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Dr. Barnard is a family physician with a special interest in allergy. He obtained his medical degree MB.ChB from the University of Pretoria, South Africa in 1989 and moved to Canada in 1998 where he worked in a rural community as a family physician until 2004. Subsequently, he established a focused practice in allergy in Regina in 2005. He is a member of the European Academy of Allergy and Clinical Immunology. Dr. Barnard is also an Assistant Clinical Professor at the University of Saskatchewan and has served as a consultant on various advisory Boards.

ANTIHISTAMINES IN CSU: PRACTICE POINTS

INTRODUCTION

Urticaria is a mast cell mediated condition characterized by transient, raised, pruritic wheals on an erythematous background, with each individual lesion resolving within 24-48 hours without bruising or scarring. Angioedema (AE) is localized subcutaneous swelling which may occur with urticaria, or independently. Urticaria is classified as acute or chronic depending on the duration. Chronic urticaria is further subdivided into inducible or chronic spontaneous. The focus of this article will be chronic spontaneous urticaria (CSU), which is characterized by wheals and/or swelling occurring spontaneously on most days of the week for 6 weeks or more **(Figure 1)**. The prevalence of chronic urticaria has been estimated to be 0.5–5%. Chronic urticaria is more common in adults, with a peak age of onset between 20 and 40 years, affecting women more frequently than men. In CSU, an external trigger cannot usually be identified.[1]

Current global urticaria consensus guidelines recommend that first line treatment for CSU consists of regular daily use of a second-generation long-acting non-sedating antihistamine at standard dose. If no response or inadequate response is observed in 2-4 weeks or sooner, second line treatment is advised with two, three or four times the standard dose, usually divided in two daily doses. **(Figure 2)** Spontaneous remission of CSU occurs in up to 50% of patients within 6 months or less, but the average duration is 3-5 years.

While disease-modifying drugs are currently not available for CSU, the objective of treatment is to control or suppress symptoms impacting on the patient's quality of life until remission occurs. Due to the chronic nature of the disease and the requirement for continuous treatment for months or years, it is important that therapies used are well-tolerated and without significant long-term morbidity.

SECOND GENERATION (NON-SEDATING) H1 ANTIHISTAMINES

Second generation antihistamines available in Canada include cetirizine, loratadine, desloratadine, fexofenadine, bilastine and rupatadine. Although comparative studies suggest that all second-generation antihistamines may not be equally effective in CSU, there is not sufficient evidence to make strong recommendations for or against any of these antihistamines at the current time.

All the therapies mentioned have proven efficacy in CSU as evidenced by their key registration trials, which include a total of nearly 4,000 patients and all have demonstrated safety and efficacy with no significant adverse effects. Reported levels of somnolence and sedation are consistently comparable with placebo-treated patients and significant improvements in health-related quality of life, work performance and activities of daily living have also been reported. Minor adverse events have been noted in a minority of patients, including headache, drowsiness, constipation, and abdominal pain.[2-25]

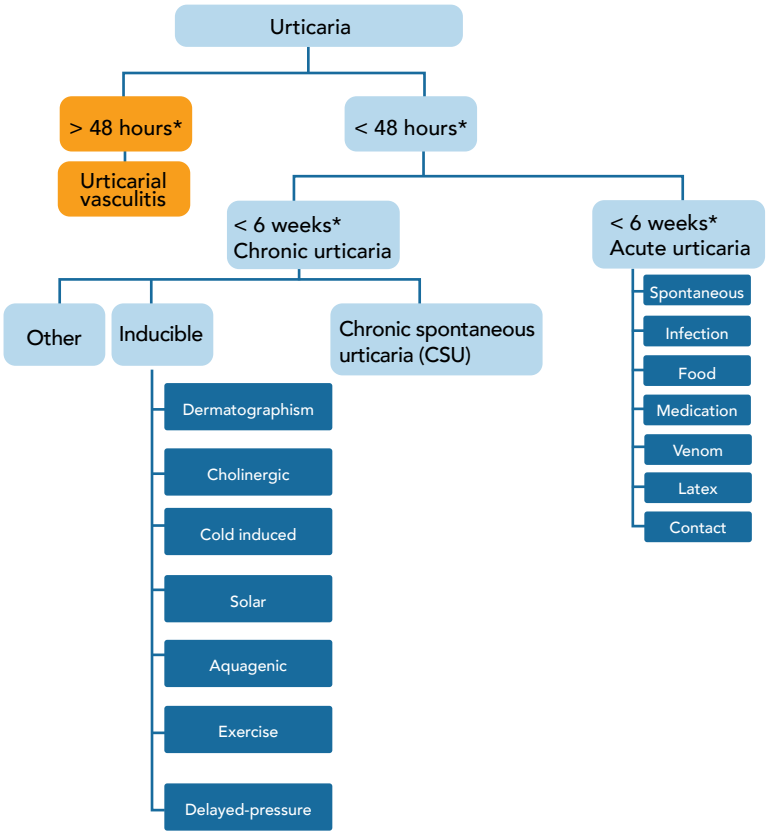

*Figure 1. Classification of urticaria: overview. *The 48-h cut-off refers to individual lesions, while the 6-week cut-off refers to the condition as a whole; adapted from Kanani et al, 2018*

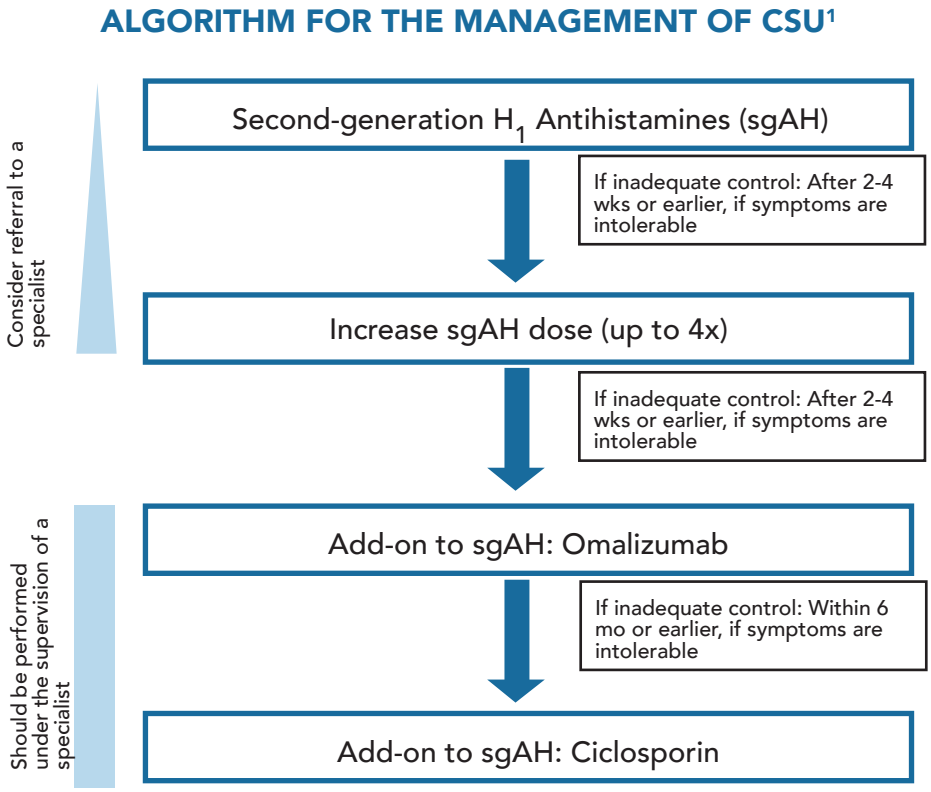

Figure 2. Recommended treatment algorithm for urticaria; adapted from Zuberbeir et al, 2018

Second-generation H1 antihistamines are generally well tolerated by most patients, even at high doses. A recent retrospective analysis examined data from one centre in which antihistamines were up-dosed at doses greater than four times the standard dose. The objective of this study was to investigate the frequency of ineffectiveness of treatment with antihistamines up to fourfold the standard dose in patients with CSU, and to determine the effectiveness and safety of antihistamine treatment above fourfold the standard dose. The investigators reported that of 200 screened patients, 178 were included in the final analysis and that treatment started with a once-daily dose of antihistamines. Persisting symptoms meant that up-dosing up to fourfold occurred in 138 (78%) of patients, yielding sufficient response in 41 (23%). Up-dosing antihistamines was necessary in 110 (80%) patients with weals alone or weals with AE and 28 (64%) with AE only ($p = 0.039$) and side effects after up-dosing higher than fourfold were reported in 10% of patients (6/59).[26] 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.

TREATMENT OF CSU IN PEDIATRIC POPULATIONS

Evidence to date suggest that the prevalence and causes of CSU in the pediatric population are similar to that in adults[35,36] and second-generation long-

	Bilastine[27]	Cetirizine[28]	Desloratadine[29]	Fexofenadine[30]	Loratadine[31]	Rupatadine[32]
Onset of action	1 hour	0.7 hours to suppression of skin wheal and flare[33]	Within 1 hour	1-2 hours[34]	1-3 hours	1-2 hours
Duration of action	24-26 hours	≥24 hours suppression of skin wheal and flare[33]	24 hours	24 hours[34]	≥24 hours	24 hours
Absorption	Rapid	Rapid	Rapid	Rapid	Rapid (Food increases total bioavailability by 48%)	Rapid
Protein binding	84-90%	93%	82-87%	69.4%	97-99% loratadine, 73-76% metabolite	98.5-99%
Metabolism	Minimal (~5% of dose) No induction or inhibition of CYP450	Limited hepatic	Desloratadine is extensively metabolized. The enzyme responsible for the metabolism of desloratadine has not been identified yet.	Metabolism of fexofenadine is negligible. The methyl ester of fexofenadine and MDL 4829 were the only potential metabolites of fexofenadine detected.	Extensively; hepatic via CYP2D6 and 3A4 to active metabolite	Mainly by CYP3A4, to lesser extent by CYP2C9, CYP2C19 and CYP2D6.
Bioavailability	~61%	n/a	n/a	Estimated at ~33%	n/a	n/a
Half-life	~14.5 hours	Children 6.2 hrs, Adults 8 hrs	~27 hours	13-14 hours	7.8-11.0 hours for loratadine; 28 hours for metabolite	Children 2-5 years 15.9 hours; Children 6-11 years 12.3 hours; Adults 4-6 hours; Elderly 8.7 hours
Time to peak	1.3 hours	1.1 hours	~3 hours	~1.5 hours	1.3 hours loratadine, 2.3 hours metabolite	0.75 - 1 hour
% somnolence	4.0%	9.6%	1.9%	1.3%	8.0%	2.0%
Pregnancy Category	N/A	B	C	C	B	B
Excretion	Feces 67% as unchanged bilastine, Urine 28% as unchanged bilastine	Urine 70% (50% as unchanged drug), feces 10%	87% (equally distributed in urine and feces as metabolic products)	~11% urine; 80% feces	Urine 40% and feces 40% as metabolites	Urine 34.6%, Feces 60.9%
Pediatric (<12 y.o.)	Safety not established	Not recommended	Safety not established	Safety not established	Not to be administered to children between 2 and 12 for longer than 14 days	Tablets not recommended > 2 and < 12 y.o.; suspension should be used instead
Geriatric (> 65 y.o.)	No dosage adjustment warranted	Dosage adjustments required	No dosage adjustment warranted	Dosage adjustments required	No dosage adjustment warranted	Limited information on use in 65 y.o. and older

acting antihistamines remain the mainstay of treatment. First-generation antihistamines should be avoided due to the higher incidence of adverse events

TREATMENT OF CSU IN PREGNANCY AND LACTATION

During pregnancy therapeutic agents used to achieve control of symptoms, particularly pruritus should be used sparingly. The majority of patients can be treated during pregnancy and lactation with second-generation H1 antihistamines. There is no data available on the advisability of escalating the currently recommended doses of antihistamines in pregnancy, and careful discussion regarding benefits and risks of available treatment options is advised.

PRACTICE POINTS

- ✓ Second-generation long-acting (non-sedating) antihistamines are used in standard prescribed doses as first-line treatment in patients with CSU
- ✓ Second-generation long-acting (non-sedating) antihistamines are used in two, three or four times the standard dose as second-line treatment in patients with CSU with inadequate response to first-line treatment, often given as a double dose twice daily
- ✓ First-generation sedating antihistamines should not be used for treatment in patients with CSU, due to significant side effects and safety concerns
- ✓ The choice of second-generation H1 antihistamine depends largely on physician preference, taking into account patient preference, previous antihistamine therapy, patient age and underlying conditions such as renal impairment, hepatic impairment, cardiac conditions, and financial considerations
- ✓ 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 quality of life.[37]
- ✓ Patients with CSU who do not respond to second line treatment within 2 weeks, should be referred for evaluation by an allergist or dermatologist

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