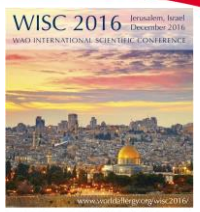
Session: WISC 2016 Symposium - Advances in the Evaluation and Management of Chronic Urticaria and Angioedema

Saturday, 17 October 2015: 01:30 PM - 03:00 PM, Coex Convention Center, Room 203 A & B (Floor 2)



Urticaria Guidelines: Consensus and Controversies in the European and American Guidelines

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Conflict of Interests

- Author of urticaria and angioedema practice parameters
- Principal Investigator Shire/Viropharma, CSL Behring, Dyax, Salix, Biocryst, Novartis and Genentech
- Consultant and Speaker Shire/Viropharma, CSL Behring, Dyax, Salix, Novartis and Genentech
- AAAAI BOD

Learning Objectives

- Discuss similarities between US and European chronic urticaria/angioedema guidelines (The Good)
- Describe differences between the two guidelines (The Bad)
- Define controversial areas that require further investigation between the two guidelines (The Ugly)

Learning Materials

- **The EAACI/GA(2) EN/EDF/WAO Guideline for the definition, classification, diagnosis, and management ofurticaria: the 2013 revision and update.**
  - **Grade system**
- **The diagnosis and management of acute and chronic urticaria: 2014 update**
  - **Category and Strength of Evidence**

Zuberbier T, et al. Allergy. 2014;69(7):868-87
Bernstein JA, et al. J Allergy Clin Immunol. 2014;133(5):1270-7.

Comparison between Urticaria Guidelines

	EAACI	Practice Parameters JTFPP
Terminology	Intermittent, spontaneous, Inducible	Acute, physical
Objective assessment and QOL	UAS-7 CU-Q2oL	Objective assessment recommended; QOL instrument not discussed
ASST/ASFT or serologic assays	Recommended	Not recommended
First generation antihistamines	Not recommended	Recommended second and third steps
LTRA	Recommended third step	Recommended second step
Anti-H2 antihistamines	Not recommended	Recommended second step
Alternative Therapies	Omalizumab and Cicloporin	Hydroxychloroquine, Sulfasalazine, Dapsone, Colchicine, Omalizumab, Cyclosporine
Pseudoallergen-free diet	Recommended[1,2]	Not recommended[3]
AIGT	Recommended	Not recommended
Evaluation and Treatment for H. pylori infection	Recommended	Not recommended
Systemic corticosteroids for exacerbations	Up to 10 days at all times	1-3 weeks at all times
Other alternative therapies	Low levels of evidence	Low levels of evidence

Terminology

- There are differences in terminology related to describing hives.
  - The EAACI/WAO document uses the terms "intermittent" and "spontaneous"
  - The EAACI/WAO uses the term "Inducible" to describe physical stimuli causing urticaria (i.e., cold, pressure, exercise, UV light, heat, vibration, water)

  vs.
  - The JTF practice parameter uses the terms "continuous" and "intermittent" to describe the variable nature of hives.
  - The JTF PP uses the term "physical" to describe hives caused by physical triggers

Urticaria Activity and Quality of Life Instruments

- The EAACI/WAO guidelines addresses objective specific ways of quantifying urticaria and quality of life
  - Advocate the urticaria activity score (UAS), a validated scoring system for hives, for clinical use
  - Rates severity of pruritus and wheals to create a score ranging from 0 to 6. This score can be summed over 24 h for 7 consecutive days to create the UAS7 for that patient (possible total score of 0–42).
  - This score was recently used as a primary or secondary endpoint in recent omalizumab treatment of chronic urticaria (CU) unresponsive to H1 antihistamines trials
  - Also advocate the CU-Q2oL is a quality of life instrument, validated in multiple languages, which is available for assessing the severity of chronic urticaria quality of life impairment
- The 2014 JTF practice parameter does not specifically address quality of life or assessment of impairment in quality of life in urticaria
  - It does recommend obtaining objective measurements that quantify the severity of itch (itch severity score - ISS) and the percentage of the body covered in hives at any given time (visual analog scale - VAS) in order to assess severity of hives and response to treatment every visit

Zuberbier T, et al. Allergy. 2014;69(7):868-87.
Bernstein JA, et al. JACI. 2014;133(5):1270-7.

Table I Assessment of disease activity in urticaria patients (UAS7 [4, 17])

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 h 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 (Sum scores over 7 days for UAS7)

Zuberbier T, et.al. Allergy. 2014;69(7):868-87.

Clinical Evaluation

- Both guidelines recommend a limited work up for chronic urticaria as a cause is seldom found
  - CBC with, WSR, CRP and elimination of potential underlying causes
  - Additional testing such as TSH and LFTs may be also appropriate
  - There is latitude for additional testing if there is clinical suspicion for an underlying cause
  - Routine assessment for Helicobacter pylori is not recommended by either guideline
  - Neither recommend routine skin testing to aeroallergens or foods

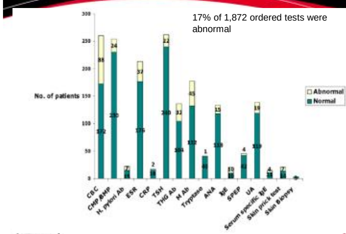
Summary Statement 25: For patients with CU who present with an otherwise unremarkable history and physical examination findings, skin or in vitro testing for IgE to inhalants or foods and/or extensive laboratory testing are not recommended because such testing is not cost-effective and does not lead to improved patient care outcomes. (C) Targeted laboratory testing based on history or physical examination findings is appropriate, and limited laboratory testing can be obtained. (E)

Should routine diagnostic measures be performed in acute urticaria?
We recommend against any routine diagnostic measures in acute urticaria (strong recommendation/clinical consensus).

Should routine diagnostic measures be performed in chronic spontaneous urticaria?
We recommend for only very limited routine diagnostic measures in chronic spontaneous urticaria (strong recommendation/clinical consensus).

Zuberbier T, et.al. Allergy. 2014;69(7):868-87.
Bernstein JA, et.al. J Allergy Clin Immunol. 2014;133(5):1270-7.

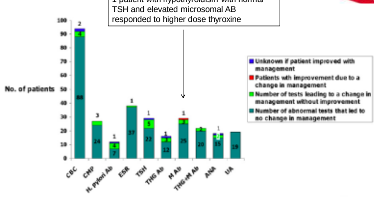
17% of 1,872 ordered tests were abnormal



Tarbox JA et al. Ann Allergy Asthma Immunol 2011;107:239–243.

1/356 (0.28%) benefitted from testing!

1 patient with hypothyroidism with normal TSH and elevated microsomal AB responded to higher dose thyroxine



Tarbox JA et al. Ann Allergy Asthma Immunol 2011;107:239–243.

Chronic Urticaria and Autoimmunity: Associations Found in A Large Population Study

TABLE I. Autoimmune diseases in patients with CU and control subjects

Disease	Total population OR	95% CI	P value	Female subjects OR	95% CI	P value	Male subjects OR	95% CI	P value
Hypothyroidism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hyperthyroidism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Type 1 diabetes mellitus	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sjögren syndrome	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Celiac disease	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SLE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE II. Timing of first diagnosis of autoimmune disease in relation to diagnosis of CU

Disease	Before diagnosis of CU: Women	Men	Total	After diagnosis of CU: Women	Men	Total
Hypothyroidism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hyperthyroidism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Type 1 diabetes mellitus	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sjögren syndrome	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Celiac disease	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SLE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE III. Abnormal serologic markers presented as total numbers and percentages of total tests performed

Marker	Female patients with CU (%)*	Female control subjects (%)*	P value	Male patients with CU (%)*	Male control subjects (%)*	P value	Total patients with CU	Total control subjects
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Antithyroid peroxidase antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Antinuclear antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rheumatoid factor	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Antithyroglobulin antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anti-transglutaminase IgA antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anti-parietal cell antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anti-double stranded DNA antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Anticardiolipin antibodies	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*Percentage represents positive results of total number of tests performed.

Limitations: Evidence is Still Circumstantial

[illegible]

Confino-Cohen R, et.al. JACI 2012; 1307-13.

Clinical Evaluation of Patients with Chronic Urticaria (cont.)

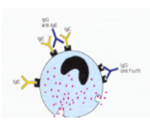
Summary Statement 15: Serology to diagnose underlying autoimmune diseases (eg, connective tissue disease) is not warranted in the initial evaluation of CU in the absence of additional features suggestive of a concomitant autoimmune disease. (B)

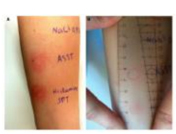
Summary Statement 16: Thyroid autoantibodies are frequently identified in patients with CU. (C) The clinical relevance of these tests for patients with CU has not been established.

Should extended diagnostic measures be performed in chronic spontaneous urticaria?
We recommend for only limited extended diagnostic measures in chronic spontaneous urticaria based on patient history (strong recommendation/clinical consensus).

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.
Zuberbier T, et.al. Allergy. 2014;69(7):868-87.

Autoantibody Associated Chronic Urticaria (a.k.a. chronic autoimmune urticaria)





Konstantinou GN, et.al. Allergy 2009; 64: 1256-68.

ASST Shows Large Variation Of Positivity in Health Control Subjects

Reference	CIU	Controls
Mari[4]	58%	45%
Tedeschi *et al.*[5]	–	0% (3 cases)
Sabroe *et al.*[6]	44.51%	2.5%
Asero *et al.*[7]	–	0% (20 cases)
Sabroe *et al.*[8]	34.61%	2.56%
Guttman-Yassky *et al.*[9]	53.1%	40.5%
Taskapan *et al.*[3]	52.5%	55.55%

Taskapan O, et.al. Eur Acad Derm Venereology 2009; 23:954-82.

ASST vs. APST in Patients With CU

Table 1. Clinical characteristics of the patients and controls.

		Control group		Study group			OR 95% CI
Age		39.31±14.12		40.66±12.68		t:0.5 p=0.564	
Gender	Female	52	83.90%	54	77.10%	χ^2:0.94	0.65
	Male	10	16.10%	16	22.90%	p=0.332	0.27-1.56
ASST	Positive (+)	9	14.50%	44	62.90%	χ^2:31.97	9.97
	Negative (-)	53	85.50%	26	37.10%	p=0.0001	4.23-23.48
APST	Positive (+)	10	16.10%	27	38.60%	χ^2:8.21	3.26
	Negative(-)	52	83.90%	43	61.40%	p=0.004	1.42-7.49
Anti-TPO	Positive (+)	5	8.30%	16	22.90%	χ^2:3.41	3.26
	Negative (-)	55	91.70%	54	77.10%	p=0.065	0.88-12.05

Table 2. Results of ASST and APST in CU patients.

	ASST (+)		ASST (-)		p
APST (+)	25	56.80%	2	7.70%	χ^2:14.8
APST (-)	19	43.20%	24	92.30%	0.0001

Table 3. The association between anti TPO antibodies and the results of ASST and APST.

	Anti-TPO (+)		Anti-TPO (-)	
ASST (+)	9	[illegible]	35	[illegible]
ASST (-)	[illegible]	[illegible]	19	[illegible]
APST (+)	6	[illegible]	21	[illegible]
APST (-)	10	[illegible]	33	[illegible]

No differences between ASST+ and ASST- or APST+ and APST- with regards to disease duration, Anti-TPO Abs, urticaria activity scores, Dermatology Life Quality Index scores (DLQI), CU QOL scores.

Kocaturk E, et.al. Eur J Dermatol 2011; 21:339-43.

US Guidelines Recommendations For FcER1 Testing

- Summary Statement 21: Approximately 30-50% of patients with CU produce specific IgG antibodies against FcεR1α subunit component of the high affinity IgE receptor. (C)
- Summary Statement 22: The utility of the ASST and APST is unclear because evidence has not clearly demonstrated that this testing identifies a distinct subgroup of patients with CU. Current evidence does not support routine performance of ASSTs or APSTs in patients with CU. (C)
- Summary Statement 30: While commercial assays are now available, the utility of testing for auto-antibodies to the high-affinity IgE receptor or auto-antibodies to IgE has not been determined. (C)
- Summary Statement 23: There are no definitive studies that demonstrate that patients with refractory CU and a positive ASST result respond differently to certain medication regimens compared with those patients with CU with a negative ASST result. (C)

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

Low Dose Cyclosporine A (CsA) in Treatment of Severe CIU

- ***Toubi E, et.al. Allergy 1997;52:312-6***

Aim: To determine the safety of CsA treatment in CU patients and whether treatment is affected by an ASST

Study population: 35 patients with severe CU

Methods: 19 treated with CsA for 3 months and observed for 3 months

Results: 13/19 went into complete remission; ASST didn't correlate with disease severity or response to treatment

Factors That Predict The Success Of Cyclosporine Treatment For Chronic Urticaria

Table 6. Factors Predicting Complete Remission of CU on Cyclosporine

	Number of patients analyzed	P value
Sex	68	.10
Race	60	.85
Age	68	.50
CU duration	68	.03[a]
History of angioedema	58	.51
Prior history of hives	62	.01[a]
Urticaria responding to antihistamines	68	.44
Urticaria responding to corticosteroids	56	.80
Underlying psychiatric diagnosis	68	.95
Atopic status	35	.44
ASST	58	.34
ANA ≥ 1:80	27	.10
Anti-thyroid antibodies	33	.92
Chronic urticaria index	24	.05[a]

Abbreviations: CU, chronic urticaria; ASST, autologous serum skin testing; ANA, antinuclear antibodies.
[a] Values are ≤ .05 and are deemed significant.

Hollander SM, et.al. Ann Allergy Asthma Immunol 2011; 107:523-527.

Autoimmune Characteristics of CU Patients

Objective: To study demographic, laboratory, clinical patterns of a group of CU patients

Table 1. Baseline Characteristics of the Study Population

Characteristic	Females	Males	Total
Patients, No. (%)	181 (77)	55 (23)	236
Age, mean, y	39	43	40
Duration of urticaria before diagnosis, mean, mo	35.6	30.8	34.5
Associated angioedema, %	34	40	35
Associated dermographism, %	28	31	29

Table 2. Laboratory Test Results in the Study Population

Characteristic	Patients, No./total No. (%)		
	Females	Males	Total
BAT-CD203+	19/50 (38)	1/8 (13)	20/58 (34)
TA+	50/146 (34)	7/42 (17)	57/188 (30)
ANA+	18/57 (32)	4/12 (33)	22/69 (32)
ASST+	4/7 (57)	0/1	4/8 (50)
Serum IgE >200 kU/L	17/82 (21)	8/23 (35)	25/105 (24)

Table 3. Results of Autoimmunity Studies[a]

	BAT-CD203+ (n = 20)	BAT-CD203− (n = 38)[b]	ASST+ (n = 4)	ASST− (n = 4)[c]
TA+	9 (45)	12 (32)	0	0
IA	11 (55)	25 (66)	4	3

Najib U, et.al. Ann Allergy Asthma Immunol 2009; 103:496-51.

Autoimmune Characteristics In CU Patients

Table 5. Correlations Among ANA, BAT-CD203, and TA[a]

ANA titer	Patients, total (F/M), No.	BAT-CD203+	BAT-CD203−	TA+	TA−
Negative	47 (38/9)	7/19 (37)	12/19 (63)	16/47 (34)	31/47 (66)
Positive	22 (18/4)	4/11 (36)	7/11 (64)	7/21 (33)	14/21 (67)
1:40	11 (10/1)	1/6[b]	5/6	4/10	6/10
1:80	5 (4/1)	2/3	1/3	1/5	4/5
1:160	3 (2/1)	1/2	1/2	1/3	2/3
1:320	2 (2/0)	0	0	0/2	2/2
Unknown	1 (0/1)	0	0	1/1	0/1

Table 6. Pattern of Medication Use

Medications	Study population, No. (%)
H_1 antagonists (as sole agents)	63 (27)
H_1 + H_2 antagonists (combined)	60 (26)
H_1 antagonists + prednisone/cyclosporine	23 (10)
H_1 + H_2 antagonists + prednisone/cyclosporine	39 (17)
Patients receiving prednisone/cyclosporine, total	63 (28)
Other agents (used with or without prednisone/cyclosporine)	37 (16)
Maximum No. of agents used in the study population (n = 236), mean (range)	2.0 (1–7)

Conclusions: No correlations between ANAs and BAT-CD203; No difference in the maximum number of medications used in subgroups based on the presence or absence of BAT-CD203 and TA.

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Positive	22 (18/4)	4/11 (36)	7/11 (64)	7/21 (33)	14/21 (67)
1:40	11 (10/1)	1/6[b]	5/6	4/10	6/10
1:80	5 (4/1)	2/3	1/3	1/5	4/5
1:160	3 (2/1)	1/2	1/2	1/3	2/3
1:320	2 (2/0)	0	0	0/2	2/2
Unknown	1 (0/1)	0	0	1/1	0/1

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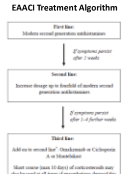
European vs. US Treatment Guidelines

EAACI Treatment Algorithm



US Treatment Algorithm

Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.
Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

H1-Antagonists: US recommendations

Summary Statement 76: H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. (C)
Summary Statement 77: Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents. (A)
Summary Statement 78: Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. (B)
Summary Statement 79: First-generation antihistamines have proved efficacy in the treatment of CU. Efficacy of first generation antihistamines is similar to that of second-generation antihistamines, but sedation and impairment are greater with first-generation antihistamines, especially with short-term use. (A) First-generation antihistamines can be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines. (D)
Summary Statement 82: Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second generation antihistamines and the addition of H2-antihistamines, first-generation H1-antihistamines at bedtime, and/or antileukotrienes. (D)

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

H1-Antagonists: European Recommendations

Are modern second generation H1-antihistamines first line treatment in urticaria and to be preferred against other licensed medication?

We recommend that modern second generation H1-antihistamines are to be used as first line treatment of urticaria (strong recommendation/high level of evidence).

Is an increase in the dose to fourfold of modern second generation H1-antihistamines useful as second line treatment and to be preferred over other treatments in urticaria?

We recommend a trial of up to fourfold dose of modern second generation H1-antihistamines as second-line in the algorithm of treatment.

Should modern second generation H1-antihistamines be taken regularly or as needed?

We recommend modern second generation oral H1-antihistamines to be taken continuously in the lowest necessary dose rather than on demand (strong recommendation/high-quality evidence).

Are modern second generation H1-antihistamines to be preferred over first generation H1-antihistamines in treatment of urticaria?

We recommend that modern second generation H1-antihistamines are to be preferred over first generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence).

Should different H1-antihistamines be used at the same time?

We recommend preferably to updose modern second generation oral H1-antihistamines that do not cause sedation up to fourfold (strong recommendation/high-quality evidence) instead of combining different H1-antihistamines at the same time (strong recommendation/low-quality evidence).

Internal Medicine

Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87..

University of Cincinnati

H2-Antagonists

US Guidelines

Summary Statement 80: H2-antihistamines taken in combination with first- and second-generation H1-antihistamines have been reported to be more efficacious compared with H1-antihistamines alone for the treatment of CU. (A) However, this added efficacy might be related to pharmacologic interactions and increased blood levels of first-generation antihistamines. (B) Because these agents are well tolerated, the addition of H2-antagonists can be considered when CU is not optimally controlled with second-generation antihistamine monotherapy. (D)

European Guidelines:

Not recommended

Internal Medicine

Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.
Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

University of Cincinnati

Leukotriene Modifying Agents

US Guidelines

Summary Statement 81: Leukotriene receptor antagonists have been shown in several, but not all, randomized controlled studies to be efficacious in patients with CU. (A) Leukotriene receptor antagonists are generally well tolerated (A). Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.

European Guidelines

Should leukotriene antagonists be used in the third line treatment of urticaria?

We suggest a trial of montelukast as add on therapy to modern second generation H1-antihistamines as third-line in the treatment of urticaria (weak recommendation/low level of evidence).

Internal Medicine

Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.
Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

University of Cincinnati

Alternative Therapies

Summary Statement 84: Patients with CU whose symptoms are not adequately controlled on maximally tolerated antihistamine therapy (eg, doxepin at a dose of 75-125 mg/d) might be considered to have refractory CU. (E)

Summary Statement 85: A number of alternative therapies have been studied for the treatment of CU; these therapies merit consideration for patients with refractory CU. (D)

Internal Medicine

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

University of Cincinnati

Step 4 Alternative Therapies: US Guidelines

Summary Statement 86: Anti-inflammatory agents, including dapsone, sulfasalazine, hydroxychloroquine, and colchicine, have limited evidence for efficacy in patients with CU, and some require laboratory monitoring for adverse effects. (C) These agents are generally well tolerated, might be efficacious in properly selected patients, and can be considered for treatment of patients with antihistamine-refractory CU. (D)

Summary Statement 87: Several immunosuppressant agents have been used in patients with antihistamine-refractory CU. Cyclosporine has been studied in several randomized controlled trials. Taken in the context of study limitations, potential harms, and cost, the quality of evidence supporting use of cyclosporine for refractory CUA is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CUA refractory to conventional treatment. (A)

Internal Medicine

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

University of Cincinnati

TABLE 12-1—Evidence for Therapies in Chronic Urticaria

Drug	Level of Evidence	Quality & Amount of Evidence	Potential for Serious Adverse Effects	Cost
H1 antihistamines	Ia	High	Low	Low
H2 antihistamines	Ib	Low	Low	Low
doxepin	Ib	Moderate	Low	Low
Systemic corticosteroids	IV	Low	High	Low
Leukotriene modifiers	Ib	Moderate	Low	Moderate
dapsone	IIb	Low	Moderate	Low*
sulfasalazine	III	Low	Moderate	Low*
hydroxychloroquine	Ib	Low	Low	Low
colchicine	III	Low	Low	Low
Calcineurin inhibitors	Ib	Moderate	High	High*
mycophenolate	IIb	Low	Moderate	High*
omalizumab	Ib	Low	Moderate	High
IVIG	IIb	Low	Moderate	High*
Beta agonists	Ib (no effect) III (effect)	Moderate Low	Moderate	Low
NSAIDs	III	Low	Moderate	Low
Methylxanthines	Ib	Moderate	Moderate	Low*
Phototherapy	Ib	Moderate	Moderate	High
Androgens	Ib	Low	Moderate	Moderate*
Methotrexate	III	Low	High	Low*
Anticoagulants	III	Low	High	Low*

*required laboratory monitoring increases cost;

Internal Medicine

Khan DA. In: Maibach HI, Gorouhi F ed. Evidence Based Dermatology 2nd ed. 2011

University of Cincinnati

Laboratory Monitoring of Alternative Agents for Refractory Chronic Urticaria

Alternative Agent	Baseline Labs	Monitoring on Therapy
Montelukast	none	none
Hydroxychloroquine	G6PD LFT, BUN/Cr	none
Dapsone	G6PD, CBC, LFT	Monthly: CBC, LFT x 6 months then periodically
Sulfasalazine	CBC, LFT, BUN/Cr	Monthly: CBC, LFT, BUN/Cr x 3 months then every 3 months
Methotrexate	CBC, LFT, BUN/Cr, CXR	Every 2-4 weeks: CBC, LFT, BUN/Cr
Colchicine	LFT, BUN/Cr	none
Cyclosporine	CBC, LFT, BUN/Cr, K, lipids	Every 2-4 weeks: BUN/Cr, K, Cyclosporine level Periodic: lipids, glucose
Tacrolimus	CBC, LFT, BUN/Cr, K, lipids	Same as cyclosporine except check tacrolimus levels
Mycophenolate	CBC, LFT, BUN/Cr	1st month: weekly CBC Then CBC every 2 weeks for 2-3 months then monthly
Omalizumab	none	none
Immune globulin	BUN/Cr, CBC	Periodic monitoring of BUN/Cr, CBC

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Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.

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TABLE IV. Medications on which complete control of chronic urticaria was achieved at any clinic visit

Step 1-3 therapies per guidelines	No. of patients with complete control (no. of patients taking the medication at any clinic visit, %) (n = [illegible])
1st gen H1-antagonist + 2nd gen H1-antagonist	10 (147, 6.8%)
1st gen H1-antagonist + H2-antagonist	4 (107, 3.7%)
2nd gen H1-antagonist + H2-antagonist	26 (188, 13.8%)
LTRA	18 (137, 13.1%)
1st gen H1-antagonist + LTRA	1 (72, 1.4%)
2nd gen H1-antagonist + LTRA	16 (72, 22.2%)
1st gen H1-antagonist + 2nd gen H1-antagonist + LTRA	1 (80, 1.3%)
1st gen H1-antagonist + doxepin	3 (51, 5.9%)
2nd gen H1-antagonist + doxepin	3 (73, 4.1%)
1st gen H1-antagonist + 2nd gen H1-antagonist + doxepin	3 (70, 4.3%)
1st gen H1-antagonist + 2nd gen H1-antagonist + doxepin + LTRA	-

Step 4 therapies per guidelines*	No. of patients with complete control (no. of patients taking the medication at any clinic visit, %) (n = [illegible])
Prednisone	33 (178, 18.5%)
Cyclosporine 200 mg a day	10 (30, 33.3%)
Hydroxychloroquine 200 mg twice a day	13 (89, 14.6%)
Sulfasalazine 500 mg twice a day	4 (16, 25%)
Dapsone 25-50 mg a day	5 (23, 21.7%)
Colchicine 0.6 mg twice a day	16 (90, 17.8%)
Omalizumab 300 mg once a month	1 (3, 33.3%)
Tacrolimus 1000 mg twice a day	0 (2, 0%)

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Amin P, et.al. JACI: In Practice 2015.

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Complete Control Alternative Treatments Summary

- Cyclosporine – 33%
- Hydroxychloroquine – 15%
- Sulfasalazine – 25%
- Dapsone – 22%
- Colchicine – 18%
- Omalizumab – 33% (*only 3 patients)

Internal Medicine

Amin P, et.al. JACI: In Practice 2015.

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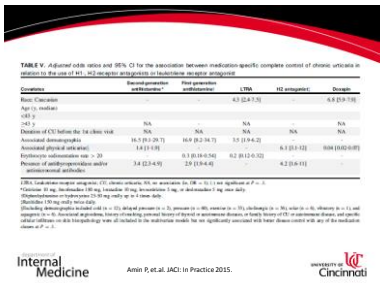


TABLE V. *Adjusted odds ratios and 95% CI for the association between medication-specific complete control of chronic urticaria in relation to the use of H1-, H2-receptor antagonists or leukotriene receptor antagonist*

Covariates	Second-generation antihistamine*	First-generation antihistamine†	LTRA	H2 antagonist‡	Doxepin
Race: Caucasian	-	-	4.3 [2.4-7.5]	-	6.8 [5.9-7.9]
Age (y, median)					
<40 y	-	-	-	-	-
>43 y	NA	-	NA	NA	NA
Duration of CU before the 1st clinic visit	NA	NA	NA	NA	NA
Associated dermatographia	16.5 [9.1-29.7]	16.9 [8.2-34.7]	3.5 [1.9-6.2]	-	-
Associated physical urticaria§	1.4 [1.1-1.9]	-	-	6.1 [3.1-12]	0.04 [0.02-0.07]
Erythrocyte sedimentation rate > 20	-	0.3 [0.18-0.54]	0.2 [0.12-0.32]	-	-
Presence of antithyroperoxidase and/or antinuclear antibodies	3.4 [2.3-4.9]	2.9 [1.9-4.4]	-	4.2 [1.6-11]	-

LTRA, leukotriene receptor antagonist; CU, chronic urticaria; NA, no association (ie, OR = 1); [ ] not significant at $P = .1$.
*Cetirizine 10 mg, fexofenadine 180 mg, loratadine 10 mg, desloratidine 5 mg, or desloratadine 5 mg once daily.
†Diphenhydramine or hydroxyzine 25-50 mg orally up to 4 times daily.
‡Ranitidine 150 mg orally twice daily.
§Including dermatographia included cold (n = 11), delayed pressure (n = 7), pressure (n = 40), exercise (n = 35), cholinergic (n = 36), solar (n = 6), vibratory (n = 1), and aquagenic (n = 6). Associated angioedema, history of smoking, personal history of thyroid or autoimmune diseases, or family history of CU or autoimmune disease, and specific cellular infiltrates on skin histopathology were all included in the multivariate models but are significantly associated with better disease control with any of the medication classes at $P = .1$.

Amin P, et.al. JACI: In Practice 2015.

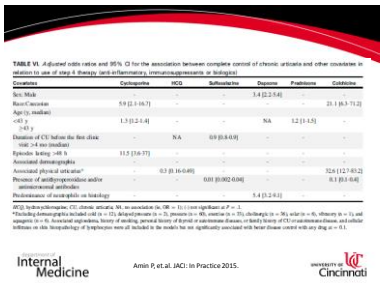


TABLE VI. *Adjusted odds ratios and 95% CI for the association between complete control of chronic urticaria and other covariates in relation to use of step 4 therapy (anti-inflammatory, immunosuppressants or biologics)*

Covariates	Cyclosporine	HCQ	Sulfasalazine	Dapsone	Prednisone	Colchicine
Sex: Male	-	-	-	3.4 [1.2-9.4]	-	-
Race: Caucasian	5.9 [2.1-16.7]	-	-	-	-	21.1 [6.3-71.2]
Age (y, median)						
<40 y	1.3 [1.2-1.4]	-	-	NA	1.2 [1.1-1.5]	-
>43 y						
Duration of CU before the first clinic visit: ≥4 mo (median)	-	NA	0.9 [0.8-0.9]	-	-	-
Episodes lasting >48 h	11.5 [3.6-37]	-	-	-	-	-
Associated dermatographia	-	-	-	-	-	-
Associated physical urticaria*	-	0.3 [0.16-0.49]	-	-	-	32.6 [12.7-83.2]
Presence of antithyroperoxidase and/or antinuclear antibodies	-	-	0.01 [0.002-0.04]	-	-	8.1 [0.1-0.4]
Predominance of neutrophils on histology	-	-	-	5.4 [1.2-9.1]	-	-

HCQ, hydroxychloroquine; CU, chronic urticaria; NA, no association (ie, OR = 1); [ ] not significant at $P = .1$.
*Including dermatographia included cold (n = 11), delayed pressure (n = 7), pressure (n = 40), exercise (n = 35), cholinergic (n = 36), solar (n = 6), vibratory (n = 1), and aquagenic (n = 6). Associated angioedema, history of smoking, personal history of thyroid or autoimmune diseases, or family history of CU or autoimmune disease, and cellular infiltrates on skin histopathology of lymphocytes were all included in the models but are not significantly associated with better disease control with any drug at $\alpha = 0.1$.

Amin P, et.al. JACI: In Practice 2015.

Limitations

- Retrospective
  - No control group or placebo to compare various treatment combinations
- May not be generalizable to other populations
- No analysis of intra-class dosing iterations
  - Weighting the effect of one drug in combination with another not possible

Amin P, et.al. JACI: In Practice 2015.

Omalizumab (Xolair™)

US Guidelines

Summary Statement 88: In contrast to other alternative agents for refractory CU, the therapeutic utility of omalizumab has been supported by findings from large double blind, randomized controlled trials and is associated with a relatively low rate of clinically significant adverse effects. On the basis of this evidence, omalizumab should be considered for refractory CU if, from an individualized standpoint, a therapeutic trial of omalizumab is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with the patient's values and preferences. (A)

European Guidelines

Is omalizumab useful in the treatment of patients unresponsive to high doses of H1-anti-histamines as third-line treatment?

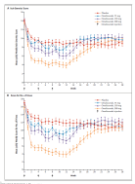
We recommend a trial of omalizumab as add on therapy to modern second generation H1-antihistamines as third-line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence).

Is ciclosporin A useful as add on treatment in patients unresponsive to high doses of H1-antihistamines as third-line treatment?

We recommend a trial of ciclosporin A as add on therapy to modern second generation H1-antihistamines as third-line in the algorithm of treatment of urticaria (strong recommendation/high level of evidence).

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.
Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.

Omalizumab For The Treatment of Chronic Idiopathic Or Spontaneous Urticaria



Issues Pertaining To Omalizumab

- Good safety profile but administered subcutaneously
- Risk of Anaphylaxis requires administration in physician's office; risk in patients with urticaria is unknown but all patients would require an epinephrine injector
- Optimal dose, frequency of administration, treatment duration, and how to step down over time to establish a minimal effective dose with omalizumab is still unclear
- No validated biomarkers or clinical markers predicting response
- Patient selection – does burden of disease warrants the cost of omalizumab over time.
  - Cost may be counterbalanced by lower rates of health service utilization and indirect medical expenditures due to improved quality of life and fewer flares of CU over time

Maurer et al. NEJM 2013; 368:924-35.
Bernstein JA, et al. JACI 2014 May;133(5):1270-7.

Pseudoallergen Diets: Clinical Studies

European (n=6)

- Zuberbier T, et.al. Acta Derm Venereol. 1995 Nov;75(6):484-7.
- Ehlers I, et.al. Allergy. 1998 Nov;53(11):1074-7.
- Di Lorenzo G, Pacor ML, Mansueto P, Martinelli N, Esposito-Pellitteri M, LoBianco C, et al. Int Arch Allergy Immunol 2005;138: 235-42.
- Bunselmeyer B, et.al. Clin Exp Allergy. 2009 Jan;39(1):116-26.
- Magerl M, et.al. Allergy. 2010 Jan;65(1):78-83.
- Akoglu G, et.al. Arch Dermatol Res. 2012 May;304(4):257-62.

American (n=0)

- None

Zuberbier T, et.al. Acta Derm Venereol. 1995 Nov;75(6):484-7.

METHODS:

- 64 patients without common causes of urticaria were placed on a pseudoallergen-free diet.
- Double-blind, placebo-controlled oral provocation tests with food additives were performed on those patients benefitting from diet

RESULTS:

- 73% of patients had reduced hives or no hives within 2 weeks on diet
- Only 19% of them responded to individual pseudoallergens on provocation tests.
- 11% responded to treatment of an underlying inflammatory disease; 16% were idiopathic
- 6 month follow-up revealed complete remission on the pseudoallergen diet in 46% of patients and improvement in all but one patient

CONCLUSION: An additive-free, stringently controlled diet thus provides a simple means of diagnosing and treating the majority of patients with chronic urticaria.

Magerl M, et.al. Allergy. 2010 Jan;65(1):78-83.

METHODS:

- Patients with moderate or severe chronic spontaneous urticaria unresponsive to antihistamines treated for 3 weeks with a a pseudoallergen-free diet.
- Patients were classified into nine response categories, according to the changes in symptom severity (UAS4), quality of life (DLQI) and medication usage.

RESULTS:

- 140 subjects participated; 20 (14%) were considered strong responders, 19 (14%) partial responders, 9 (6%) were able to reduce medications without effecting QoL

CONCLUSIONS:

- Pseudoallergen-free diets were beneficial approximately 33% of patients
- Because they are safe, healthy and low cost the authors recommended advising patients with spontaneous urticaria to avoid pseudoallergens

LIMITATIONS:

- Open label; not controlled

Akoglu G, et.al. Arch Dermatol Res. 2012 May;304(4):257-62.

OBJECTIVE: To evaluate the response to a pseudoallergen diet therapy in patients with CU and changes in LT levels in patients responsive and non-responsive to the diet

METHODS:

- 34 patients with CU were put on a pseudoallergen diet for 4 weeks.
- An urticarial activity score (UAS) was calculated based on the sum of pruritus and wheal score for each patient. The sum score of the first 7 consecutive days (UAS7-first week) and last 7 days (UAS7-fourth week) were used to compare the clinical outcome of the diet. A reduction of ≥50% in UAS7-fourth week compared to UAS7-first week was considered as "response".
- Urinary LTE4 (uLTE4) level of each patient was measured at baseline and after the 4 week of diet therapy.

RESULTS: 14/34 patients (41.2%) responded to the diet. Compared to baseline uLTE4 levels after 4 weeks of diet were lower in the responsive compared to unresponsive patients.There was a significant correlation between the change in uLTE4 levels and the change in mean urticarial activity scores ($r = 0.554$, $P = 0.001$).

CONCLUSIONS: Low pseudoallergen diet reduce the urticarial activity in CU which correlates with changes in LT levels.

Pseudoallergen Diets

US guidelines:

Summary Statement 98: The evidence is weak that pseudoallergen-free diets improve CU.(C) Given the lack of evidence and burden of adhering to these diets, their use in CU patients is not recommended.(D)

European Guidelines:

Are pseudoallergen-free diets useful in the extended diagnostic program of chronic spontaneous urticaria?

We recommend the use of pseudoallergen (non-allergic-hypersensitivity reaction agents) free diets in the extended diagnostic program of chronic spontaneous urticaria in patients with daily or almost daily symptoms only (strong recommendation/ high-quality evidence).

Bernstein JA, et.al. JACI. 2014 May;133(5):1270-7.
Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.

Other Recommendations

European Guidelines:

Same treatment recommendations for children, pregnant and lactating women.

US guidelines:

No specific recommendations

Bernstein JA, et.al. JACI 2014 May;133(5):1270-7.
Zuberbier, T. et.al. Allergy. 2014 Jul;69(7):868-87.

Conclusions:

- We agree **more** than we disagree regarding evaluation and ongoing assessment of CU patients
  - Assessment using validated QOL and UAS – 7 vs. VAS/ISS is important for assessing therapeutic responses
- Therapeutic recommendations for alternative therapies are more narrow for the European vs US guidelines
  - Pseudoallergic and low histamine diets require better studies to confirm efficacy for CU
- More research is required to understand the pathobiology of urticaria
  - Biomarkers to predict response to biologic treatments would be helpful
  - Need to better understand how to use omalizumab long term