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)

Terminology

- There are differences in terminology related to describing hives.
  - The EAACI/WAO document uses the terms “intermittent” and “spontaneous”
  - The EAACI/GA(2) EN/EDF/WAO uses the term “physical” to describe hives caused by physical triggers

Comparison between Urticaria Guidelines

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Learning Materials

- The EAACI/WAO EN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update.
  - Category and strength of evidence

Urticaria Activity and Quality of Life Instruments

- The EAACI/WAO guidelines address objective specific ways of quantifying urticaria and quality of life.
  - UAS7: a validated scoring system for hives, for clinical use
  - Q2oL: a validated quality of life instrument
  - The UAC (Urticaria Activity and Quality of Life Instruments) is a validated and cross-validated assessment of chronic urticaria (CU) unresponsive to H1 antihistamines trials
  - This score was recently used as a primary or secondary endpoint in several multicenter trials of chronic urticaria and the UAC endpoint was superior to outcomes traditionally used in urticaria trials
  - This score is used for assessing the severity of chronic urticaria in clinical trials
  - The UAC and the Q2oL are used in clinical studies to assess the efficacy of treatments

- The JTF practice parameter uses the terms “continuous” and “intermittent” to describe the variable nature of hives.
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Clinical Evaluation

- Both guidelines recommend a limited workup for chronic urticaria as a cause is seldom found.
- CBC, with, WBC, RBC, platelets, and evaluation of potential underlying causes
- Additional testing with VDRL, HIV, and Lyme may also be 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)


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


*Limitations: Evidence is Still Circumstantial

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

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


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

ASST Shows Large Variation Of Positivity in Health Control Subjects

ASST vs. APST in Patients With CU

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.
**Summary Statement 21:** There are no definitive studies

**Summary Statement 22:** The utility of the ASST and APST

**Summary Statement 23:** Autoimmune Characteristics In CU Patients

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

**Autoimmune Characteristics of CU Patients**

- European vs. US Treatment Guidelines

- European vs. US Treatment Guidelines

**Autoimmune Characteristics In CU Patients**

**Factors That Predict The Success Of Cyclosporine Treatment For Chronic Urticaria**

| Evidence Level | Factors Predicting Success | Success Rate%
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**US Guidelines Recommendations For FeR1 Testing**

- Approximately 90-95% of patients with CU produce specific IgE antibodies against Fel d 1, a major allergen in cats.

- There is no reliable test to predict the occurrence of anaphylaxis in patients with CU.

- While commercial tests are available, the utility of these tests is not established.

**Low Dose Cyclosporine A (Csa) In Treatment of Severe CU**

- **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

**Conclusions:** No correlations between ANAs and BAT

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H1-Antagonists: European Recommendations

US Guidelines

Summary Statement 86: H1-antihistamines are generally well tolerated. They might be efficacious in patients with CU. (D)

European Guidelines

Summary Statement 87: These agents are generally well tolerated, might be efficacious in patients with CU, and can be considered when CU is not optimally controlled with second-generation antihistamine monotherapy. (D)

H2-Antagonists

US Guidelines

Summary Statement 88: H2-antagonists taken in combination with first- and second-generation H1-antihistamines have been reported to be more efficacious compared with H1-antihistamine alone for the treatment of CU. (A) However, this added efficacy might be related to pharmacologic interactions or 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

Summary Statement 89: H2-antagonists have been shown in several, but not all, randomized controlled studies to be efficacious in patients with CU. (A) H2-antagonists are generally well tolerated. Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.

Leukotriene Modifying Agents

US Guidelines

Summary Statement 90: Leukotriene receptor antagonists have been shown to be efficacious in patients with CU. (A) Leukotriene receptor antagonists are generally well tolerated. Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.

European Guidelines

Summary Statement 91: Leukotriene receptor antagonists can be used in the first-line treatment of CU. (B) These agents might be related to pharmacologic interactions or increased blood levels of first-generation antihistamines. Because these agents are well tolerated, they can be considered for patients with refractory CU. (E)

Summary Statement 92: Several immunosuppressant agents have been used in patients with urticaria refractory to H1-antihistamines. 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 CU is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CU refractory to conventional treatment. (A)

Step 4 Alternative Therapies: US Guidelines

Summary Statement 93: 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. (E)

Summary Statement 94: 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 CU is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CU refractory to conventional treatment. (A)

Alternative Therapies

Summary Statement 95: Patients with CU whose symptoms are not adequately controlled on maximally tolerated antihistamine therapy (eg, diphenhydramine at a dose of 75–125 mg/d) might be considered to have refractory CU. (E)

Summary Statement 96: A number of alternative therapies have been studied for the treatment of CU; these therapies merit consideration for patients with refractory CU. (D)

Complete Control Alternative Treatments

Summary

- Cyclosporine – 33%
- Hydroxychloroquine – 15%
- Sulfasalazine – 25%
- Dapsone – 22%
- Colchicine – 18%
- Omalizumab – 33% (*only 3 patients)
Magerl M, et al. Allergy. Because they are safe, healthy none may not be generalizable to other populations. Only 6 month follow pseudoallergen. Retrospective Urinary Patients with moderate 64 patients without common Ehlers I, et al. Allergy. 34 Bunselmeyer 73 Open label; not controlled Akoglu Patients were classified No analysis of intra Double 140 subjects participated; 10/4/2015

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

CONCLUSIONS: • Open label; not controlled

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

METHODS: • All 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 benefiting from diet.

RESULTS: • 70% of patients had induced hives or pruritus within 3 weeks on diet. • Only 60% of patients responded to individual pseudoallergens on provocation tests. • 12% responded to treatment of an underlying inflammatory disease. 10% were idiopathic. • A 6 month follow-up needed complete remission on the pseudoallergen diet in 60% of patients and improvement in 40% of patients. CONCLUSIONS: An additional free, stringently controlled diet that provides a single means of diagnosing and treating the majority of patients with chronic urticaria.
Pseudoallergen Diets

US guidelines:
Summary Statement 58: The evidence is weak that pseudoallergen-free diets improve CU. Given the lack of evidence and burden of adhering to these diets, their use in CU patients is not recommended.

European Guidelines:

The evidence is weak that pseudoallergen-free diets improve CU. Given the lack of evidence and burden of adhering to these diets, their use in CU patients is not recommended.

Conclusions:

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

Other Recommendations

European Guidelines:
Same treatment recommendations for children, pregnant and lactating women.

US guidelines:
No specific recommendations.