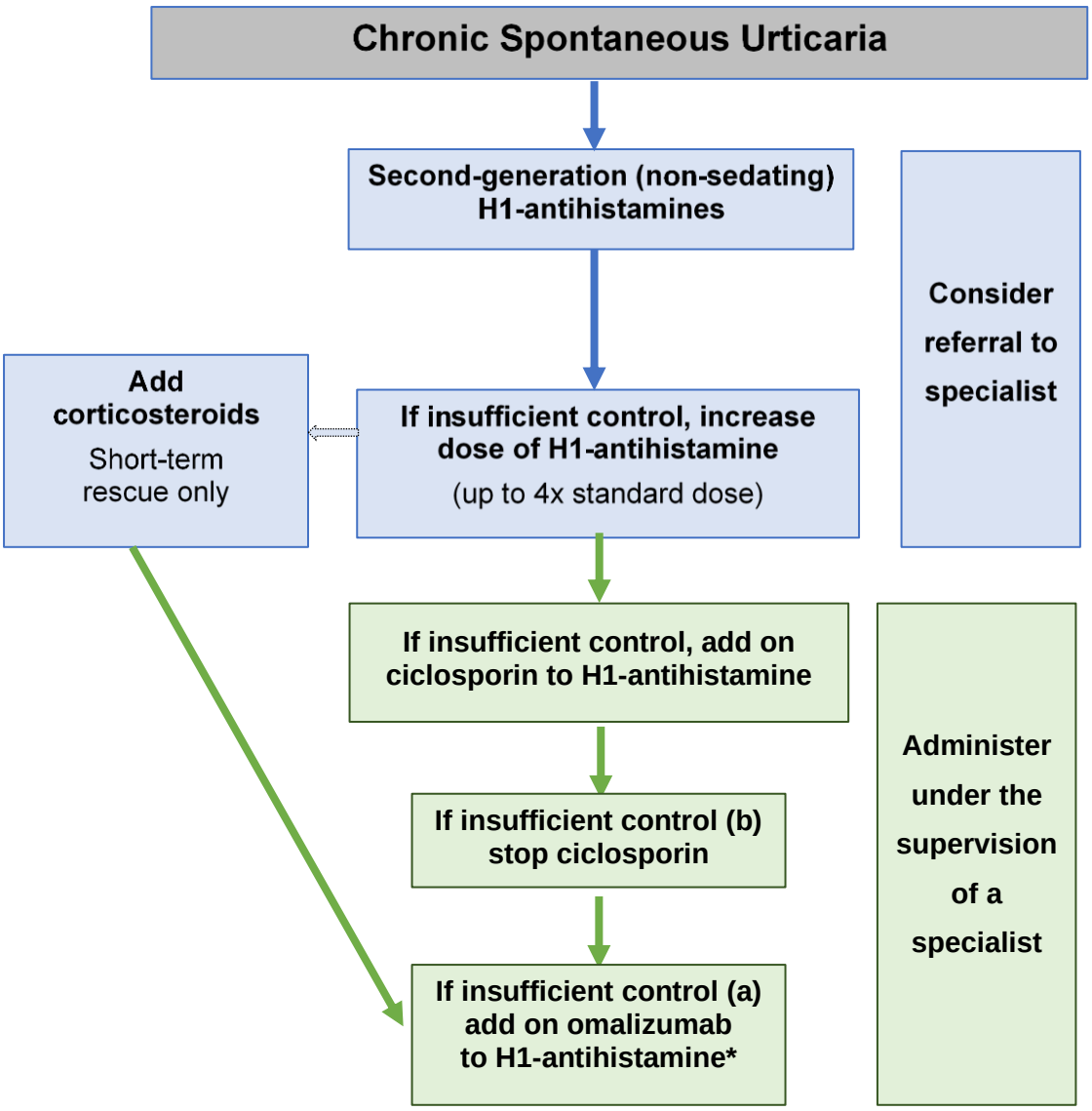
* Note: H2 antagonists are now difficult to source and the evidence base for efficacy in CSU is weak, so ASCIA recommends a treatment trial of high dose antihistamines in combination with montelukast, before applying for omalizumab.



ASCIA treatment guideline for chronic spontaneous urticaria (New Zealand)

Referral to a specialist should be considered for patients treated according to the pathway shaded blue. Treatment in the pathway shaded green is only to be administered under the supervision of a specialist.

Treatment in the pathway shaded green is only to be administered under the supervision of a specialist.



*Add on to antihistamines: In patients ≥ 12 years with a UAS7 ≥20; and a DLQI ≥10; or an UCT of ≤ 8.

a. Patient has been taking high-dose antihistamines (e.g. 4 times standard dose) and at least 3 courses of systemic corticosteroids (>20 mg prednisone per day for at least 5 days) in the previous 6 months; OR the patient has developed significant adverse effects whilst on ciclosporin.

b. Patient has been taking high-dose antihistamines (e.g. four times standard dose) and ciclosporin (>3 mg/kg per day) for at least 6 weeks; OR the patient had developed significant adverse effects whilst on corticosteroids or ciclosporin.

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