

# Successful Treatment of Recalcitrant Chronic Idiopathic Urticaria With Sulfasalazine

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**Background:** Antihistamines are the standard treatment for chronic idiopathic urticaria (CIU). For patients whose urticaria is unresponsive to antihistamines, the treatment options are limited. During the previous decade, there have been several case reports demonstrating success with sulfasalazine therapy. In this article, we present a case series evaluating sulfasalazine therapy for antihistamine-unresponsive CIU.

**Observations:** Nineteen patients with antihistamine-unresponsive CIU were treated with sulfasalazine between 2002 and 2005. During sulfasalazine therapy, 14 patients (74%) reported significant improvement, 4 patients (21%) reported minimal improvement but were not satisfied with their symptom relief, and 1 patient (5%) reported a worsening of symptoms. Of the 13 patients

who required systemic steroids to control their urticaria, all were able to reduce or discontinue steroid use during sulfasalazine therapy. Although 7 patients (37%) had adverse effects (eg, nausea, headache, mild or transient leukopenia, and transaminitis) that were thought to be caused by the use of sulfasalazine, they all kept taking the drug.

**Conclusions:** This case series demonstrates that sulfasalazine can be a successful and safe treatment option for patients with CIU who have not responded adequately to treatment with antihistamines. Sulfasalazine was steroid sparing in all subjects who were steroid dependent.

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**C**HRONIC IDIOPATHIC URTICARIA (CIU) is defined as the occurrence of close-to-daily wheals and pruritus for a duration of at least 6 weeks, without an obvious cause. The wheals usually resolve in less than 24 hours. It has been estimated that 15% to 23% of the US population will experience acute or chronic urticaria at some point in their lifetime, and there is an approximately 0.5% lifetime prevalence of CIU in the general population.<sup>1-3</sup> Chronic idiopathic urticaria more commonly affects women than men (2:1), is more commonly seen in the adult population,<sup>4</sup> and is associated with angioedema in 50% to 90% of cases.<sup>5,6</sup> The discomfort and negative cosmetic impact experienced with chronic urticaria, as well as the elusive pathogenesis and the lack of satisfactory control of symptoms with standard therapies, can be very frustrating for patients and health care providers. It has also been estimated that the disability suffered by those with CIU is equal to that observed with triple-vessel coronary artery disease.<sup>7</sup>

Great efforts have been made to identify the pathogenesis of this disease, with the 2 most commonly proposed theories

being an infectious or autoimmune origin. Infectious agents have long been thought to play a role in the development of CIU, but definitive proof is still lacking. For example, *Helicobacter pylori* has been extensively studied as a possible causative agent, specifically in reference to its ability to cause formation of autoantibodies through the immunogenicity of its cell envelope.<sup>8</sup> Currently, there is conflicting evidence in the literature as to an association between the eradication of *H pylori* and improvement of urticaria.<sup>9-12</sup> Fungi, such as *Candida albicans* and *Malessezia furfur*, have also been implicated.<sup>13,14</sup>

More recently, there have been studies that have found that approximately 30% to 60% of patients with CIU have an autoimmune component.<sup>15-17</sup> Anti-IgE antibodies and functional antibodies against the  $\alpha$  chain of the high-affinity IgE receptor found on mast cells, basophils, and antigen-presenting cells have been isolated from the serum of patients with CIU.<sup>18-20</sup> The role that autoimmunity plays in CIU is also supported by the association of CIU with autoimmune thyroid disease. Abnormal thyroid function has been found in 12% to 19% of patients with CIU,<sup>21-23</sup> with 2 studies demonstrating that 14% to 27%

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of patients with CIU have thyroid autoantibodies compared with 6% of the general population.<sup>23,24</sup>

Currently, antihistamines, which generally work by alleviating the symptoms rather than enacting a cure, are the standard treatment for CIU.<sup>25,26</sup> With the recent advent of nonsedating or minimally sedating H<sub>1</sub> receptor antagonists, some patients with CIU have found relief from symptoms without the adverse effect of excessive drowsiness. Unfortunately, there are those whose urticaria does not respond to treatment with antihistamines, with some studies reporting a 5% to 12% failure rate with fexofenadine hydrochloride therapy.<sup>27,28</sup> For those individuals, H<sub>2</sub> receptor antagonists, leukotriene antagonists, and systemic corticosteroids have also been used, with varying degrees of success.<sup>29,30</sup> The potential role of an autoimmune mechanism in at least some cases of CIU has led to the use of alternative therapies focusing on immunomodulation. For example, recent randomized trials have demonstrated the efficacy of cyclosporine.<sup>31,32</sup> There have also been smaller, uncontrolled studies indicating a potential benefit from dapsone<sup>33</sup> and hydroxychloroquine,<sup>34</sup> and additional case reports have shown promise with other medications such as methotrexate<sup>35,36</sup> and cyclophosphamide.<sup>37</sup> Despite these advances, many persons still suffer from therapy-resistant CIU. There is a need for further investigation of immunoregulatory agents with more benign adverse effect profiles that can effectively reduce or eradicate the symptoms of urticaria and decrease the need for systemic steroids.

Over the last decade, there have been sporadic case reports demonstrating successful alleviation of symptoms with the use of sulfasalazine.<sup>38-40</sup> We present a review of the literature and a retrospective review of our own institutional experience with sulfasalazine for the treatment of recalcitrant CIU. In 2 patients taking sulfasalazine, we also noted a functional change in the histamine-releasing capabilities of their basophils before and after sulfasalazine treatment, a finding that coincided with clinical improvement (data not shown).

## METHODS

### RETROSPECTIVE CHART REVIEW

We performed a retrospective medical chart review of 19 patients diagnosed with CIU and subsequently treated with sulfasalazine at Johns Hopkins Bayview Medical Center, Baltimore, Md, from 2002 to 2005. The study was approved by the institutional review board at the Johns Hopkins Medical Institutions, Baltimore. The diagnosis of CIU was based on clinical history and physical examination and was supported by skin biopsy findings in 17 cases (89%). The remaining 2 patients did not have any biopsy data on record and were diagnosed as having CIU solely on their disease presentation. The following information was obtained: disease duration, history of angioedema, presence of thyroid autoantibodies (antimicrosomal and antithyroglobin), thyroid function, dosage of sulfasalazine therapy, subjective clinical response to sulfasalazine therapy, adverse effects during sulfasalazine therapy, therapies for CIU used before and after sulfasalazine therapy, and skin biopsy findings. Before the initiation of sulfasalazine therapy, baseline blood work, including kidney and liver function tests, a complete blood cell count, and determination of thyrotropin

and antimicrosomal and antithyroglobin antibodies, was performed. A punch biopsy of an urticarial wheal was performed to rule out other diagnoses such as urticarial vasculitis and to further characterize the urticaria as lymphocyte or neutrophil predominant. Patients were counseled on the potential adverse effects of sulfasalazine, including headache, photosensitivity, gastrointestinal distress, liver and kidney abnormalities, leukopenia, and reversible oligospermia. The sulfasalazine therapy was started at a dosage of 500 mg/d and increased by 500 mg each week until a satisfactory clinical response was achieved or until a daily dose of 2 to 4 g/d was reached. During dose escalation, blood work was repeated weekly and then every 3 months after the final dosage had been reached.

Based on subjective reports, the patients were categorized into the following groups: significant or nonsignificant improvement, no change, or worse with the use of sulfasalazine. Patients with significant improvement had at least a 50% reduction of their urticaria according to a subjective report of response using either a symptom severity scale from 1 to 10 or a report of symptom frequency. One of patients with significant improvement was classified as such based on the statement in his medical record that during sulfasalazine therapy his urticaria was "minimally symptomatic." Nonsignificant improvement included those who noted a minimal decrease in urticaria but were not satisfied enough to continue taking sulfasalazine. Anyone not classified as having significant improvement was considered a treatment failure. Patients generally had a clinical response to sulfasalazine within 2 to 4 weeks but required a full 8-week course before being classified as a treatment failure.

## REVIEW OF THE LITERATURE

A computer search of the MEDLINE database (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) was performed, as was a review of the reference section of each primary source. All cases of chronic urticaria that were treated with sulfasalazine and described in the English-language medical literature between the years of 1966 and 2005 were identified.

## RESULTS

Nineteen patients from the Johns Hopkins Bayview Medical Center were diagnosed as having CIU and started sulfasalazine therapy between the years of 2002 and 2005. Fifteen patients (79%) were female, and the mean  $\pm$  SD age was  $39 \pm 3$  years. The mean  $\pm$  SD duration of CIU symptoms before the initiation of sulfasalazine therapy was  $81 \pm 25$  months, with a median of 60 months. The dosage ranged from 0.5 to 4 g/d, with a mean  $\pm$  SD dose of  $2 \pm 0.16$  g/d. Fourteen patients (74%) had a history of angioedema, and of the 16 patients with thyroid studies, 6 (38%) had evidence of thyroid autoimmunity (**Table 1**). All 19 patients had tried at least 2 different antihistamines (including sedating and nonsedating). According to the patients' reports, they had taken as much antihistamine as they could tolerate (in terms of adverse effects) and still did not have adequate control of their CIU symptoms.

Fourteen patients (74%) reported significant improvement with the use of sulfasalazine. Four patients (21%) reported nonsignificant improvement, and 1 patient (5%) felt that the urticaria worsened during sulfasalazine therapy (**Table 2**). The average maximum dosage of

**Table 1. Individual Patient Demographics and Response to Sulfasalazine Therapy**

Patient No./ Age, y/ Sex	Duration of CIU, mo	Sulfasalazine Dose, g/d	Duration of Sulfasalazine Therapy, mo	% Symptom Reduction or Subjective Report	Previous Maximum Antihistamine Therapy	Systemic Steroids Before Sulfasalazine Therapy	Systemic Steroids During Sulfasalazine Therapy	Sulfasalazine Taper	Response to Sulfasalazine Taper
1/68/F	72	2	12	100	Cetirizine HCl (10 mg/d), hydroxyzine HCl (25 mg nightly)	Prednisone (couple of bursts, 10 mg/d × 3 d)	Prednisone (10 mg once in last year, none for 5 mo)	Yes	Tapered off all urticaria medications, urticaria free for 3 mo
2/60/M	360	2	11	100	Cetirizine HCl (10 mg/d)	Prednisolone dose packs (approx 5 courses)	None	No	...
3/58/F	204	2	3	85	Fexofenadine HCl (180 mg/d), cetirizine HCl (10 mg/d), hydroxyzine HCl (25 mg nightly)	None	None	Yes	Tapered sulfasalazine to 1 g/d, mild urticaria flare
4/26/F	10	2	8	70	Fexofenadine HCl (180 mg/d), hydroxyzine HCl (75 mg nightly)	None	None	No	...
5/42/F	120	1.5	11	66	Fexofenadine HCl (180 mg/d), cetirizine HCl (10 mg twice daily), hydroxyzine HCl (50 mg nightly)	None	None	No	...
6/42/F	Unknown	2	11	100	Cetirizine HCl (10 mg/d), cyproheptadine HCl (8 mg nightly)	Prednisone (multiple 4-wk courses, unknown dose)	None	Yes	Tapered off all urticaria medications, urticaria free for 13 mo
7/41/F	96	2	3	100	Fexofenadine HCl (180 mg/d), cetirizine HCl (10 mg/d), hydroxyzine HCl (25 mg nightly)	Prednisone (30 mg/d)	None	Yes	Tapered off all urticaria medications, urticaria free for 12 mo; urticaria flare, back taking sulfasalazine
8/41/F	Unknown	2	12	100	Diphenhydramine HCl (25 mg 4 times daily)	Prednisolone dose packs (approx 10-15 courses)	None	Yes	Tapered sulfasalazine to 1 g/d, urticaria free for 12 mo
9/41/M	12	2	24	85	Cyproheptadine HCl (4 mg 3 times daily), cetirizine HCl (10 mg/d)	Prednisone (couple of 40-mg tapers)	Prednisone (couple of 10-mg bursts, none for 6 mo)	No	...
10/31/F	48	2	2	50	Fexofenadine HCl (180 mg/d), desloratadine (10 mg/d)	Prednisone (20 mg/d)	Prednisone (5 mg/d)	Unknown	...
11/18/F	72	2	11	50	Fexofenadine HCl (180 mg/d), loratadine (10 mg/d)	None	None	No	...
12/18/M	Unknown	2	Unknown	Urticaria minimally symptomatic	Cetirizine HCl (10 mg/d)	History of steroid use	None	Unknown	...
13/17/F	18	0.5	Unknown	100	Fexofenadine HCl (180 mg/d), cetirizine HCl (10 mg/d)	History of steroid use	None	Yes	Tapered off all urticaria medications, urticaria free for 4 months; urticaria flare, back taking sulfasalazine
14/45/F	12	1	7	100	Cyproheptadine HCl (4 mg 3 times daily), cetirizine HCl (10 mg/d)	None	None	Unknown	...
15/42/F	9	2	2	20-30	Fexofenadine (180 mg/d), hydroxyzine HCl (25 mg nightly)	History of steroid use	None	Stopped sulfasalazine use	...
16/36/M	2	4	9	Marginal improvement	Cetirizine HCl (10 mg/d), hydroxyzine HCl (75 mg nightly), cyproheptadine HCl (4 mg 3 times daily)	History of steroid use	None	Stopped sulfasalazine use	...
17/38/F	121	2	2	Minimal improvement	Cetirizine HCl (10 mg/d), hydroxyzine HCl (75 mg nightly)	None	Prednisone (1 burst, unknown dose)	Stopped sulfasalazine use	...
18/33/F	Unknown	3	9	Minimal improvement	Cyproheptadine HCl (4 mg 3 times daily), cetirizine HCl (10 mg twice daily)	Prednisone (multiple months, 20-40 mg/d)	None	Stopped sulfasalazine use	...
19/49/F	60	2	2	Worse	Loratadine (10 mg/d), cetirizine HCl (10 mg/d)	Prednisone (20-40 mg/d)	Prednisone (5-10 mg/d)	Stopped sulfasalazine use	...

Abbreviations: approx, approximately; CIU, chronic idiopathic urticaria; ellipses, not applicable; HCl, hydrochloride.

**Table 2. Clinical Response to and Adverse Effects Associated With Sulfasalazine Therapy**

Variable	No. (%)
Subjective clinical response (n = 19)	
Significant improvement	14 (74)
Nonsignificant improvement	4 (21)
No change	0
Worse	1 (5)
Effects on corticosteroid use (n = 14)	
Reduced use	4 (29)
Stopped use	9 (64)
Increased use	1 (7)
Adverse effects due to sulfasalazine therapy (eg, headache, gastrointestinal complaints, leukopenia, and transaminitis) (n = 19)	
Yes	7 (37)

sulfasalazine therapy was 1.8 g/d for those with significant improvement and 2.6 g/d for those who failed treatment. Treatment failure was not associated with sex, ethnicity, duration of CIU symptoms, characteristics of the cellular infiltrate in the biopsy specimen, history of angioedema, thyrotropin level, presence of antimicrobial or antithyroglobin antibodies, or previous steroid use.

Thirteen patients required intermittent or long-term daily treatment with systemic steroids before initiation of sulfasalazine therapy for control of their urticaria. Of those patients, 9 did not require any steroid use during treatment with sulfasalazine, and the other 4 were able to reduce their dose of steroids 3- to 4-fold. One patient classified as a treatment failure did require steroids during sulfasalazine therapy, whereas she had not required any previously.

Six patients have been able to completely stop taking all other urticaria medication, including antihistamines and systemic steroids. Two of the aforementioned patients have tapered off sulfasalazine, and another has reduced her dosage of sulfasalazine by 50%, all without a recurrence of urticarial symptoms. Sulfasalazine therapy was tapered in the 3 others, and they developed increased urticaria, requiring a reinitiation of or an increase in the dosage.

Adverse effects attributed to sulfasalazine use were reported by 7 patients (37%). They ranged from mild headache and gastrointestinal discomfort to mild leukopenia (white blood cell count,  $3.7 \times 10^3/\mu\text{L}$  and  $4.2 \times 10^3/\mu\text{L}$ ) in 2 patients and elevated liver enzyme levels (aspartate aminotransferase/alanine aminotransferase, 54/75 IU/L) in 1 patient. All of these patients were able to continue the use of sulfasalazine, and the cases of leukopenia and elevated liver enzyme levels resolved spontaneously or with dose reduction.

There have been a few small case reports in the literature citing successful treatment of CIU with sulfasalazine in 6 subjects (5 men and 1 woman; mean age, 39.6 years). Three subjects were diagnosed as having CIU and 3 as having pressure-induced urticaria.<sup>38-40</sup> All 6 subjects had been diagnosed as having urticaria that was refractory to standard antihistamine treatment, and all required treatment with systemic steroids for control. Complete resolution of

the urticaria was seen in all patients after they took the sulfasalazine for anywhere from a few days to multiple weeks. The dosage of sulfasalazine therapy required for response ranged from 2 to 4 g/d, with a mean of 3.2 g/d. All subjects were able to stop using corticosteroids but did require a maintenance dose of sulfasalazine (2-3 g/d). The urticaria flared in 3 patients who attempted dose reduction below their maintenance dose. The mean follow-up period was 9 months. No adverse effects were reported, and 50% of the patients were reported to have undergone routine blood work during the treatment. Two patients also received folate supplementation (1 mg/d) during treatment. In summary, these patients were reported to have complete clearance of their urticaria, were able to stop taking systemic steroids, and had no reported adverse effects.

## COMMENT

Sulfasalazine is composed of a sulfapyridine covalently linked to 5-aminosalicylic acid. The sulfa moiety is known to have antimicrobial properties, whereas the salicylate component acts as an anti-inflammatory agent. Despite our knowledge of the structure and activity of sulfasalazine, we have a poor understanding of how it produces therapeutic effects in disease. It has been used most extensively in the treatment of inflammatory bowel disease (ie, Crohn disease and ulcerative colitis), and it also been used to treat rheumatoid arthritis, psoriasis, ankylosing spondylitis, and other spondyloarthropathies.<sup>41-46</sup>

We are reporting our use of sulfasalazine over the previous 3 years to treat 19 patients with CIU that was not adequately controlled with standard therapy. We classified 14 patients (74%) as having significant improvement with sulfasalazine therapy, and 6 of the patients were able to stop taking all other medication for CIU. Five patients (26%) were not satisfied with sulfasalazine and were considered treatment failures despite the fact that 4 of them did experience minimal improvement in symptoms. We also found that all 13 patients who had previously required systemic steroids for CIU control were able to completely stop or reduce their steroid intake during sulfasalazine therapy.

It is also worth noting that the patients in our study had different demographics from those of previously described CIU populations. Our cohort had a greater female-male ratio (4:1 vs 2:1)<sup>4</sup> and an increase in thyroid autoimmunity (38% vs 14%-27%).<sup>23,24</sup> Although we were unable to perform quality-of-life measurements owing to the retrospective nature of this study, it is likely that our cohort represents a more severe form of the disease. All patients seen in clinic were referred for recalcitrant CIU, as their urticaria had been inadequately controlled by antihistamines and other standard therapies. Also, more than half of the patients (68%) had required systemic steroids, and the mean CIU duration before the initiation of sulfasalazine therapy was 81 months. It is possible that being female and having evidence of thyroid autoimmunity may be associated with a more severe form of CIU, as both females and thyroid autoimmunity were over-represented in our cohort.

Our follow-up period ranged from a few months to 3 years, and because of that we have extremely variable longitudinal data on our patients. We do know that 6 patients with significant improvement were able to taper their sulfasalazine dosage. Two of the 6 patients were able to stop taking all other urticaria medications and then successfully tapered off sulfasalazine therapy and have been urticaria free for anywhere from 3 to 13 months. Another 2 were able to taper off sulfasalazine and all other urticaria medication for 4 to 12 months but then developed a recurrence. The last 2 patients tapered their dosage of sulfasalazine therapy from 2 g/d to 1 g/d, and 1 developed a mild increase in urticaria.

The dosage of sulfasalazine therapy for various inflammatory conditions has ranged widely from 2 to 6 g/d. We initially set our maximum dose at 4 g/d, but after we treated a number of patients, it became apparent that those without improvement at 2 g/d rarely improved at higher doses. Also, adverse effects have been reported to occur with greater frequency at higher doses, so we rarely prescribe a dose higher than 2 g/d. Of the patients who responded, most started to see an improvement after a few weeks, although some required closer to 1 month for any appreciable change in symptoms.

Seven patients (37%) reported adverse effects from the use of sulfasalazine, including gastrointestinal discomfort, nausea, and mild headache, as well as leukopenia and elevated liver enzyme levels. These complications have been reported previously, and all of the patients were able to continue taking sulfasalazine, although some reduced their dose from 2 g/d to 1.5 g/d. Also, the abnormal liver enzyme levels and leukopenia had resolved on follow-up testing. Because of the adverse effect profile of sulfasalazine and the laboratory monitoring required, we do not suggest it as a first-line agent for CIU. Instead, we believe that sulfasalazine therapy is most beneficial when antihistamines and other common medications with a more benign adverse effect profile (eg, H<sub>2</sub>-receptor antagonists and leukotriene antagonists) do not adequately control symptoms. Based on the current risk-benefit profile, it is reasonable to try sulfasalazine therapy instead of treatment with medications such as systemic steroids or cyclosporine. Because of concerns about prescribing sulfasalazine for patients reported to be sulfa allergic, 1 patient (not included in our data set) was started on olsalazine therapy (maximum dose, 1.5 g/d). Of note, she also experienced significant improvement in her urticaria.

We are aware that the retrospective nature of our case series does introduce certain biases, as we are relying on the patient record as the sole source of information. We were not able to have any objective measurement of change in disease during sulfasalazine therapy, and we were not able to standardize follow-up for all patients. Despite these problems, we do believe that the steroid-sparing effects and the impressive reduction in urticaria that the majority of our patients with fairly severe and long-standing, recalcitrant CIU experienced indicate that sulfasalazine therapy should be considered for patients with CIU that does not respond adequately to antihistamines.

It is not clear how sulfasalazine is able to reduce and even resolve CIU, but looking at the proposed causes of

CIU may help to elucidate the mechanism of action exerted by sulfasalazine. Overall, there has not been enough evidence to firmly establish a causal relationship between any infectious agent and CIU,<sup>47</sup> but if there were such a relationship, sulfasalazine might be able to reduce the urticaria, at least in part, through its antimicrobial properties. Interestingly, sulfasalazine has also been effective in the treatment of other autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. While we do not know whether our patients have an autoimmune basis for their urticaria, it is possible that sulfasalazine therapy is combating the autoimmune processes that lead to CIU.

In addition to a potential autoimmune component and/or infectious pathogenesis, basophils and mast cells are thought to play a role in CIU. A recent publication reports a difference in the FcεRI-signaling molecules in basophils and mast cells of patients with CIU that may be critical for development of urticaria.<sup>48</sup> In the 1990s, Lee and Kim<sup>49</sup> demonstrated reduced histamine release in the peritoneal mast cells of rats, when treated with sulfasalazine. Similar studies on human mast cells and basophils found the opposite, ie, that sulfasalazine enhanced IgE-induced histamine release.<sup>50,51</sup> Interestingly, the metabolite of sulfasalazine, 5-aminosalicylic acid, caused a reduction of IgE-induced release of histamine in human basophils and mast cells.<sup>50</sup> Although it is unclear how this alteration in basophil and mast cell function affects the presentation of CIU, we believe that it is possible that the clinical improvement seen with sulfasalazine therapy may be associated with a distinct phenotypic change in the histamine-releasing capabilities of basophils and/or mast cells.

Chronic idiopathic urticaria continues to be a frustrating disease for many patients. Therefore, we must look for new treatments and evaluate potential causes of this disease. In summary, we believe that the findings we report suggest that sulfasalazine therapy can be an effective and safe treatment for patients with recalcitrant CIU. Its ability to improve symptoms in the majority of our patients and to greatly reduce systemic steroid use indicates that it should be considered when standard therapies fail. We also believe that our initial results warrant further studies to better elucidate the efficacy of sulfasalazine in the treatment of CIU and to help clarify the mechanism of action of sulfasalazine in patients with CIU.

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**Author Contributions:** Dr Beck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* McGirt and Beck. *Acquisition of data:* McGirt, Vasagar, Gober, Saini, and Beck. *Analysis and interpretation of data:* McGirt, Vasagar, Gober, Saini, and Beck. *Drafting of the manuscript:* McGirt, Saini, and Beck. *Critical revision of the manuscript for important intellectual content:* McGirt, Saini, and Beck. *Statistical analysis:* McGirt and Beck. *Obtained funding:* Saini and Beck. *Ad-*

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## REFERENCES

1. Swinney B. The atopic factor in urticaria. *South Med J*. 1941;34:855-858.
2. Sheldon JM, Mathews KP, Lovell RG. The vexing urticaria problem: present concepts of etiology and management. *J Allergy*. 1954;25:525-560.
3. Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol*. 2003; 3:363-368.
4. Sibbald RG, Cheema AS, Lozinski A, Tarlo S. Chronic urticaria: evaluation of the role of physical, immunologic, and other contributory factors. *Int J Dermatol*. 1991;30:381-386.
5. Sabroe RA, Seed PT, Francis DM, Barr RM, Black AK, Greaves MW. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcεsilonRI or anti-IgE autoantibodies. *J Am Acad Dermatol*. 1999; 40:443-450.
6. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angioedema: a review of 554 patients. *Br J Dermatol*. 1969;81:588-597.
7. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136:197-201.
8. Greaves MW. Chronic Idiopathic urticaria and *H pylori*: not directly causative but could there be a link? *ACI Int*. 2001;13:23-26.
9. Federman DG, Kirsner RS, Moriarty JP, Concato J. The effect of antibiotic therapy for patients infected with *Helicobacter pylori* who have chronic urticaria. *J Am Acad Dermatol*. 2003;49:861-864.
10. Gaig P, Garcia-Ortega P, Enrique E, Papo M, Quer JC, Richard C. Efficacy of the eradication of *Helicobacter pylori* infection in patients with chronic urticaria: a placebo-controlled double blind study. *Allergol Immunopathol (Madr)*. 2002; 30:255-258.
11. Hook-Nikanne J, Varjonen E, Harvima RJ, Kosunen TU. Is *Helicobacter pylori* infection associated with chronic urticaria? *Acta Derm Venereol*. 2000;80:425-426.
12. Moreira A, Rodrigues J, Delgado L, Fonseca J, Vaz M. Is *Helicobacter pylori* infection associated with chronic idiopathic urticaria? *Allergol Immunopathol (Madr)*. 2003;31:209-214.
13. Serrano H. Hypersensitivity to "*Candida albicans*" and other fungi in patients with chronic urticaria [in Spanish]. *Allergol Immunopathol (Madr)*. 1975;3:289-298.
14. Tang XP, Zeng K, Chen GH, Bi LY, Fan LZ, Shao CF. Study of the association of *Malassezia furfur* with chronic urticaria among the ship crews [in Chinese]. *Di Yi Jun Yi Da Xue Xue Bao*. 2003;23:870-872.
15. Fiebigger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest*. 1995;96:2606-2612.
16. Tong LJ, Balakrishnan G, Kochan JP, Kinet JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol*. 1997;99: 461-465.
17. Zweiman B, Valenzano M, Atkins PC. Modulation of serum histamine releasing activity in chronic idiopathic urticaria. *Immunopharmacology*. 1998;39:225-234.
18. Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol*. 1996;106:1001-1006.
19. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med*. 1993;328:1599-1604.
20. Grattan CE. Histamine-releasing autoantibodies in chronic urticaria. *Skin Pharmacol*. 1991;4(suppl 1):64-70.
21. Kandeel AA, Zeid M, Helm T, Lillie MA, Donahue E, Ambrus JL Jr. Evaluation of chronic urticaria in patients with Hashimoto thyroiditis. *J Clin Immunol*. 2001; 21:335-347.
22. Turktas I, Gokcora N, Demirsoy S, Cakir N, Onal E. The association of chronic urticaria and angioedema with autoimmune thyroiditis. *Int J Dermatol*. 1997; 36:187-190.
23. Zauli D, Grassi A, Ballardini G, Contestabile S, Zucchini S, Bianchi FB. Thyroid autoimmunity in chronic idiopathic urticaria: implications for therapy. *Am J Clin Dermatol*. 2002;3:525-528.
24. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol*. 1989;84:66-71.
25. Kaplan AP. Chronic urticaria—new concepts regarding pathogenesis and treatment. *Curr Allergy Asthma Rep*. 2002;2:263-264.
26. Stanaland BE. Treatment of patients with chronic idiopathic urticaria. *Clin Rev Allergy Immunol*. 2002;23:233-241.
27. Kulthanan K, Gritiyarangsana P, Sitakalin C, et al. Multicenter study of the efficacy and safety of fexofenadine 60 mg twice daily in 108 Thai patients with chronic idiopathic urticaria. *J Med Assoc Thai*. 2001;84:153-159.
28. Vena GA, Cassano N, Filieri M, Filotico R, D'Argento V, Coviello C. Fexofenadine in chronic idiopathic urticaria: a clinical and immunohistochemical evaluation. *Int J Immunopathol Pharmacol*. 2002;15:217-224.
29. Sanada S, Tanaka T, Kameyoshi Y, Hide M. The effectiveness of montelukast for the treatment of anti-histamine-resistant chronic urticaria. *Arch Dermatol Res*. 2005;297:134-138.
30. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114:465-475.
31. Grattan CE, O'Donnell BF, Francis DM, et al. Randomized double-blind study of cyclosporin in chronic "idiopathic" urticaria. *Br J Dermatol*. 2000;143:365-372.
32. Di Gioacchino M, Di Stefano F, Cavallucci E, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc*. 2003;24: 285-290.
33. Cassano N, D'Argento V, Filotico R, Vena GA. Low-dose dapsone in chronic idiopathic urticaria: preliminary results of an open study. *Acta Derm Venereol*. 2005; 85:254-255.
34. Reeves GE, Boyle MJ, Bonfield J, Dobson P, Loewenthal M. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J*. 2004;34:182-186.
35. Gach JE, Sabroe RA, Greaves MW, Black AK. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol*. 2001;145: 340-343.
36. Weiner MJ. Methotrexate in corticosteroid-resistant urticaria. *Ann Intern Med*. 1989;110:848.
37. Bernstein JA, Garramone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol*. 2002;89:212-214.
38. Jaffer AM. Sulfasalazine in the treatment of corticosteroid-dependent chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1991;88:964-965.
39. Hartmann K, Hani N, Hinrichs R, Hunzelmann N, Scharffetter-Kochanek K. Successful sulfasalazine treatment of severe chronic idiopathic urticaria associated with pressure urticaria. *Acta Derm Venereol*. 2001;81:71.
40. Engler RJ, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. *Ann Allergy Asthma Immunol*. 1995; 74:155-159.
41. Dougados M, Boumier P, Amor B. Sulphasalazine in ankylosing spondylitis: a double blind controlled study in 60 patients. *Br Med J (Clin Res Ed)*. 1986; 293:911-914.
42. Willoughby CP, Cowan RE, Gould SR, Machell RJ, Stewart JB. Double-blind comparison of olsalazine and sulphasalazine in active ulcerative colitis. *Scand J Gastroenterol Suppl*. 1988;148:40-44.
43. Pinals RS, Kaplan SB, Lawson JG, Hepburn B. Sulfasalazine in rheumatoid arthritis: a double-blind, placebo-controlled trial. *Arthritis Rheum*. 1986;29:1427-1434.
44. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology*. 1979;77:847-869.
45. Gupta AK, Ellis CN, Siegel MT, et al. Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol*. 1990;126:487-493.
46. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondylarthropathy: a randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum*. 1995;38:618-627.
47. Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs*. 2004;64:2515-2536.
48. Vonakis BM, Saini SS. Basophils and mast cells in chronic idiopathic urticaria. *Curr Allergy Asthma Rep*. 2005;5:270-276.
49. Lee EH, Kim HM. Inhibition of anaphylaxis by sulfasalazine in rats. *Pharmacology*. 1998;56:223-229.
50. Fox CC, Moore WC, Lichtenstein LM. Modulation of mediator release from human intestinal mast cells by sulfasalazine and 5-aminosalicylic acid. *Dig Dis Sci*. 1991;36:179-184.
51. Barrett KE, Tashof TL, Metcalfe DD. Inhibition of IgE-mediated mast cell degranulation by sulphasalazine. *Eur J Pharmacol*. 1985;107:279-281.