Chronic Urticaria: Updates on Diagnostic Testing and Therapy from the Practice Parameter

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Conflict of Interests

- Author of urticaria practice parameters
- Principal Investigator Novartis and Genentech
- IIS Novartis/Genentech
- AAAAI BOD
- Editor in Chief Journal of Asthma

At the end of this lecture the participant will be able to:

1) Discuss the diagnostic approach to acute and chronic urticaria
2) Explain the dos and don’ts of evaluating patients with chronic urticaria
3) Determine the best treatment approach for patients with chronic urticaria

History of the Updated Urticaria Parameter

- Began as Urticaria and Angioedema early 2008
- Divided into Angioedema and Urticaria parameters
- Angioedema parameter accepted JACI March 14, 2013
- Urticaria guideline accepted JACI February 12, 2014
  - 198 pages; 54,053 words
  - 11 tables and 4 figures; annotations with flow diagrams for acute and chronic urticaria
  - 658 graded references
  - Grade process used for analysis of cyclosporine
  - Highly vetted by the JTF, AAAAI, ACAAI, external reviewers nationally and internationally

Areas of Controversy

- Diagnostic testing
  - Laboratory testing
  - ASST/APST
  - d-dimers
  - Skin testing
- Treatments
  - Euthyroid patients with autoantibodies
  - Autoantibody associated urticaria (aka autoimmune urticaria)
  - Autoimmune disease
  - Helicobacter pylori, Celiac disease
  - Low histamine diets
  - High dose H1-antihistamines
  - Step care treatment approach
  - Role of Omalizumab (trials would have been omitted if guideline was published earlier)
Case Presentation

- SG is a 26 y/o female with new onset hives with lip swelling for 5 days
- Past history of mild asthma, allergic rhinitis with oral allergy syndrome to melons and avocado, gastroesophageal reflux disease and psoriasis
- Also with gluten intolerance (negative celiac work-up)
- Denies relationship of hives to foods or prescription/OTC medications.
  - Took ibuprofen the last two nights for headache
  - Also was taking an over the counter pure saffron extract supplement for weight loss which she stopped two days prior to her visit
- No history of thyroid disease, chronic infections, autoimmune disorders or malignancies; hives not associated with any physical stimuli
- The hives are evanescent, very pruritic affecting 45% of her body
- Family history significant for father and identical twin sister with history of urticaria
- Primary care prescribed a methylprednisolone dose pack and diphenhydramine 25mg as needed with some benefit but still with hives at the time of the visit, feels nervous from the corticosteroids

Question #1

What diagnostic testing would you order for this patient at the time of her initial visit?

A. CBC with differential and WSR
B. ANA, RF
C. TSH and thyroid antibodies
D. All of the above
E. None of the above

SUMMARY STATEMENT 6: Most often acute urticaria is a self-limiting condition that will resolve spontaneously in less than six weeks. Extensive evaluation for causes not suggested by the history or physical examination is not cost effective and has not been associated with improved outcomes. (C)

SUMMARY STATEMENT 7: Common causes of acute urticaria and angioedema, including medications and foods, should be identified by a detailed history and eliminated if possible. (C)

Question #2

What should the initial treatment be for this patient?

A. A non-sedating second generation H1-antagonist once a day
B. A non-sedating second generation H1-antagonist in the AM and first generation sedating antihistamine at bedtime
C. Double the dose of non-sedating second generation antihistamine with as needed first generation antihistamine at bedtime
D. A non-sedating second generation H1-antagonist in the AM + an H2 antagonist twice a day
E. All of the above

SUMMARY STATEMENT 8: In most cases, antihistamines are efficacious for therapy of acute urticaria and angioedema. (B)

SUMMARY STATEMENT 9: In severe cases, oral corticosteroids may be necessary to treat acute urticaria and angioedema. In patients with poor response to antihistamines, a brief course of oral corticosteroids may also be required while attempting to eliminate suspected triggers and develop an effective treatment plan. (C)
Follow Up Visit – 2 weeks later

- Still with daily hives covering 35-45% of body and very pruritic
- Using diphenhydramine 25mg as needed 2/day as the daily second generation antihistamine by itself is ineffective
  - Experiencing fatigue
- Concerned the hives may be due to food but not sure which one
- Also wandering if she has an autoimmune disorder causing the hives as there is a family history
  - No symptoms of other rashes, arthritis, weight loss, stomatitis, fevers...

Laboratory Evaluation

Routine evaluation. Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical exam.

A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features:
- Complete blood count with differential
- Erythrocyte sedimentation rate and/or C-reactive protein
- Liver enzymes
- Thyroid stimulating hormone

The utility of performing the above tests routinely for CU patients has not been established.

Summary Statement #28 (cont)

Limited testing may be justified based on its “reassurance value”; however, extensive routine testing is not favorable from a cost-benefit standpoint, and does not lead to improved patient care outcomes.

Additional evaluation may be warranted based upon patient circumstances, and may include but not be limited to the diagnostic tests listed below. A thorough history and meticulous physical exam is essential for determining whether these additional tests are appropriate:

- Skin biopsy
- Physical challenge tests
- Complement system: e.g. C3, C4, and CH50
- Stool analysis for ova and parasites
- Urinalysis
- Hepatitis B and C serologies
- Chest radiograph and/or other imaging studies
- Antinuclear antibody (ANA)
- Rheumatoid factor, anti-citrullinated protein
- Cryoglobulin levels
- Serologic and/or skin testing for immediate hypersensitivity
- Thyroid autoantibodies
- Serum protein electrophoresis

More detailed laboratory testing and/or skin biopsy merits consideration if urticaria is not responding to therapy as anticipated.

Additional laboratory testing may be required prior to initiation of certain medications, e.g. glucose-6-phosphate dehydrogenase (G6PD) screening prior to prescribing dapsone.
Question #3

The most appropriate next step for management of this patient are:

A. Increase second generation antihistamines to 4 times the recommended dose
B. Increase second generation antihistamines to 4 times the recommended dose; order CBC with diff, WSR, CRP, TSH
C. Continue second generation antihistamine in the morning and add doxepin 50mg at bedtime
D. Continue second generation antihistamine in the morning and as needed first generation antihistamine; order CBC with diff, WSR, CRP, TSH, ANA, RF, C4, C1INH quantitative and functional levels
E. Refer to a dermatologist

Recommendations on Specific Tests

- Testing not indicated on routine basis
  - Autoimmune serology (SS #14, 15)
  - Thyroid Autoantibodies (SS #16, 29)
  - Malignancies (SS #20)
  - Testing for H pylori or celiac disease (SS #19)
  - CU Autoantibody Tests (SS #21-23, 30)
  - Urticarial vasculitis (SS #17,18)
  - Skin Biopsy (SS #32)
  - Hypersensitivity Testing (e.g. skin testing) (SS #33)

Utility of routine laboratory testing in management of chronic urticaria/angioedema

- Retrospective study to investigate the proportion of abnormal test results in patients with CU leading to a change in management and in outcomes of care
- 356 CU patients seen at Cleveland Clinic

17% of 1,872 ordered tests were abnormal

1/356 (0.28%) benefitted from testing!
High Dose Antihistamines in Chronic Urticaria

- Cetirizine: conflicting studies
- Fexofenadine: no difference between 60 mg, 120 mg and 240 mg twice a day
- Desloratadine
  - 20 mg > 5 mg in cold urticaria
- Levocetirizine and desloratadine
  - Higher doses better


Return Visit #2 – 4 weeks later

- Lab testing normal
- Hives are improved but still with daily hives covering 15% of body; itch severity is “6” on scale 1-10
- Still requires as needed first generation antihistamines
  - Complaining of more fatigue

Follow up visit – 4 weeks later

- Still with daily hives
- Affecting work and leisure activities
- Very frustrated not being able to identify cause of hives

Question #4

All of the following are appropriate next steps except:

A. Add an H2-antagonist to current regimen
B. Add a LTMA to current regimen
C. Change to a different second generation antihistamine in the AM
D. Start hydroxychloroquine 200mg twice a day
E. A, B or C
Choosing Alternative Agents for Treatment of Refractory Urticaria

SUMMARY STATEMENTS 86-92—discusses alternative treatments

SUMMARY STATEMENT 93: Multiple factors are involved in selecting an alternative agent in refractory CU patients, including but not limited to the presence of comorbid factors, frequency of treatment-related visits, cost, rapidity of response, adverse effects, and patient values and preferences. The potential for harm and burden associated with a given alternative agent is extremely important and needs to be weighed against the patient’s potential for benefit, current quality of life, and any adverse effects from current therapy for their CU. (D)

Table 1. Evidence for Therapies in Chronic Urticaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level of Evidence</th>
<th>Quality &amp; Amount of Evidence</th>
<th>Potential for Serious Adverse Effects</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 antihistamine</td>
<td>1b</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>H1 antihistamine</td>
<td>1b</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>H2 antagonist</td>
<td>1b</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Leukotriene receptor antagonist</td>
<td>1b</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>1b</td>
<td>Low</td>
<td>Moderate</td>
<td>Low*</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1b</td>
<td>Low</td>
<td>Moderate</td>
<td>High*</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>1b</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Other biologics</td>
<td>1b</td>
<td>Low</td>
<td>Moderate</td>
<td>Low*</td>
</tr>
</tbody>
</table>

Kaplan et al. JACI. 2008; 122(3)

Autoantibody Associated Urticaria

• Chronic autoimmune urticaria/angioedema = CAU
  – 45% of chronic urticaria is autoimmune, more severe
  – IgG against α-subunit of FcεRI (35-40%) or to IgE (5-10%), cross-links IgE causing degranulation of basophils and mast cells
  – Histamine release also augmented by complement activation, C5a
  – 25% anti-thyroid Ab = Hashimoto thyroiditis
  – ζ2-antihistamines, H2 blockers, LTRA, systemic steroids, cyclosporine

• Proof of concept study
  – Can Omalizumab will reduce FcεRI expression to prevent IgG-mediated cross-linking of IgE?

Kaplan et al. JACI. 2008; 122(3)

Table 2. Patient characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Disease duration (months)</th>
<th>Total score (5-40)</th>
<th>Thrombocytopenia</th>
<th>Baseline (5-10)</th>
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<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>M</td>
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<td>120</td>
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<td>36</td>
<td>M</td>
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<td>10</td>
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<td>5</td>
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<tr>
<td>6</td>
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</table>

Kaplan et al. JACI. 2008; 122(3)
Omalizumab For The Treatment of Chronic Idiopathic Or Spontaneous Urticaria: Enrollment and Outcomes

Mauer et.al. NEJM 2013; 368:924-35

Table 10: Laboratory Monitoring of Alternative Agents for Refractory Chronic Urticaria

<table>
<thead>
<tr>
<th>Alternative Agent</th>
<th>Baseline Labs</th>
<th>Monitoring on Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>G6PD, CBC, LFT</td>
<td>Monthly: CBC, LFT x 10 months then periodically</td>
</tr>
<tr>
<td>Dapsone</td>
<td>G6PD, CBC, LFT</td>
<td>Monthly: CBC, LFT x 3 months then every 3 months</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>CBC, LFT, BUN/Cr</td>
<td>Monthly: CBC, LFT, BUN/Cr x 1 month then monthly</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>CBC, LFT, BUN/Cr, CXR</td>
<td>Every 2-4 weeks: CBC, LFT, BUN/Cr</td>
</tr>
<tr>
<td>Colchicine</td>
<td>LFT, BUN/Cr</td>
<td>none</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>CBC, LFT, BUN/Cr, K, lipids</td>
<td>Daily 2-4 weeks: BUN/Cr, K, CXA, Periodic lipids, glucose</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>CBC, LFT, BUN/Cr, K, lipids</td>
<td>Daily 2-4 weeks: CBC, LFT, BUN/Cr, K, lipids, glucose</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>CBC, LFT, BUN/Cr</td>
<td>1 st month: weekly CBC</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Immune globulin</td>
<td>BUN/Cr, CBC</td>
<td>Periodic monitoring of BUN/Cr, CBC</td>
</tr>
</tbody>
</table>

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 patient values and preferences.(A)

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.

Omalizumab should be considered for properly selected patients who have been unresponsive to step 3 care and for whom other immunosuppressive and/or anti-inflammatory agents would be associated with greater potential for harm, have lacked efficacy, and/or have not been well tolerated.

Natural Course/Prognosis of Chronic Urticaria


- 220 adults with chronic urticaria were followed prospectively for 1-3 years at the University of Amsterdam
- After one year, 35% were free of all symptoms and 30% had decreased symptoms
- 47% of patients with CIU had spontaneous remission over 3 years compared to only 16% who had a component of physical urticaria
- Conclusion: Prognosis for spontaneous remission of chronic urticaria is reasonable with the exception of the subgroup with a physical component
Urticaria Practice Measures

1) Percentage of patients seen at one or more visits within a 12-month period with a diagnosis of chronic urticaria/angioedema, who underwent diagnostic testing for connective tissue disease in the absence of a history or symptoms consistent with or suggestive of a connective tissue disease.

2) Percentage of patients seen at one or more visits within a 12-month period with a diagnosis of chronic urticaria/angioedema, who underwent skin or in vitro testing for food allergies.

3) Percentage of patients seen at one or more visits within a 12-month period with a diagnosis of chronic urticaria/angioedema, who underwent skin or in vitro testing for inhalant allergens.

4) Percentage of patients seen at one or more visits within a 12-month period with a diagnosis of chronic urticaria with or without angioedema, who underwent diagnostic testing for a C1 inhibitor deficiency syndrome.

5) The proportion of patients with chronic urticaria that is uncontrolled on monotherapy with approved doses of 2nd generation antihistamines, who are advanced as tolerated to one or more of the following: higher doses of second generation antihistamines; addition of another 2nd generation antihistamine, addition of a leukotriene antagonist, addition of an H2 blocker, or addition of a 1st generation antihistamine to be taken at bedtime.

Questions and Answers