



Chronic urticaria: assessment of current treatment

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Chronic urticaria is heterogenous, long-persisting and has a severe impact on quality of life and daily work. Effective treatment is essential but remains a confounding problem. This review summarizes available treatment strategies for chronic urticaria and their strength of evidence. Besides treatment of identified triggering factors such as chronic persistent bacterial infections (e.g., with *Helicobacter pylori*, streptococci, staphylococci or yersinia), standard treatment consists of non-sedating H₁-antihistamines. Most patients require increasing (off-label) dosages that should be taken daily and regularly, however, this still fails in a third of cases. Reliable alternatives in the world literature are rare and the level of evidence is low. Certain subgroups may display benefit from additional treatment with cyclosporine A, cysteinyl leukotriene receptor antagonists, chloroquine, dapsone or other alternatives. A practicable step-wise treatment approach is given to optimize and individualize the treatment of patients with chronic urticaria.

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Chronic urticaria: overview of the disease Definition, epidemiology & pathophysiology

Urticaria is a heterogenous condition. The four main subtypes of urticaria should be clearly differentiated: acute, chronic, physical and a heterogenous group of other types that do not fit in this scheme (e.g., urticaria pigmentosa/mastocytosis, urticaria vasculitis, familial cold urticaria and hereditary or acquired angioedema with C1-INH deficiency) [1–3].

Urticaria is characterized by the occurrence of itchy, short-lived wheals ranging from a few millimeters to several centimeters in diameter anywhere on the skin. They result from the transudation of fluid due to increased vascular permeability. The wheals often appear paler than the surrounding skin due to the compressing effect of the edema on the postcapillary venules. Wheals are mediated by degranulation of mast cells releasing histamine, leukotrienes (LTs), prostaglandins, proteases and cytokines.

The itching can be pricking or burning and is usually worse in the evening or night-time. Typically, the lesions are rubbed and not scratched, therefore, excoriated skin is usually not a consequence of urticaria.

By definition, urticaria is chronic if wheal and flare reactions persist daily, or nearly daily, for at least 6 weeks. Lifelong prevalence is approximately 0.5% and does not vary greatly across the world. There is also evidence for a genetic background of the disease [1].

At least half of patients suffer from concomitant and often life-threatening angioedema, which most typically involves the face, lips, tongue, pharynx, genitalia and extremities [2]. Systemic symptoms such as fatigue, respiratory, gastrointestinal and arthralgic symptoms are rare. Between 15 and 20% of patients have recurrent angioedema without urticaria.

Two (or rarely more) subtypes of urticaria can occur in the same patient (e.g., chronic urticaria [CU], dermatographism or delayed pressure urticaria) [2]. In these cases, urticaria is at its worst [3].

CU usually persists for a long period of time. Less than 50% of patients who consulted a university dermatology department were symptom-free within 10 years [4]. Quality of life is significantly impaired similar to that experienced by patients with severe atopic dermatitis, psoriasis or triple coronary arterial disease [5–7].

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Immunoglobulin (Ig)E-mediated hypersensitivity due to exogenous allergens is very rarely the cause of symptoms in CU and there is no increased frequency of atopy. Nevertheless, many direct and indirect releasing factors may be involved, for example, autoimmune and pseudoallergic mechanisms, infectious diseases (e.g., viral, bacterial, fungal or parasites) and internal diseases/malignancies. It is often overlooked that several of these mechanisms may be active in a single patient.

Details of the autoimmune pathogenesis of CU have recently been reviewed [8,9]. A positive autologous serum skin test (ASST) is indicative for autoreactive mechanisms in CU, however, the clinical relevance remains to be determined (ASST can still be positive if urticarial symptomatology has disappeared).

The number of basophil granulocytes is significantly decreased in CU [10,11] and is negatively correlated with disease activity [12]. This suggests that basophils may be actively recruited from the circulation to the wheals. In autoimmune urticaria, basophil counts are even lower compared with nonautoimmune urticaria [10]. Additional data demonstrated that basophils and mast cells may be activated [13].

The differential diagnosis of CU includes scabies, arthropod reactions, urticarial stages of autoimmune bullous skin diseases, such as bullous pemphigoid, and the early stages of vasculitis and erythema multiforme.

Diagnostic approaches

Diagnostic approaches are based upon a detailed history that considers potential triggering factors, a physical examination including a test for dermatographism, laboratory investigations and, if necessary, additional specific procedures.

Detailed items to define the subtype of urticaria and identify potential related causes have been established within an international consensus [14].

Patient diaries are very helpful to become aware of the fluctuating intensity of the disease. Physical examination should determine number and size of wheals, angioedema and include dermatographism. If physical triggering is suspected, appropriate and standardized physical tests should be performed such as a pressure test with defined weights [15–18]. Standardized scores should be used in treatment trials to evaluate activity of the disease [14,19] and quality of life [5].

If single wheals persist for longer than 24 h, are associated with petechiae, purpura or pigmentation and/or patients present with fever or arthralgias, histologic and immunofluorescence examination of biopsies should exclude vasculitis that may indicate systemic disease such as lupus erythematosus [20].

Routinely, differential count and general inflammatory parameters such as erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) should be determined [14,21].

The authors' results during the last years have revealed a reliable and successful diagnostic program to search for infections, autoreactivity and nonallergic hypersensitivity reactions (pseudoallergies) (BOX 1) [2,22–26].

Box 1. Reliable and successful diagnostic approach in chronic urticaria.

Infections:

- *Helicobacter*: urea breath test or gastroscopy with biopsies and biopsy urease test
- Streptococci: anti-DNAse B, antistreptolysin (throat culture)
- Staphylococci: antistaphylolysin
- *Yersinia*: *Yersinia*-immunoglobulin A and G, and immunoblot

Autoreactivity:

- Autologous serum skin test
- Serum-induced cellular activation (basophil histamine release, CD63 expression or cysteinyl leukotriene production)
- Thyroid autoantibodies and thyroid-stimulating hormone
- Antinuclear antibodies

Nonallergic hypersensitivity

- Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs
- Possibly pseudoallergen-low diet for 4 weeks [27]

The role of persistent, and often subclinical infections (e.g., *Helicobacter pylori*, streptococci, staphylococci and *Yersinia*), has recently been reviewed in detail [22].

A positive ASST may indicate autoimmune/autoreactive urticaria, although several authors recommend a functional cellular activity assay, such as basophil histamine release, for confirmation. In addition, the determination of sulfidoleukotriene *de novo* production in LT suspensions (cellular antigen stimulation test) and flow cytometric CD63 surface expression on basophils are possible [28–30], however, histamine release appears to be more specific. Patients with autoreactive urticaria are more resistant to treatment.

The association between CU and autoimmune thyroiditis is well-established and the determination of thyroid autoantibodies and thyroid-stimulating hormone (TSH) is recommended in women with CU [31–33]. In selected cases, assessment of antinuclear antibodies or other autoantibodies may be advisable to exclude systemic lupus erythematosus or other autoimmune diseases.

A similar approach is useful in childhood CU [22]. Chronic persistent bacterial infections (e.g., streptococci, staphylococci, *H. pylori* and *Yersinia*) are most common [34,35]. Furthermore, positive ASST indicating autoreactivity was found in approximately 30% of children with CU [35,36]. In children and young adults, serology for Epstein–Barr virus and cytomegalovirus should be included in the diagnostic program.

If angioedema are reported principally, the functional activity of the C1-esterase inhibitor should be assessed to exclude deficiency or dysfunction [37]. Angiotensin-converting enzyme

(ACE)-inhibitors and perhaps also angiotensin (AT)II receptor antagonists should be avoided. Angioedema, which are often located in the oropharynx, can occur within several weeks after initiation of treatment or after several years of intake [38].

Recurrent angioedema without wheals may be caused by hereditary or acquired C1-esterase inhibitor deficiency or dysfunction, drugs (particularly ACE inhibitors and ATII receptor antagonists) [39,40], and also persistent infections (e.g., *H. pylori*-associated gastritis or yersiniosis) [41–43].

Available therapeutic approaches

General recommendations

First, every identified triggering factor should be avoided/eradicated. General recommendations include avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, which aggravates urticaria in 20–30% of patients [44]. In the case of angioedema (with or without wheals), avoidance of ACE-inhibitors and ATII receptor blockers is advisable. In addition, alcohol, stress and overheating can induce urticarial episodes. In addition to patient diaries, a good doctor–patient-relationship may be helpful in the management of CU.

Persistent bacterial infections

In the case of an identified infection, targeted eradication should be performed and treatment success carefully examined.

Systematically reviewing existing studies addressing the effect of antibiotic therapy for CU patients infected with *H. pylori* revealed that resolution of urticaria was more likely when antibiotic therapy was successful in the eradication of helicobacter [45]. Eradication of *H. pylori* was both quantitatively and statistically associated with remission of urticaria, with an odds ratio of 2.9 (95% confidence interval: 1.4–6.8; $p = 0.005$) [45].

The authors recommend careful eradication of *H. pylori* in CU for several years [22,23,25,26,46,47]. Several regimens are available, however, even the best fail in approximately 20% of patients. Treatment should start with a triple regimen consisting of a proton pump inhibitor (PPI) twice daily, amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily for 1 week.

In patients who are allergic to amoxicillin, treatment with PPI, metronidazole plus clarithromycin is recommended. After 4–6 weeks following eradication, treatment success should be checked by urea-breath test, given the increasing prevalence of drug-resistant *H. pylori* infections. Patients receiving antibiotics for intercurrent illnesses or prolonged PPI therapy may show a false-negative urea-breath test result. If helicobacter is still present, a second course should be given. Should this also prove insufficient, a second-line quadruple regimen (e.g., PPI twice daily, bismuth 120 mg four-times daily, metronidazole 400 mg three-times daily and tetracycline 500 mg four-times daily) should be used for 10–14 days.

Culture and susceptibility testing are required after a failed second attempt to select a third-line treatment. Reinfection following successful eradication is rare (1% per year), however, some patients become reinfected after 2–3 years.

Helicobacter, however, is not the only triggering factor. Other persistent, chronic, and in most cases, subclinical infections (e.g., streptococci, staphylococci and yersinia), can also be found [22]. Infections with streptococci/staphylococci can be treated, for example, with oral cephalosporins (e.g., cefuroxime 2 × 500 mg daily for 12 days). Persistent yersiniosis can be treated with fluoroquinolones (e.g., ciprofloxacin 2 × 500 mg daily for 10 days) or trimethoprim/sulfamethoxazole 2 × (800 mg/160 mg)/days for 10 days.

Thyroid hormones

A subset of patients with associated thyroid autoimmunity may respond to therapy with TSH, although a controlled study is lacking [33]. Recent unblinded and uncontrolled data suggested an immune stimulatory effect of increasing doses of L-thyroxine until total suppression of TSH levels, which resulted in a significant reduction of the clinical urticaria score after 12 weeks. Randomized controlled trials (RCTs) are needed to clarify, which patients, if any, respond to L-thyroxine [31].

Other therapeutic approaches

Henderson and colleagues addressed the question of which agents were commonly used to treat urticaria in 9.2 million visits to office-based practices between 1990 and 1997 in the USA [48]. This group found that H₁-antihistamines were prescribed in 56% of consultations, systemic corticosteroids in 14% and other drugs in 12%. Interestingly, allergists were least likely to prescribe corticosteroids, whereas internists were the most likely [48]. When addressing alternatives, H₂-antihistamines, β -agonists, doxepin, nifedipine and, interestingly, methotrexate were prescribed.

An Italian study described prescription of antihistamines in 351 patients with CU, with a good response in only 40%. [49]. In this study, 221 patients were treated with other drugs such as steroids, cyclosporin A, cromolyn, LT receptor antagonists and epinephrine.

A systematic review of RCTs in CU was performed using evidence-based medicine criteria [50]. A literature search using MEDLINE and EMBASE, as well as manual hand-searching was performed. Studies that had no English abstract or primarily investigated first-generation antihistamines (e.g., diphenhydramine, hydroxyzine, terfenadine, acrivastine or astemizole) were excluded. First-generation antihistamines were excluded since they display no benefits compared with newer generation antihistamines, but have a higher frequency of side effects such as sedation and anticholinergic effects. Studies were rated depending on criteria of the Scottish Intercollegiate Guidelines Network (SIGN) 50 Methodology Checklist 2 for RCTs (++ , + , -). This result, together with the study type, defined the level of evidence (1++ , 1+ , 1- , 2++ , 2+ , 2- , 3 , 4). The rating of all published RCTs collectively led to the Grade of Recommendation (A, B, C or D) [201].

In the treatment of CU, the best evidence exists for non-sedating H₁-antihistamines such as azelastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine and mizolastine (TABLE 1). The quality of these RCTs is high and the number of patients that received verum varied from 11 to approximately 350.

Table 1. Randomized controlled trials: nonsedating H₁ antihistamines .

Drug*	Daily dose (mg)	Duration	n drug (n PL) [‡]	Study design	p < 0.05 vs. PL	Compared drug, daily dosage (n)	p < 0.05 vs. compared drug	Remarks	Ref.
AZ	4	2 weeks	69 (28)	DB PC COMP	Yes	CET 10 mg (21)	No	Pruritus: AZ > CET; Whealing: CET > AZ	[87]
AZ	4	3 weeks	17 (18)	DB PC MC COMP	Yes	Ebastine 10 mg (17)	No		[88]
CET	10–20	15 days	30	DB CRO	Yes	NA	No	Patients with AOE were excluded	[89]
CET	5–20	4 weeks	60 (68)	DB PC MC	Yes	Hydroxyzine 25–75 mg (60)	No		[90]
CET	10	4 weeks	19	DB COMP	NA	Astemizole 10 mg (17)	Yes	Wheal AS: CET > AST (0.04)	[91]
CET	10	1 week	28	DB PC CRO	Yes	NA	NA		[92]
CET	10	15 days	30	DB PC CRO	Yes	NA	NA	CRO phase in n = 6 with CET 10 vs. 20 mg	[93]
CET	10	20 days	15	DB COMP	NA	TERF 2 × 60 mg (15)	Yes	CET > TERF	[94]
CET	10	2 weeks	64	DB PC COMP	Yes	TERF 2 × 60 mg (64)	No (efficacy), yes (side effects)	TERF caused fewer side effects	[95]
CET	10	4 weeks	62	DB PC MC COMP	Yes	Astemizole 10 mg (62)	No	CET acted more rapidly	[96]
CET	10	4 weeks	62	DB PC MC COMP	Yes	Hydroxyzine 3 × 25 mg (62)	Yes: after 1 day, no: day 2 until study endpoint		[97]
CET	5	4 weeks	28	DB MC COMP (children 2–6 years)	NA	Oxatomide 25 mg (29)	No	Children with angioedema were excluded	[98]
CET	10	4 weeks	52	DB COMP	NA	FEXO 180 mg (45)	Yes		[99]
Desloratadine	5	6 weeks	95 (94)	DB PC MC	Yes	Na	NA		[100]
Desloratadine	5	6 weeks	97 (75)	DB PC MC	Yes	NA	NA		[101]
Ebastine	10	2 weeks	102 (102)	DB PC MC	Yes	NA	NA		[102]
Ebastine	10	12 weeks	69 (64)	DB PC MC COMP	Yes	TERF 2 × 60 mg (78)	No		[103]
FEXO	20, 60, 120 or 240	4 weeks	349 (90)	DB PC MC	Yes	NA	NA	FEXO 60 (n = 86) = 120 (n = 89) = 240 (n = 83) > 20 mg (n = 91)	[104]
FEXO	20, 60, 120 or 240	4 weeks	418 in 5 groups	DB PC MC	Yes	NA	NA	FEXO 60 = 120 = 240 > 20mg	[105]
FEXO	2 × 60	4 weeks	169 (148)	DB PC MC	Yes	NA	NA		[106]

*Studies were arranged alphabetically by drug name and by year of publication.

[‡]If available, the number of patients that completed the trial were used.

AOE: Angioedema; AZ: Azelastine; CET: Cetirizine; COMP: Comparison; CRO: Crossover (duration given is for one drug); DB: Double-blind; FEXO: Fexofenadine; MC: Multicenter; NA: Not applicable; PC: Placebo-controlled; PL: Placebo; TERF: Terfenadine.

Table 1. Randomized controlled trials: nonsedating H₁ antihistamines (cont.).

Drug*	Daily dose (mg)	Duration	n drug (n PL) [‡]	Study design	p < 0.05 vs. PL	Compared drug, daily dosage (n)	p < 0.05 vs. compared drug	Remarks	Ref.
FEXO	2 × 10, 2 × 60 or 2 × 120	1 week	226	DB dose-finding	NA	NA	Yes (compared with FEXO 2 × 10 mg)	FEXO 2 × 60 (n = 75) and 2 × 120 (n = 76) > 2 × 10 mg (n = 75)	[107]
FEXO	180	3 weeks	11	DB PC	Yes	NA	NA		[108]
Levocetirizine	2.5, 5 or 10	4 weeks	194 (63)	DB PC MC	Yes	NA	NA	Benefit and somnolence with increasing dose	[109]
Levocetirizine	5	4 weeks	166	DB PC MC	Yes	NA	NA		[109]
Loratadine	10	4 weeks		DB PC COMP	Yes	TERF 2 × 60 mg	Clinically more effective		[110]
Loratadine	10	4 weeks	67	DB PC MC COMP	Yes	Hydroxyzine 3 × 25 mg (67)	No		[111]
Loratadine	10		20	DB PC COMP	Yes	Hydroxyzine 3 × 25 mg (20)	No		[112]
Mizolastine	10	4 weeks	28	DB PC MC	Yes	NA	NA		[113]
Mizolastine	10	4 weeks	88	DB PC MC COMP	Yes	Loratadine 10 mg (79)	No	No difference with respect to AOE	[114]
Mizolastine	10	4 weeks	39	DB PC MC	Yes	NA	NA		[115]
Mizolastine	10	4 weeks	26	DB COMP	NA	Loratadine 10 mg (35)	No	Mizolastine had a better reduction of AOE and of the mean total duration of episodes	[116]

*Studies were arranged alphabetically by drug name and by year of publication.

[‡]If available, the number of patients that completed the trial were used.

AOE: Angioedema; AZ: Azelastine; CET: Cetirizine; COMP: Comparison; CRO: Crossover (duration given is for one drug); DB: Double-blind; FEXO: Fexofenadine; MC: Multicenter; NA: Not applicable; PC: Placebo-controlled; PL: Placebo; TERF: Terfenadine.

Taken together from an evidence-based view, nonsedating H₁-antihistamines can be recommended with evidence-level 1++ and Grade A recommendation. However, it should be considered that most of these studies included only patients with mild-to-moderate urticaria since patients with severe disease were not able to come through the washout phase before study enrollment. In addition, most, if not all, clinical studies were sponsored by pharmaceutical companies. High quality RCTs comparing nonsedating H₁-antihistamines are not available and from the existing evidence it appears that differences are rather small if ever existing. However, from clinical experience it is well-known that nonresponders with one nonsedating antihistamine may respond favourably to another. Urticaria experts often use increased dosage and this is clearly needed in most patients with CU. However, RCTs addressing this point in CU are missing. Higher doses (off-label use) may lead to increased side effects, although this finding has also not been well studied.

Four low-level evidence RCTs of the H₂-antagonist cimetidine in combination with sedating H₁-antagonists (hydroxyzine or chlorpheniramine) involving 15–20 patients receiving

verum are available for CU with inconsistent results [51–54]. The questionable synergism between H₁- and H₂-antagonists may be caused by a pharmacokinetic effect, (i.e., increased blood levels of the sedating H₁-antagonist due to the H₂-antagonist) [55]. This effect could not be shown for coadministration of cimetidine with cetirizine or ebastine. Thus, there appears to be no therapeutic rationale for coadministration of nonsedating H₁-antihistamines with H₂-antagonists [55]. RCTs that combined H₂-antagonists with nonsedating H₁-antagonists in CU do not exist. Therefore, the addition of H₂-antagonists is not recommended, however, they may be attempted in single cases.

Available data for LT receptor antagonists are inconsistent and difficult to compare, as shown in TABLE 2 [56–61]. Within seven published RCTs, a total of 15–48 patients, respectively, received verum. These drugs may be of benefit in subgroups of patients with CU that have a positive ASST and/or suffer from aspirin and/or food additive intolerance. The clinical but unproven observation is of benefit to patients with angioedema.

Table 2. Randomized controlled trials: leukotriene antagonists.

Drug*	Daily dose (mg)	Duration (weeks)	n active drug (n PL) [‡]	Study design	p < 0.05 vs. PL	Compared drug, daily dosage (n)	p < 0.05 vs. compared drug	Remarks	Ref.
Montelukast	10	4	17	DB PC COMP	Yes	CET 10 mg (17)	Yes	Patients had positive challenge test with aspirin and/or additives; montelukast significantly increased the percentage of symptom-free days; urticaria scores decreased (0.001 vs. CET or vs. placebo), interference with sleep decreased (0.001), median number of days without rescue medication increased (0.001 vs. CET or vs. placebo)	[117]
Montelukast	10	4	15	DB COMP	NA	FEXO 180 mg (12)	Yes?	Text: the TSS of the FEXO-treated patients was on average, worse than of the montelukast-treated patients (<0.005). ? The figure in the publication shows the opposite!	[118]
Montelukast	10 (CET 10 on demand, also in placebo group)	6	30	SB PC CRO	Yes	NA	NA	2-week washout period between CRO	[59]
Montelukast	10 + DLOR 5	6	26 (25)	DB PC	Yes	DLor 5 mg (25)	Yes: wheal number, pruritus, no: number of urticarial episodes	1 week placebo run-in, 1 week placebo-washout phase	[58]
Montelukast	10 + DLOR 5	6	40 (40)	DB PC DD	Yes	Dlor 5 mg (40)	No	ASST ⁺ , patients intolerant to ASA and additives were excluded, patients had rare angioedema	[57]
ZFLK	2 × 20	6	46	DB PC CRO	No	NA	NA	No subgroup with benefit could be identified	[60]
ZFLK	2 × 20 (plus CET 10, also in placebo group; diphenhydramine 25–50 as rescue medicine)	3	48 (47)	DB PC MC	Yes	NA	NA	Only patients resistant to prior run-in phase with CET 10 mg/day were randomized; only ASST ⁺ CU refractory to H ₁ -AH monotherapy showed benefit from the addition of ZFLK to CET	[119]

*Studies were arranged by year of publication.

[‡]If available, the number of patients that completed the trial were used.

AH: Antihistamine; ASST: Autologous serum skin test; CET: Cetirizine; COMP: Comparison; CRO: Crossover (duration given is for one drug); DD: Double dummy; DB: Double-blind; FEXO: Fexofenadine; MC: Multicenter; NA: Not applicable; PC: Placebo-controlled; PL: Placebo; SB: Single blind; TSS: Total symptom score; ZFLK: Zafirlukast.

Antidepressants (doxepin), mast cell stabilizers (ketotifen, oxatomide), calcium channel blockers (nifedipine) and sympathomimetic agents (terbutaline) have been investigated in RCTs with variable results (all Grade D recommendation) (TABLE 3). The number of patients included varied between seven (nifedipine) and 151 (ketotifen) (TABLE 3). Given the high rate of side effects and limited clinical benefit, these agents cannot be generally recommended. Treatment with tranexamic acid or cromolyn were ineffective in single RCTs (TABLE 4) [62,63].

Low-evidence RCTs exist for other alternatives such as warfarin or stanazolol (TABLE 4). For several drugs, such as dapsone [64], sulfasalazine [65,66], tacrolimus [67], methotrexate [68], cyclophosphamide [69], interferon [70], coxibs [71,72], plasmapheresis [73] and intravenous Igs [74–77], RCTs do not exist. Evidence is based on case series or single-case reports, or uncontrolled, open-label trials. Furthermore, some drugs have only (e.g., colchicine [78]) or preferentially (e.g., dapsone or sulfasalazine) been used in different entities, such as hypocomplementemic urticaria vasculitis syndrome or urticaria vasculitis. In MEDLINE and EMBASE, there is no study addressing the efficacy of corticosteroids in CU, however, corticosteroids are widely used. Sometimes corticosteroids are needed for example to achieve rapid control to cover social or occupational events but it is agreed that prolonged daily treatment should be clearly avoided due to severe side effects. A careful risk–benefit profile should be performed, the most effective, lowest dose should be used (single patients fit well with 5 mg prednisolone equivalent every day or every other day).

Cyclosporine A may be a valuable alternative in severely affected patients, although potential side effects must be considered. Grattan and colleagues investigated a dose of 4 mg/kg per day in combination with a doubled dose of cetirizine in ASST positive patients (TABLE 4) [79]. This study is a well-designed RCT (Grade C recommendation) and the data are confirmed by unblinded and uncontrolled studies. For example, an unblinded study by Baskan and colleagues also included ASST positive patients and used the same dose, however, their aim was to compare 4- versus 12-week treatment [80]. The unblinded and uncontrolled study by Toubi investigated the effect of low-dose cyclosporin [81]. This group stated that the efficacy of cyclosporin was independent of ASST reactivity. Nevertheless, all these studies included very few patients.

In the authors experience, long-term treatment with dapsone (100 mg/day, 6 days per week for 3–9 months) and particularly chloroquine (250 mg chloroquine phosphate/day for 3–9 months) are effective in patients with autoimmune urticaria in addition to nonsedating antihistamines [25,46,UNPUBLISHED OBSERVATIONS]. Several years ago, the authors found significant *in vitro* inhibitory effects of chloroquine and dapsone on serum activity of ASST-positive patients [30]. Both drugs inhibited histamine release, basophil CD63 expression and LT *de novo* production that

was induced by ASST-positive CU sera. The benefit of chloroquine may also be confirmed by an Australian open-label study [82] and a recent randomized placebo-controlled trial [83], however, both studies have several flaws.

Optimal therapy

The goal is to maximize quality of life and the ability to work or attend school, and to minimize drug-related side effects such as sedation.

Therefore, symptomatic treatment with (increased off-label dosage) nonsedating H₁-antihistamines is the mainstay of initial treatment. Sedating H₁-antihistamines have no benefit but a significantly higher incidence of side effects, and are therefore not recommended [50]. The sedative effects, however, are beneficial (e.g., to prevent awakening at night). Nevertheless, antihistamines are insufficient in severely affected patients even at increased dosage.

In the case of an identified infection, targeted eradication should be performed and carefully examined to elucidate whether eradication was successful. Adequate care should be taken to identify infection with *H. pylori*.

The addition of LT antagonists to nonsedating H₁-antagonists may be worthy of further research in patients with ASST reactivity and/or aspirin/food additive intolerance. If not contraindicated in at least severely affected patients with positive ASST, cyclosporin A can be given, however, after withdrawal relapses are possible.

The incidence of side effects using corticosteroids is substantial and no RCTs are available. Therefore, prolonged treatment with corticosteroids should be clearly avoided and any corticosteroid-sparing manoeuvre is worth seeking.

A practicable approach for the treatment based upon the authors' year-long clinical and experimental experience in the management of more than 1500 patients with CU, and on the results of the evidence-based literature review, is listed in TABLE 5.

Factors influencing choice of therapy

Interactions/adverse effects

Second-generation antihistamines are generally well-tolerated. Treatment withdrawal due to adverse effects is required in less than 3% of treated patients. Nevertheless, one concern regarding the use of antihistamines, particularly in a higher dose range, is sedation and impairment of performance. Another concern is serum accumulation of some antihistamines that are metabolized by hepatic cytochrome (CYP3A4). The concomitant administration of macrolide antibiotics (e.g., clarithromycin within triple treatment for helicobacter) and imidazole antifungals can, in particular, produce QTc prolongation that may result in life-threatening cardiac arrhythmia (torsade de pointes). This has been reviewed in detail elsewhere [84,85]. In hepatic or renal impairment, dosages of some antihistamines must be adjusted.

Corticosteroids should be avoided in diabetes, glaucoma, osteoporosis, ulcer disease and obesity. If cyclosporin A is given, blood pressure, blood urea nitrogen, creatinin

Table 3. Randomized controlled trials: antidepressants, mast cell stabilizers, calcium channel blockers and sympathomimetic agents.

Drug	Daily dose (mg)	Duration (weeks)	n active drug (n PL) [‡]	Study design [§]	p < 0.05 vs. PL	Compared drug, daily dosage (n) [¶]	p < 0.05 vs. compared drug	Remarks	Ref.
<i>Tricyclic antidepressants</i>									
Doxepin	3 × 10	4	50	DB CRO	NA	Diphenhydramine 3 × 25 mg	Yes	*	[120]
Doxepin	2 × 5	2	24	DP PC CRO	Yes	Mequitazine 2 × 5 mg	No		[121]
Doxepin	3 × 25	4	16	DB PC CRO	Yes	NA	NA		[122]
<i>Mast cell stabilizers</i>									
Cromolyn	4 × 200	4	15	DB PC CRO	No	NA	NA		[123]
Oxatomide	2 × 30	5	18	DB PC	Yes	NA	NA		[124]
Oxatomide	2 × 30	5	13	DB COMP	NA	Mequitazine 2 × 5 mg (13)	Yes	‡	[125]
Oxatomide	2 × 30	6	15	DB COMP	NA	Clemastine 2 × 1 mg (15)	No	§	[126]
Ketotifen	2 × 1	2	151 (137)	DB MC COMP	NA	Clemastine 2 × 1 mg (152)	Yes	¶	[127]
<i>Calcium channel blockers</i>									
Nifedipine	Titration study drug dosage 2 × 10 to 3 × 20 (AH was allowed, also in placebo group)	4	7	DB PC CRO	Yes	NA	NA		[128]
<i>Sympathomimetic agents</i>									
Terbutaline	3 × 2.5	2	9	DB PC	No	NA	NA		[129]
Terbutaline	4 × 2.5 (plus hydroxyzine 4 × 25, also in placebo group)	7–10 days	19	DB PC COMP	No				[130]

*Patients included (1) urticaria simplex, (2) lymphocytic urticaria, and (3) leukocytoclastic urticaria. Patients with urticaria simplex had a more favorable response to doxepin than the two other groups.

‡In the 13 oxatomide-treated patients, papules, erythema and pruritus were significantly suppressed after 2 weeks, which was markedly more rapid than with mequitazine.

§If the effect was insufficient, the dose of oxatomide or clemastine could be increased to four capsules daily. A total of 5 mg cinnarizin was allowed every 4 h. Oxatomide and clemastine displayed the same efficacy.

¶Ketotifen alleviated eruption and itching to a significantly greater extent than clemastine. The utility rating of ketotifen was significantly higher than that of clemastine.

‡If available, the number of patients that completed the trial were used.

AH: Antihistamine; DB: Double-blind; COMP: Comparison; CRO: Crossover (duration given is for one drug); NA: Not applicable; PC: Placebo-controlled; PL: Placebo.

measurement and lipids should be performed regularly. Cyclosporin is contraindicated in patients with a history of cancer, a positive cervical smear or renal impairment.

The risk–benefit profile of every alternative drug should be carefully considered before off-label prescription in CU. This is particularly true for immunosuppressive drugs.

Cell infiltrate

In antihistamine-resistant CU, one might prefer certain drugs depending on the type of the cutaneous inflammatory cell infiltrate. For example, dapsone may be of more benefit if neutrophils or eosinophils predominate whereas corticosteroids or cyclosporin A may be preferred if a lymphocytic infiltrate is found.

Table 4. Randomized controlled trials: miscellaneous agents.

Drug [*]	Daily dose	Duration (weeks)	n active drug (n PL) [‡]	Study design	p < 0.05 vs. PL	Compared drug, daily dosage (n)	p < 0.05 vs. compared drug	Remarks	Ref.
Tranexamic acid (cyklokapron)	3 × 1 g	4 for each drug (1 week washout)	17	DB PC CRO	No	NA	NA	NA	[131]
Cinnarizine (antihistamine and inhibitor of complement activation)	3 × 10 mg	4	23	DB PC CRO	Yes	Dexchlorpheniramine	No	NA	[132]
Cyclosporin A	4 mg kg ⁻¹ (plus cetirizine 20 mg/day, also in PL group)	4	19 (10)	DB PC	Yes	NA	NA	NA	[133]
Warfarin	Individual dose, aim: INR between 2.0–2.5	3 months	3	DB PC CRO	Yes	NA	NA	1 [§]	[134]
Stanazolol	2 × 2 mg plus cetirizine 10 mg/day, also in PL group)	12	26 (25)	DB PC	Yes	NA	NA	NA	[135]
Hydroxychloroquine	200 mg plus symptomatic urticarial therapy (corticosteroids, H ₂ -AH, H ₁ -AH, doxepin)	12	9 (9)	DB PC	Yes	NA	NA	NA	[83]

^{*}Studies were arranged by year of publication and drug.

[‡]If available, the number of patients that completed the trial were used.

[§]Prior open study: Six out of eight antihistamine resistant patients responded to warfarin: two patients with complete remission, two with temporary relief, two did not respond; three of them (all ASST negative) with dramatic response were included in the DB PC study: one patient was symptom-free for 2 months, one for 3 weeks.

AH: Antihistamine; ASST: Autologous serum skin test; DB: Double-blind; CRO: Crossover (duration given is for one drug); INR: International normalized ratio;

NA: Not applicable; PC: Placebo-controlled; PL: Placebo.

Pregnancy & lactation

Although some antihistamines are listed on the US Food and Drug Administration (FDA) pregnancy category B (cetirizine, loratadine) or C (fexofenadine, desloratadine, azelastine) list, it is best to avoid all antihistamines in pregnancy, especially during the first trimester.

It is suggested that sedating antihistamines, such as brompheniramine, chlorpheniramine, diphenhydramine and clemastine fumarate (all FDA category B), may be used due to their greater longevity and clinical experience in pregnancy. However, safety concerns linger with some of these agents. Second-generation antihistamines are not well-studied in breast-feeding. Fexofenadine and loratadine (and by implication desloratadine) appear to be compatible with breast-feeding [84].

Children

Among the second-generation antihistamines in Germany, desloratadine has approved indications down to the age of 1 year,

cetirizine, levocetirizine and loratadine down to 2 years of age, and fexofenadine (30 mg) and azelastine down to 6 years of age, ebastine and mizolastine down to the age of 12 years. Among the first-generation antihistamines in Germany, dimetindene and clemastine fumarate have been approved down to 1 year of age, doxylamine succinate down to 2 years, and hydroxyzine down to 6 years. The sedating mast cell stabilizer ketotifen can be given from 6 months. Cetirizine has FDA approval down to 6 months.

Older sedating antihistamines may result in paradoxical CNS stimulation in children and, therefore, newer antihistamines should be preferred.

Summary & conclusions

Flawless studies investigating therapeutic approaches in CU are rare and difficult to compare. From an evidence-based view, only nonsedating H₁-antihistamines are Grade A recommendations. However, even at an increased dosage, approximately a third of patients are insufficiently treated. All other

Table 5. Step-wise approach for the treatment of chronic urticaria.

Line	Recommended treatment	May be of particular benefit in patients with	Consider
First	A. Nonsedating H ₁ -receptor antagonists daily (consider increasing dose up to fourfold)		A. Choose antihistamine depending on the drug risk regarding sedation, metabolism via CYP450, QTc-interval prolongation or weight gain
	B. Adequate treatment of identified triggering factors (e.g., triple therapy for <i>Helicobacter</i> , antibiotics for streptococci, staphylococci or yersinia or L-thyroxine if evidence of thyroid autoimmunity)		B. Control success of treatment
	C. Avoid overheating, tight clothing, alcohol, aspirin, NSAR, ACE-inhibitors and ATII antagonists)		
	D. Reassure patient about the benign nature of the condition and the difficulties in treatment		
	E. Topical treatment (2% menthol or 2% polidocanol in aqueous cream or lotion) is optional	E. Efficacy is questionable	E. Avoid topical treatment with risk of sensitization (e.g., topical antihistamines)
Second	1. Try different nonsedating H ₁ -receptor antagonists and/or		
	2. Addition of leukotriene antagonist	2. NSAR/food additive intolerance Positive ASST	
Third	Consider nonstandard therapies:		
	1. (Hydroxy-)chloroquine	1. Positive ASST	1. Retinopathy, G6PDH deficiency, hepatic/renal disease
	2. Dapsone	2. Positive ASST, granulocytic urticarial infiltrate, pressure-associated wheals	2. G6PDH deficiency, anemia, liver disease, sulfonamide hypersensitivity
	3. Oral corticosteroids if titratable to an effective dose of less than 10 mg prednisolone equivalent (every day or every other day)	3. Lymphocytic urticarial infiltrate, pressure-associated wheals	3. Long-term steroid toxicity, diabetes, glaucoma, osteoporosis, ulcer disease, obesity
	4. Cyclosporin A	4. Positive ASST	4. Renal toxicity, hypertension, immunosuppression, elevation of lipids
	Consider other nonstandard therapies:		
	5.1 Doxepin	5.1 Agitated depression	5.1 Sedation, dry mouth or constipation
	5.2 Oxatomide		5.2 Sedation
	5.3 Ketotifen		5.3 Sedation, weight gain, male impotence
	5.4 Sulfasalazine	5.4 M. Crohn, rheumatoid arthritis	5.4 Sulfa hypersensitivity
	5.5 IVIG, plasmapheresis	5.5 Positive ASST	5.5 Costs, temporary effect
	5.6 Interferon α		5.6 Flu-like symptoms, leukopenia
	5.7 Methotrexate	5.7 Delayed-pressure urticaria	5.7 Bone marrow and liver toxicity, lung fibrosis, ulcer
	5.8 Cyclophosphamide		5.8 Immunosuppression, bone marrow toxicity, cystitis
	5.9 Colchicine		5.9 Toxicity
	5.10 Warfarin	5.10 Urticaria with angioedema	5.10 Bleeding, haemorrhage
	5.11 Stanozolol		5.11 Androgenic effects, hepatic disturbances
	5.12 Coxibs	5.12 Arthritis, pain	5.12 Cardiotoxicity

ACE: Angiotensin-converting enzyme; ASST: Autologous serum skin test; AT: Angiotensin; IVIG: Intravenous immunoglobulin; NSAR: Nonsteroidal antiinflammatories.

alternatives have a Grade C to D recommendation. It should also be remembered that most of these studies included a maximum of 20 patients that received verum. Evidence suggests that certain subgroups (i.e., patients with intolerance to aspirin/additives and/or positive ASST) may benefit from additional treatment with cysteinyl LT antagonists. Taken together, there is still a tremendous need to perform RCTs with potential alternatives and to develop better agents for this condition. Several questions must be addressed in the future and there is hope that during the next few years new therapeutic strategies will be developed to facilitate the management of this long-lasting and life-quality restricting disease.

Expert commentary & five-year view

Based upon the authors year-long experience in the management of more than 1500 patients with CU, and the available literature, the authors propose a treatment approach for CU (TABLE 5). Due to their apparently good safety profile, immunomodulating alternatives, such as (hydroxy-)chloroquine and dapsone, may be worthy of further investigation within well-designed RCTs in all types of CU.

In the future, new agents may be found that act more specifically and are more effective in the treatment of CU. For example, specific targeting of the autoantibodies to the IgE receptor may be promising for the subgroup with autoreactivity.

Future studies should also aim to clarify the abnormal reactivity of patients with CU to subclinical persistent infections and NSAID, the role of basopenia, basophil activation and autoreactivity.

To the best of the authors knowledge, there are no new treatment strategies currently under investigation with respect to CU. There are RCTs investigating new antihistamines such as olopatadine and emedastine difumarate. However, given the small clinical differences among current nonsedating antihistamines in the treatment of CU, there is little hope that these drugs are more promising. This is also the case for α -fluoromethylhistidine. This irreversible inhibitor of mammalian histidine decarboxylase has already been investigated more than 15 years ago, for example, in cold urticaria [86], and is unlikely to become a cornerstone in the treatment of CU.

There is clearly a need to develop better and more specific agents for CU. Furthermore, multicenter RCTs using older drugs, such as chloroquine or dapsone, should be encouraged, and it would be prudent to investigate increased dosage of nonsedating H₁-antihistamines including side effects. Although difficult to perform, these RCTs should include best characterized patients and attempt to minimize bias by carefully addressing critical points of internal validity.

Key issues

- The etiology of chronic urticaria is heterogenous and involves persistent, subclinical bacterial infections, nonallergic hypersensitivity reactions and autoreactivity.
- Nonspecific trigger factors should be avoided, for example, aspirin/other nonsteroidal anti-inflammatory drugs, alcohol, overheating and angiotensin-converting enzyme inhibitors in the case of angioedema.
- Specific and sufficient treatment of identified persistent bacterial infections can result in complete remission. Therefore, the diagnostic workup should include a search for *Helicobacter pylori*, streptococci, staphylococci and yersinia.
- Second-generation antihistamines are first-line drugs for symptomatic treatment (often off-label dosage is needed).
- Flawless studies investigating alternatives in chronic urticaria are rare.
- Subgroups (i.e., with positive autologous serum skin test, and/or intolerance to aspirin/food additives) may benefit from the addition of leukotriene antagonists.
- Severely affected patients may be treated with cyclosporin A.
- Chloroquine and dapsone may be worthy of further investigation within randomized controlled trials.
- There is a tremendous need for new and more specific alternative treatment strategies in chronic urticaria.

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