



# Evaluating and managing chronic idiopathic urticaria in adults

Lindsay Webster, MPAS, PA-C; Nicholas L. Rider, DO; Mark E. Archambault, DHSc, PA-C, DFAAPA

## ABSTRACT

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria, is characterized by the presence of hives on most days of the week, for 6 weeks or longer, and without an identifiable or consistent cause. Evaluation is clinical and based on the presence of episodic urticarial lesions. Although patients are subject to overtesting during the diagnosis of CIU, guidelines suggest starting with three basic laboratory tests. Treatment is a stepwise approach, involving second-generation antihistamines, histamine<sub>2</sub> antagonists, leukotriene receptor antagonists, first-generation antihistamines, and potent antihistamines. Refractory CIU requires adding alternative agents such as omalizumab, anti-inflammatory agents, and immunosuppressants.

**Keywords:** chronic idiopathic urticaria, CIU, antihistamines, hives, refractory, immunosuppressants

## Learning objectives

- Describe the key elements of the history, physical examination, and workup needed to aid in the diagnosis of chronic idiopathic urticaria.
- Discuss the stepwise approach involved in the treatment of chronic idiopathic urticaria.
- Compare the different treatment options available for refractory chronic idiopathic urticaria.

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria, is characterized by the presence of hives on most days of the week, for 6 weeks or longer, without an identifiable or consistent cause. Up to 50% of patients also have accompanying angioedema.<sup>1</sup> In both the United States and worldwide, this

**Lindsay Webster** practices at Novant Health–Wallburg Family Medicine in Winston-Salem, N.C. **Nicholas L. Rider** is an associate professor of pediatrics at Baylor College of Medicine, Texas Children's Hospital, in Houston, Tex. **Mark E. Archambault** is an associate professor in the doctor of medical science program, physician assistant education concentration, at Lynchburg (Va.) College. The authors have disclosed no potential conflicts of interest, financial or otherwise.

DOI:10.1097/01.JAA.0000534976.46365.11

Copyright © 2018 American Academy of Physician Assistants



FIGURE 1. Characteristic urticarial lesions

disorder affects from 0.1% to 3% of the general population.<sup>2</sup> Because the disorder is triggered by inconsistent or unidentifiable factors, many patients are subject to overtesting and failed treatments, which impair their quality of life.

## CLINICAL PRESENTATION

The evaluation of CIU is clinical and based on the presence of episodic urticarial lesions found during the physical examination. However, the patient's history will reveal that the lesions usually appear and resolve within 24 hours. On physical examination, patients have urticarial lesions that are circumscribed, raised, and erythematous with a possible central pallor (Figure 1). Patients who also have angioedema typically present with asymmetric nonpitting swelling that occurred over minutes to hours and affects

**Key points**

- Evaluation of CIU is clinical and based on the presence of episodic urticarial lesions.
- Begin with three basic laboratory tests: CBC count, CRP or ESR, and thyroid-stimulating hormone level.
- Treatment is a stepwise approach, involving first- and second-generation antihistamines, histamine<sub>2</sub> antagonists, and leukotriene receptor antagonists.

the lips, cheeks, periorbital areas of the face, extremities, and/or genitalia.<sup>3</sup> These affected areas often are described by patients as numb or tingling in sensation.<sup>4</sup>

**Secondary causes** A key component of evaluating CIU is to obtain a detailed history to rule out a secondary cause (such as exposure to new drugs, including antibiotics, non-steroidal anti-inflammatory drugs [NSAIDs], and hormones) or association with systemic disease. NSAIDs have been known to worsen symptoms in 25% to 50% of patients.<sup>5</sup> Ask patients about other medical conditions, recent travel, infections, and other atopic conditions to rule out dermatologic manifestations that are not true urticarial reactions.<sup>6</sup> Patients with CIU have a higher prevalence of various autoimmune disorders, including thyroid disease, celiac disease, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes.<sup>7</sup>

**INITIAL DIAGNOSIS**

Patients with CIU often are subjected to extensive laboratory testing as clinicians seek a specific cause or systemic disease. However, most tests come back without abnormalities.

Initially, obtain a limited amount of tests to rule out systemic disorders that involve urticaria: a complete blood cell (CBC) count with differential, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and a thyroid-stimulating hormone level.<sup>8-12</sup> In patients with CIU, most of these laboratory values should be within normal limits. However, patients with uncomplicated urticaria without a secondary cause may at times have a slight elevation of ESR.<sup>13</sup> In contrast, complicated urticaria can include skin manifestations of the underlying systemic cause such as vasculidites, other rheumatologic disease, malignancy, or endocrinopathies, which often will be associated with laboratory test abnormalities.

Skin biopsy typically is reserved for patients who need to have urticarial vasculitis ruled out. These patients typically have painful lesions that persist longer than 24 hours, have an elevated CRP or ESR, systemic symptoms, and/or are unresponsive to antihistamines.<sup>14,15</sup>

**MANAGEMENT**

After secondary causes and systemic diseases are ruled out and the urticaria is deemed idiopathic, clinicians can initiate

treatment. Management routinely is approached in a stepwise fashion based on the management guidelines developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology (Table 1).<sup>9,12,16</sup>

Once a patient is diagnosed with CIU, the first step in treatment is to administer a second-generation antihistamine at the standard therapeutic dose. Patients also should eliminate aggravating factors. A substantial number of patients will experience exacerbations that are occasionally, but not predominately, triggered by physical stimuli. These physical stimuli include heat, extreme humidity, cold, and pressure. Patients also should be counseled to abstain from NSAIDs, which worsen CIU symptoms in 20% to 40% of patients.<sup>5,17</sup>

If the patient's symptoms do not improve after 1 to 2 weeks of a second-generation antihistamine at a standard dose, the next step provides multiple options for increasing therapy:

- *Increase the dose of the second-generation antihistamine.* The US guidelines, in addition to others, advocate for up to four times the standard dose of a second-generation antihistamine.<sup>16,18,19</sup> Increasing the dosage works best for levocetirizine and desloratadine.<sup>20</sup>

---

No guidelines exist for  
managing refractory CIU,  
so treatment must be  
individualized.

---

- *Add a different second-generation antihistamine to the original therapy.* For example, a patient taking fexofenadine could be prescribed a loratadine, desloratadine, cetirizine, or levocetirizine.
- *Add a histamine<sub>2</sub> antagonist such as ranitidine.* This option can improve symptoms in a patient not satisfactorily controlled by histamine<sub>1</sub> antihistamines.
- *Add a leukotriene receptor antagonist.* Symptoms resistant to histamine<sub>1</sub> antihistamine monotherapy may respond to leukotriene receptor antagonists, either as monotherapy or as an adjunctive therapy. The preferred leukotriene modifiers are montelukast and zafirlukast, which do not require monitoring of any laboratory values; patients on zileuton require routine liver function testing.
- *Add a first-generation antihistamine at bedtime.* This approach is recommended for patients who have failed the previous options of higher-dosed second-generation antihistamines, the addition of histamine<sub>2</sub> antagonists, and/or the addition of leukotriene receptor antagonists.<sup>9</sup>

Patients whose symptoms fail to improve after step 2 therapy may be considered for step 3, treatment with short-acting antihistamines. The two most commonly used medications in this category are hydroxyzine and doxepin. Both are started at 10 to 25 mg daily, and increased in weekly increments. When these medications are used at high doses (such as 75 to 150 mg per day), they often are associated with control of CIU symptoms.<sup>21</sup> Patients who continue to have symptoms after failing these therapies are considered to have refractory CIU.

Systemic glucocorticoids can be periodically used at any point in a treatment plan for patients in need of temporary control of a severe urticarial exacerbation. Glucocorticoid use generally is supplementary to the other medications for CIU. Although the dose and duration of treatment is individualized based on the patient's responsiveness, experts typically suggest a starting dose of 30 to 40 mg of prednisolone daily with food, for 2 to 7 days.<sup>22,23</sup>

In patients with severe exacerbations, use systemic glucocorticoids for the shortest duration possible. Some patients may require treatment for longer periods, and may be on glucocorticoids for months at a time. When systemic glucocorticoids are used for longer periods of treatment, they should be tapered to avoid adrenal suppression and a rebound in CIU symptoms.<sup>24</sup>

### TREATING REFRACTORY SYMPTOMS

Patients with symptoms that are not controlled by standard therapy typically are treated with multiple courses of glucocorticoids, or may undergo extended periods of glucocorticoid therapy, putting them at risk for adverse reactions and toxicity. Therefore, other options for

refractory CIU are commonly sought. These treatment options include omalizumab in addition to certain anti-inflammatory drugs and immunosuppressants. When managing a patient with refractory CIU, consider referral to a subspecialist who has more experience with the administration of these medications.<sup>22</sup> No guidelines exist for managing refractory CIU, so the treatment must be individualized based on the patient's coexistent medical conditions and preferences. The treatment options have different levels of efficacy, adverse reaction profiles, and cost.<sup>21</sup>

**Omalizumab** Based on an ample amount of data showing its safety and effectiveness in treating CIU, omalizumab is the drug of choice for patients with or without glucocorticoid toxicity secondary to refractory CIU.<sup>25-28</sup> However, it may not be the preferred option for most patients. The drug is expensive, must be administered in a clinic, and provides a shorter remission time compared with other treatments.<sup>21</sup>

**Anti-inflammatory agents** For patients with refractory CIU who do not wish to take omalizumab and do not have glucocorticoid toxicity, anti-inflammatory agents are an option. The medications of this class that are most studied for refractory CIU are dapsone, sulfasalazine, and hydroxychloroquine. These drugs are less expensive than omalizumab and are all taken orally, eliminating the need for administration by medical professionals. However, the onset of symptom improvement with these drugs is between 1 and 3 months.<sup>21</sup>

Dapsone is the most commonly used drug in this group because it is well tolerated, widely available, and inexpensive. The initial dose is 50 to 100 mg daily.<sup>29</sup> Note that dapsone is associated with asymptomatic methemoglobinemia, and less commonly is associated with hepatotoxicity and other hematologic abnormalities such as DRESS syndrome. Patients should have a CBC count and liver function tests after 2 weeks of therapy; repeat these tests monthly for 3 months before gradually increasing the time between tests.<sup>21,30</sup>

Sulfasalazine also is frequently used as adjunctive therapy for patients with refractory symptoms.<sup>31-34</sup> The typical starting dosage is 500 mg once or twice a week, gradually increased to 1 g twice daily. Although most patients tolerate this drug well, some experience nausea, headache, leukopenia, and elevated transaminases.<sup>32</sup> For that reason, a CBC count, liver function tests, and urinalysis should be performed every month for the first 3 months, then less frequently as treatment progresses.<sup>21</sup>

Hydroxychloroquine has a slower onset of action compared with the other anti-inflammatory drugs, but also only modestly impairs a patient's quality of life—the only adverse reactions are nausea, rash, and headache. However, because hydroxychloroquine is associated with increased risk of retinopathy after 5 years of use, patients should have a baseline ophthalmologic examination within the first year of starting treatment.<sup>35</sup> This drug typically is

**TABLE 1. Stepwise approach to treating chronic idiopathic urticaria**

#### STEP 1

- Begin monotherapy with a second-generation antihistamine
- Avoid triggers

#### STEP 2

One or more of the following:

- Dose advancement of the second-generation antihistamine used in step 1
- Add another second-generation antihistamine
- Add a histamine<sub>2</sub> antagonist
- Add a leukotriene receptor antagonist
- Add a first-generation antihistamine to be taken at bedtime

#### STEP 3

Dose advancement of potent antihistamines (such as hydroxyzine or doxepin) as tolerated

#### STEP 4, for patients with refractory symptoms

Add an alternative agent such as omalizumab, an anti-inflammatory, or an immunosuppressant

started at 200 mg twice a day and requires a 3-month trial to determine its effectiveness.<sup>21,36</sup>

**Immunosuppressants** For patients with glucocorticoid toxicity who do not wish to take omalizumab or have failed treatment with omalizumab, immunosuppressants may be beneficial. Cyclosporine, tacrolimus, sirolimus, and mycophenolate are associated with a more rapid effect than anti-inflammatory agents, letting patients taper off glucocorticoids more rapidly.<sup>21</sup>

Cyclosporine is associated with rapid onset of action, with some reports of improvement within days, and lasting remission.<sup>37-39</sup> Two techniques can be used for prescribing this drug: Lower doses, ranging from 2 to 4 mg/kg/day, or starting with a high dose and tapering down to the lowest effective dose.<sup>38,40,41</sup> These two approaches let patients receive long-term benefit with the lowest adverse reaction profile possible. Most patients taking cyclosporine receive symptom relief within 3 months.<sup>40</sup> Regardless of the dose and duration of therapy, patients taking cyclosporine should have their BP, blood urea nitrogen, and creatinine tested monthly and fasting lipids tested periodically.<sup>42</sup>

## Medication costs can drive low-income patients to choose less-expensive but less-optimal treatments.

Tacrolimus, sirolimus, and mycophenolate also can be prescribed for patients with refractory CIU. However, data supporting these drugs is limited. The few studies that do exist show that these drugs successfully treat refractory CIU.<sup>43-46</sup> Laboratory test monitoring for tacrolimus is similar to that for cyclosporine. Tacrolimus is started at 1 mg twice daily for 1 week, and then increased to 2 mg twice daily if there is no proven benefit in 1 to 2 weeks.<sup>21</sup>

Mycophenolate typically is started at 1 g twice daily. After 2 to 4 weeks, this dose can be increased by 500 mg twice daily, up to 6 g per day.<sup>21,46</sup>

The optimal duration of immunosuppressant treatment options is not known but cyclosporine, tacrolimus, and sirolimus are typically given a 1-month trial to determine efficacy. Mycophenolate is given a longer trial because of its slower onset and because it may need to be titrated up to an effective dose. However, most patients with refractory CIU see symptom improvement within days.<sup>21</sup>

### COST OF CARE

The evaluation and management of CIU can create a financial burden regardless of a patient's socioeconomic status. Broder and colleagues reported that the average healthcare cost for a patient with CIU was more than

\$9,000 US per year.<sup>47</sup> Because CIU mostly is treated in an outpatient setting and is chronic in nature, medication costs account for more than half of the annual expenses.<sup>48</sup> Medications can range from under \$50 US per month for antihistamines to \$1,000 US per injection of omalizumab.<sup>49,50</sup> The cost of medications alone can drive low-income patients to choose a less-expensive treatment, potentially leading to suboptimal control of their condition and poorer quality of life.

### CONCLUSION

The average duration of CIU ranges from 2 to 5 years but 30% to 50% of patients achieve spontaneous remission within 1 year.<sup>51-53</sup> Up to 30% of patients continue to have symptoms past 5 years.<sup>54,55</sup>

Although the natural course of CIU is episodic and self-limited in most patients, the disorder can cause marked physical and psychological distress. The unpredictability and discomfort can interfere with a patient's activities or sleep. Clinicians must reassure patients that the condition is rarely permanent, rarely puts them in any acute risk, and can be successfully managed with time. **JAAPA**

**Earn Category I CME** Credit by reading both CME articles in this issue, reviewing the post-test, then taking the online test at <http://cme.aapa.org>. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of July 2018.

### REFERENCES

1. Sabroe RA, Seed PT, Francis DM, et al. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-Fc $\epsilon$ RI or anti-IgE autoantibodies. *J Am Acad Dermatol*. 1999;40(3):443-450.
2. Khan S, Maitra A, Hissaria P, et al. Chronic urticaria: Indian context—challenges and treatment options. *Dermatol Res Pract*. 2013;2013:651737.
3. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol*. 2004;114(3):465-474.
4. Kaplan AP. Angioedema. *World Allergy Organ J*. 2008;1(6):103-113.
5. Grattan CE. Aspirin sensitivity and urticaria. *Clin Exp Dermatol*. 2003;28(2):123-127.
6. Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol*. 2002;89(6):542-550.
7. Confino-Cohen R, Chodick G, Shalev V, et al. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129(5):1307-1313.
8. Kozel MM, Bossuyt PM, Mekkes JR, Bos JD. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: a systematic review. *J Am Acad Dermatol*. 2003;48(3):409-416.
9. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270-1277.
10. Maurer M, Magerl M, Metz M, Zuberbier T. Revisions to the international guidelines on the diagnosis and therapy of chronic urticaria. *J Dtsch Dermatol Ges*. 2013;11(10):971-977.

11. Hide M, Hiragun T, Japanese Dermatological Association. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. *Allergol Int*. 2012;61(4):517-527.
12. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69(7):868-887.
13. Jacobson KW, Branch LB, Nelson HS. Laboratory tests in chronic urticaria. *JAMA*. 1980;243(16):1644-1666.
14. Beltrani VS. Urticaria: reassessed. *Allergy Asthma Proc*. 2004;25(3):143-149.
15. Zuberbier T. Urticaria. *Allergy*. 2003;58(12):1224-1234.
16. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy*. 2007;37(5):631-650.
17. Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol*. 2004;113(4):771-775.
18. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria. *Allergy*. 2009;64(10):1427-1443.
19. Ortonne JP. Chronic urticaria: a comparison of management guidelines. *Expert Opin Pharmacother*. 2011;12(17):2683-2693.
20. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125(3):676-682.
21. Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract*. 2013;1(5):433-440.e1.
22. Schaefer P. Urticaria: evaluation and treatment. *Am Fam Physician*. 2011;83(9):1078-1084.
23. Yadav S, Bajaj AK. Management of difficult urticaria. *Indian J Dermatol*. 2009;54(3):275-279.
24. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med*. 2002;346(3):175-179.
25. Maurer M, Altrichter S, Bieber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128(1):202-209.e5.
26. Metz M, Maurer M. Omalizumab in chronic urticaria. *Curr Opin Allergy Clin Immunol*. 2012;12(4):406-411.
27. Saini S, Rosen KE, Hsieh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128(3):567-573.e1.
28. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368(10):924-935.
29. Morgan M, Cooke A, Rogers L, et al. Double-blind placebo-controlled trial of dapsone in antihistamine refractory chronic idiopathic urticaria. *J Allergy Clin Immunol Pract*. 2014;2(5):601-606.
30. Mehta A, Godse K, Patil S, et al. Treatment of refractory chronic urticaria. *Indian J Dermatol*. 2015;60(3):230-237.
31. Orden RA, Timble H, Saini SS. Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2014;112(1):64-70.
32. McGirt LY, Vasagar K, Gober LM, et al. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. *Arch Dermatol*. 2006;142(10):1337-1342.
33. Hartmann K, Hani N, Hinrichs R, et al. Successful sulfasalazine treatment of severe chronic idiopathic urticaria associated with pressure urticaria. *Acta Derm Venereol*. 2001;81(1):71.
34. Berkun Y, Shalit M. Successful treatment of delayed pressure urticaria with montelukast. *Allergy*. 2000;55(2):203-204.
35. Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. *Ophthalmology*. 2011;118(2):415-422.
36. Reeves GE, Boyle MJ, Bonfield J, et al. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J*. 2004;34(4):182-186.
37. Marsland AM, Beck MH. Cold urticaria responding to systemic ciclosporin. *Br J Dermatol*. 2003;149(1):214-215.
38. 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(4):285-290.
39. Galindo Bonilla PA, Borja Segade J, Gómez Torrijos E, Feo Brito F. Urticaria and cyclosporine. *Allergy*. 2002;57(7):650-651.
40. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long-term therapy. *Allergy*. 2010;65(11):1478-1482.
41. Hollander SM, Joo SS, Wedner HJ. Factors that predict the success of cyclosporine treatment for chronic urticaria. *Ann Allergy Asthma Immunol*. 2011;107(6):523-528.
42. Chakravarty K, McDonald H, Pullar T, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology (Oxford)*. 2008;47(6):924-925.
43. Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol*. 2005;52(1):145-148.
44. Morgan M. Treatment of refractory chronic urticaria with sirolimus. *Arch Dermatol*. 2009;145(6):637-639.
45. Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol*. 2006;45(10):1224-1227.
46. Zimmerman AB, Berger EM, Elmariah SB, Soter NA. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: experience in 19 patients. *J Am Acad Dermatol*. 2012;66(5):767-770.
47. Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. *Am J Clin Dermatol*. 2015;16(4):313-321.
48. Delong LK, Culler SD, Saini SS, et al. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. *Arch Dermatol*. 2008;144(1):35-39.
49. Consumer Reports. Using the antihistamines to treat allergies, hay fever, and hives: comparing effectiveness, safety, and price. [www.consumerreports.org/content/dam/cro/news\\_articles/health/PDFs/Antihistamines\\_Full\\_Report.pdf](http://www.consumerreports.org/content/dam/cro/news_articles/health/PDFs/Antihistamines_Full_Report.pdf). Accessed March 20, 2018.
50. America's Health Insurance Plans. High-priced drugs: estimates of annual per-patient expenditures for 150 specialty medications. [www.ahip.org/wp-content/uploads/2016/04/HighPriceDrugsReport.pdf](http://www.ahip.org/wp-content/uploads/2016/04/HighPriceDrugsReport.pdf). Accessed February 21, 2018.
51. Greaves M. Chronic urticaria. *J Allergy Clin Immunol*. 2000;105(4):664-672.
52. Kulthanan K, Jiamton S, Thumpimukvatana N, Pinkaew S. Chronic idiopathic urticaria: prevalence and clinical course. *J Dermatol*. 2007;34(5):294-301.
53. Kozel MM, Mekkes JR, Bossuyt PM, Bos JD. Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol*. 2001;45(3):387-391.
54. Toubi E, Kessel A, Avshovich N, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy*. 2004;59(8):869-873.
55. van der Valk PG, Moret G, Kiemeny LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol*. 2002;146(1):110-113.