

Diagnosing and Managing Chronic Spontaneous Urticaria in Primary Care: Examining the Latest Clinical Evidence for Improved Patient Outcomes and Quality of Life

PeerView

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Activity Description

In this activity, an expert discusses strategies to optimize the care of patients with chronic spontaneous urticaria in the primary care setting.

Target Audience

This activity has been designed to meet the educational needs of primary care physicians, and other clinicians involved in the management of patients with chronic spontaneous urticaria.

Educational Objectives

Upon completion of this activity, participants should be better able to:

- Recognize the clinical presentation of chronic spontaneous urticaria and its impact on patient quality of life
- Employ evidence-based guidelines to accurately diagnose patients with chronic spontaneous urticaria
- Apply therapeutic options for treating chronic spontaneous urticaria in the context of available evidence and current treatment algorithms
- Assess key data sets on the efficacy and safety of emerging pharmacologic treatments for chronic spontaneous urticaria

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Diagnosing and Managing Chronic Spontaneous Urticaria in Primary Care: Examining the Latest Clinical Evidence for Improved Patient Outcomes and Quality of Life

Chronic Spontaneous Urticaria: Confirming the Diagnosis

Dr. Bernstein: Hello. This is Dr. Jonathan Bernstein from the University of Cincinnati College of Medicine and Bernstein Allergy Group/Clinical Research Center in Cincinnati, Ohio. Welcome to this unique case-based educational activity on diagnosing and managing chronic spontaneous urticaria.

INTRODUCTION

This activity will give you the opportunity to explore strategies to confirm an early and accurate diagnosis in the primary care setting, as well as guide you through the labyrinth of treatment options to optimize care. So, let's get started and meet our patient, and see how management decisions can change based on variable patient-, disease-, and treatment-related factors.

Sarah: A 31-Year-Old Woman Who Presents to Her Primary Care Physician^a

Complaint

- "Randomly breaking out in hives" for ~2 months
- Cannot figure out what is triggering her symptoms

Personal History

- Recently married
- Currently employed as a flight attendant



^a Stock photo. Posed by model.

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Dr. Bernstein: This is Sarah, a 31-year-old woman who presents to you, her primary care physician, with a complaint of randomly breaking out in hives for approximately 2 months. She says she cannot figure out what is triggering her symptoms. Sarah is recently married. She works as a flight attendant. She has a very erratic schedule, and this is the reason it took her so long to make an appointment.

How should we approach the initial evaluation of this patient with persistent urticaria, which is defined as a condition characterized by the development of wheals, which are referred to as hives, angioedema, or both? First of all, urticaria needs to be differentiated from other medical conditions where wheals,

angioedema, or both can occur—for example, anaphylaxis, autoinflammatory syndromes, urticarial vasculitis, or bradykinin-mediated angioedema, including hereditary angioedema.

Wheals and Angioedema in Urticaria: Typical Features¹

Wheals in Patients With Urticaria

- Central swelling of variable size, almost invariably surrounded by reflex erythema
- An itching or sometimes burning sensation
- A fleeting nature, with the skin returning to its normal appearance, usually within 30 minutes to 24 hours

Angioedema in Patients With Urticaria

- Sudden, pronounced erythematous or skin-colored swelling of the lower dermis and subcutis or mucous membranes
- Sometimes painful, rather than itchy
- A resolution slower than that of wheals (can take up to 72 hours)

1. Zuberbier T et al. *Allergy*. 2018;73:1393-1414.

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So it's important that we understand how to classify wheals and angioedema in urticaria. Wheals in patients with urticaria have three typical features: they have a central swelling of variable size, almost invariably surrounded by a reflex erythema; they have an itching or sometimes burning sensation; and they're fleeting in nature, with skin returning to its normal appearance, usually within 30 minutes to 24 hours. We call this evanescence. In contrast, angioedema is a sudden, pronounced, erythematous or skin-colored swelling of the lower dermis and subcutis or mucous membranes. It's sometimes painful, rather than itchy. And angioedema may have a slower resolution than wheals, whereas it can take up to 72 hours.

Classification of Urticaria on the Basis of Duration and Relevance of Eliciting Factors¹

- Urticaria should be classified as acute (≤ 6 weeks) or chronic (> 6 weeks)
- Urticaria should be classified as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved)

Recommended Classification of Chronic Urticaria

Chronic Spontaneous Urticaria	Inducible Urticaria
• Spontaneous appearance of wheals, angioedema, or both for > 6 weeks due to known or unknown causes	• Symptomatic dermatographism • Cold urticaria • Delayed pressure urticaria • Solar urticaria • Heat urticaria • Vibratory angioedema • Cholinergic urticaria • Contact urticaria • Aquagenic urticaria

1. Zuberbier T et al. *Allergy*. 2018;73:1393-1414.

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Urticaria is classified as being acute when it lasts for 6 or fewer weeks, or chronic when it has lasted longer than 6 weeks. Urticaria should also be classified as spontaneous, meaning there's no specific eliciting factor involved, or inducible, where there is a specific eliciting factor involved.

CSU: Clinical Presentation and Differential Diagnosis¹⁻⁵

This is a picture of Sarah's chest



CSU

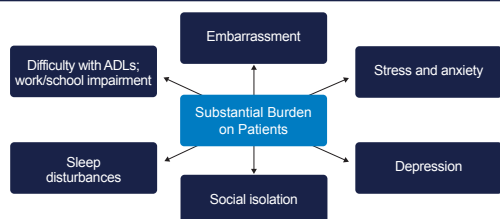
- Edematous pink or red wheals of variable size and shape with surrounding erythema; generally pruritic
- Individual urticaria lesions typically last 12-24 h, but new lesions might be developing simultaneously at other skin sites
- Urticarial vasculitis**
 - Individual wheals that last for >24 hours, are painful, and leave residual hyperpigmentation or purpura
- Cutaneous mastocytosis**
 - Orange to brown hyperpigmentation of the lesions that remain
 - Darier sign: urtication upon scratching over lesions; assumes no dermatographism



1. Schaefer P. *Am Fam Physician*. 2011;83:1078-1084. 2. Bernstein JA et al. *J Allergy Clin Immunol*. 2014;133:1270-1277. 3. Kahn S, Smith EG. In a Page: *Signs and Symptoms*. Malden, MA: Blackwell Publishing; 2004. 4. Katsaris C, Peake J. *Med J Aust*. 2006;185:517-522. 5. Hong-feng C et al. *Chinese External Medicine*. Beijing, China: People's Medical Publishing House; 2011. PeerView.com

This is a picture of Sarah's chest. And you can see that she has multiple edematous pink or red wheals of variable size and shape with surrounding erythema. And Sarah complains that they're very itchy. Individual urticaria lesions typically last 12 to 24 hours, but new lesions might be developing simultaneously at other skin sites.

Burden of Disease¹⁻⁸



1. O'Donnell BF. *Immunol Allergy Clin North Am*. 2014;34:89-104. 2. Schaefer P. *Am Fam Physician*. 2011;83:1078-1084. 3. Bertino AM et al. *Eur Ann Allergy Clin Immunol*. 2006;38:149-152. 4. Baiardini I et al. *Allergy*. 2003;58:621-623. 5. Sussman G et al. Poster presented at: 23rd World Congress of Dermatology (WCD 2015). 6. Ballo MM et al. Poster presented at: WCD 2015. 7. Nelson HS et al. *Ann Allergy Asthma Immunol*. 2000;94:517-522. 8. O'Donnell BF et al. *Br J Dermatol*. 1997;136:197-201. PeerView.com

So, needless to say, having chronic hives can cause a significant burden of disease on patients. Patients can be embarrassed by these lesions. They can induce stress and anxiety, make patients depressed, cause them to be socially isolated, have sleep disturbances, and interfere with daily activities, either work or school.

Angioedema Concomitant With CSU

Sarah has not experienced angioedema with her urticaria, but that is not the case for many patients ...

Occurs in approximately 40% of patients with CSU

Symptoms

- ☐ Swelling of the deep layers of the skin
- ☐ Overlying skin may appear normal
- ☐ May be more painful than pruritic
- ☐ Can last up to 72 hours
- ☐ Usually affects the face, lips, tongue, eyelids, throat, or extremities, but not the larynx

- If CSU is not present in patients presenting with angioedema, consider HAE or acquired C1-inhibitor deficiency
- Patients who present with angioedema have a greater chance of CSU lasting >12 months; also associated with increased CSU severity and further impact on QOL

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Sarah has not experienced angioedema with urticaria, but that is not the case for many patients. In fact, up to 40% of patients with chronic urticaria can also have associated angioedema. As mentioned, the swelling involves deeper layers of the skin, whereas the overlying skin may appear normal, and these lesions may be more painful than pruritic, and they tend to last up to 72 hours. They involve the face, lips, tongue, eyelids, sometimes the throat or extremities, but typically not the larynx.

If chronic spontaneous urticaria is not present, and patients present with isolated angioedema, one should consider hereditary angioedema or acquired C1-inhibitor deficiency. Patients who present with angioedema have a greater chance of having chronic spontaneous urticaria lasting longer than 12 months. And, again, there's an association with increased chronic spontaneous urticaria severity and impact on quality of life.

CSU Diagnostic Work-Up¹

Major Aims

1. To exclude differential diagnoses
2. To assess disease activity, impact, and control
3. To identify triggers of exacerbation or, where indicated, any underlying causes

1. Zuberbier T et al. *Allergy*. 2018;73:1393-1414.

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So we need to understand, what is the diagnostic workup for chronic spontaneous urticaria?

Recommended Diagnostic Tests in Spontaneous Urticaria¹

	Acute Spontaneous Urticaria	CSU
Routine diagnostic tests (recommended)	None	Differential blood count; ESR and/or CRP
Extended diagnostic program²	None	- Avoidance of suspected triggers (eg, drugs) - Conduction of diagnostic tests for (in no preferred order): • Infectious diseases (eg, <i>Helicobacter pylori</i>) • Functional auto-antibodies (eg, autologous skin serum test) • Thyroid gland disorders (thyroid hormones and auto-antibodies) • Allergy (skin tests and/or allergen avoidance test [eg, avoidance diet]) • Concomitant chronic inducible urticaria • Severe systemic diseases (eg, tryptase) • Other (eg, lesional skin biopsy)

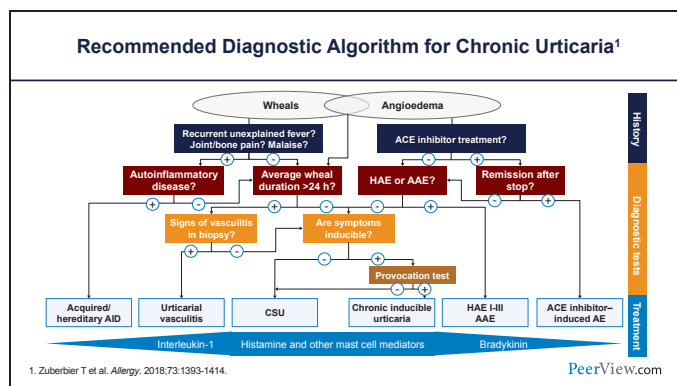
² Based on history, for identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated.

1. Zuberbier T et al. *Allergy*. 2018;73:1393-1414.

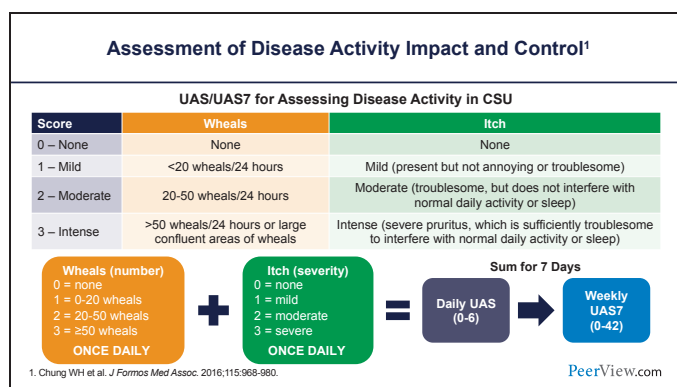
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There are some very clear recommendations and guidelines on what diagnostic tests to order in spontaneous urticaria. And in fact, in patients who have acute hives, it's actually recommended not to get any type of routine diagnostic test.

Now, when patients have chronic spontaneous hives, the guidelines recommend limited blood testing, getting a differential blood count, possibly a sedimentation rate with or without a C-reactive protein. One should avoid suspected triggers if there is something that is correlating with the onset of hives. One can also do other diagnostic tests based on the patient's history to rule out infectious diseases, whether there are underlying autoimmune conditions contributing to this, or other inducible types of urticaria.



This is a nice diagnostic algorithm for chronic urticaria that's published in the international guidelines for urticaria. And it basically breaks this down to wheals versus angioedema. And you can see that there is overlap in the case of chronic spontaneous urticaria with angioedema. And one can walk through this very nicely and try to identify, is this patient somebody who has chronic spontaneous urticaria or chronic inducible urticaria? And it helps rule out other underlying causes, such as acquired or hereditary angioedema, ACE-induced angioedema, urticaria vasculitis, and so forth.



Now, when we assess urticaria, it's important we use objective criteria so that we can at least see where patients begin at baseline and how they respond to treatment over time. And one tool is called the Urticaria Activity Score, and it's been validated and a very useful tool for assessing disease severity in chronic spontaneous urticaria. It's on a score from 0 to 3, and it's broken down into wheals and pruritus. Now, when you take these scores,

there's a total of 6 points, 3 for wheals, 3 for pruritus. You summate these scores. And then to get to 7, the UAS7, that's done for each day of the week for a week. So 7 times 6, the maximum score is 42.

Sarah^a

Order a CBC with differential and CRP and ESR laboratory tests

Laboratory tests come back normal

Diagnosis of CSU can be made in a patient with:

- ✓ Characteristic skin lesions of urticaria and/or angioedema
- ✓ Lesions appear and resolve repeatedly over a period of ≥ 6 weeks
- ✓ No other signs of systemic illness
- ✓ Laboratory testing is usually normal

^a Stock photo. Posed by model. PeerView.com

So we're back to Sarah. Just to be safe, because of her history and the chronicity, you follow the guidelines and you order a complete blood count with differential and a CRP and a sedimentation rate. These laboratory tests come back normal. So, based on her history, the diagnosis of chronic spontaneous urticaria can be made with her characteristic skin lesions and the evanescent nature of these lesions, and then the persistence of these lesions for 6 weeks or longer. Again, there should be no other signs of systemic illness, and laboratory testing is usually normal in these individuals.



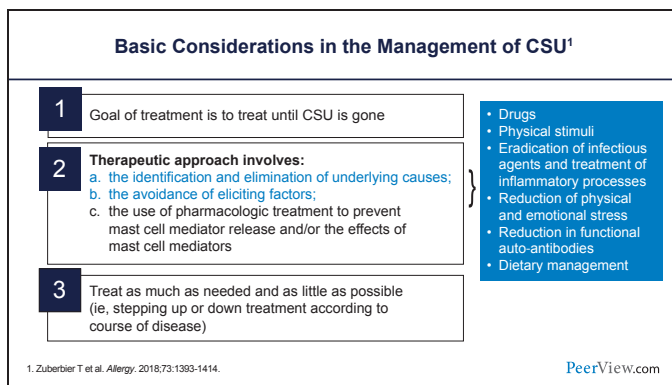
Stock photo.
Posed by model.

In this online activity, learners are introduced to Sarah, a 31-year-old woman with hives, along with a choice of Decision Points and Complicating Variables. After choosing one of each, Dr. Jonathan Bernstein reviews the implications of this unique set of factors.

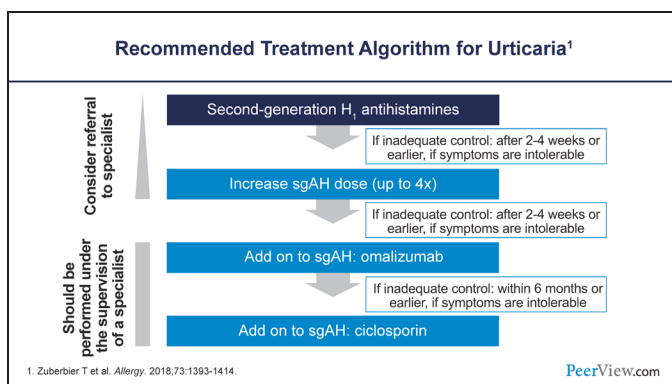
Learners are then able to choose different parameters, to see how the case and recommendations change.

Managing a Patient With Newly Diagnosed CSU

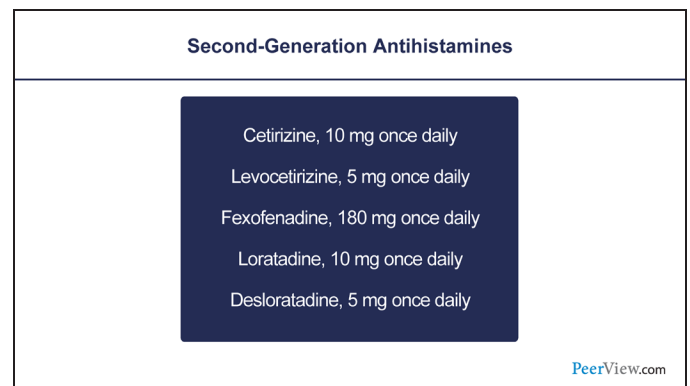
MAKE A CASE: NEWLY DIAGNOSED CSU



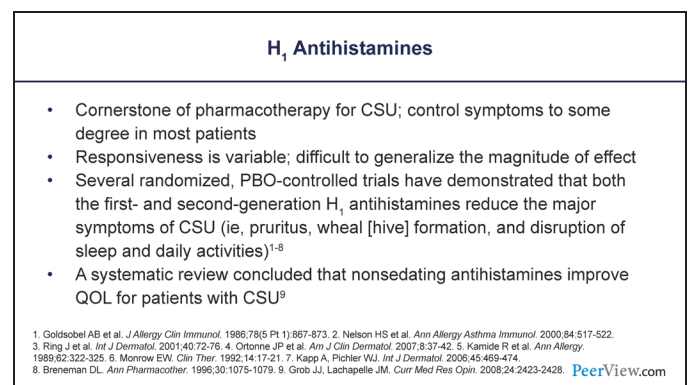
Dr. Bernstein: So we're going to introduce you to newly diagnosed chronic spontaneous urticaria. So what are the basic considerations? Well, the goal of treatment is to treat the disease until it's gone. And the therapeutic approach to chronic urticaria can involve the identification and elimination of underlying causes, the avoidance of eliciting factors, and the use of pharmacologic treatment to prevent mast cell mediator release and/or the effects of mast cell mediators. Some of the things we're ruling out are things are like drugs, inducible stimuli, infectious causes, and so forth. Treatment should follow the basic principles of treating as much as needed and as little as possible. This may mean stepping up or stepping down in the treatment algorithm according to the course of disease.



And this is the treatment algorithm, and it begins with using a second-generation antihistamine as monotherapy, and then if it's inadequate—if it doesn't control the hives after 2 to 4 weeks—one should consider the next step, which would be to actually go up to four times the recommended dose for antihistamines.



So second-generation antihistamines include cetirizine, which comes as 10-mg tablets; levocetirizine, which is 5-mg tablets; fexofenadine, 180-mg tablets; loratadine, 10-mg tablets; and desloratadine, 5-mg tablets. All of these have been studied in hives and been found to be effective.



They tend to be the cornerstone of pharmacotherapy for chronic spontaneous urticaria, and they control symptoms to at least some degree in most patients.

DECISION POINT

Newly Diagnosed CSU

COMPLICATING VARIABLE

- Sarah travels frequently for work and asks about treatment options that require minimal monitoring

Sarah^a

A systematic review of randomized trials concluded that there was insufficient evidence to make recommendations for any specific second-generation agent over another when each was used at approved doses¹

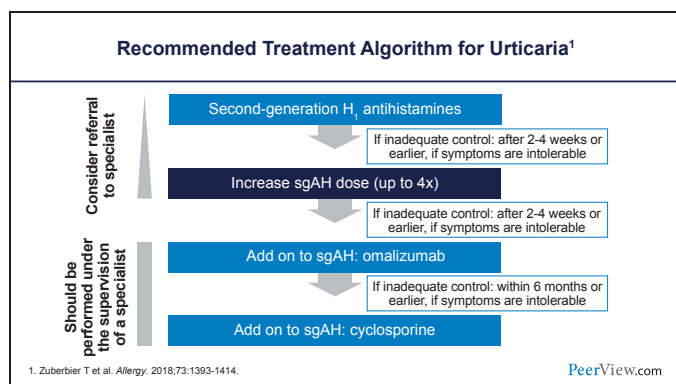


- No need for "monitoring" while taking a second-generation antihistamine

* Stock photo. Posed by model.
1. Sharma M et al. Cochrane Database Syst Rev. 2014;(11):CD006137.

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Dr. Bernstein: So now we have this newly diagnosed chronic spontaneous urticaria. What are the complicating variables that can interfere with treatment? Well, as mentioned, Sarah travels frequently for work, and she asks about the treatment options that require minimal monitoring. Sarah can be informed that there is no need for monitoring while she is taking a second-generation antihistamine.



However, symptom control should be assessed within 1 to 2 weeks, and Sarah should be aware that most patients require higher-than-approved doses of H₁ antagonists, and this can be up to four times the recommended dose for a non-sedating second-generation antihistamine.

DECISION POINT

Newly Diagnosed CSU

COMPLICATING VARIABLE

- Sarah asks about what adverse events she can expect with recommended treatment options

Safety of Antihistamines¹

- Antihistamines have been available for the treatment of urticaria since the 1950s

- First-Generation Safety Profile**
 - Pronounced anticholinergic effects and sedative actions on CNS
 - Many interactions with alcohol and drugs affecting the CNS (ie, analgesics, hypnotics, sedatives, and mood-elevating drugs)
 - Can interfere with REM sleep and impact learning and performance
- Current Recommendation**
 - First-generation, sedating antihistamines should not be used as first-line agents for routine management of CSU unless second-generation antihistamines are unavailable

1. Zuberbier T et al. Allergy. 2018;73:1393-1414.

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Dr. Bernstein: Sarah asks, "What are the adverse events that she can expect with the recommended treatment options using antihistamines?" And it's important to know that antihistamines have been available for the treatment of urticaria since the 1950s. The older first-generation antihistamines have pronounced anticholinergic effects and sedative actions on the central nervous systems, and many interactions with alcohol and drugs affecting the CNS, such as analgesics, hypnotics, sedatives, and mood-elevating drugs, have been described. They can also interfere with rapid eye movements and impact learning and performance.

Based on strong evidence regarding potential serious side effects of old sedating antihistamines, where lethal overdoses have been reported, current guidelines recommend against the use of these sedating antihistamines for routine management of chronic urticaria as first-line agents, except for the rare places worldwide in which modern second-generation antihistamines are still not available.

Sarah^{1,a}

Modern second-generation antihistamines are minimally or nonsedating and free of anticholinergic effects



Should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile

* Stock photo. Posed by model.
1. Sharma M et al. Cochrane Database Syst Rev. 2014;(11):CD006137.

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The development of modern second-generation antihistamines led to drugs that are minimally or nonsedating and free of anticholinergic effects. So Sarah can be informed that modern second-generation antihistamines should be considered as the first-line symptomatic treatment for urticaria because of their good safety profile.

DECISION POINT

✓ Newly Diagnosed CSU

COMPLICATING VARIABLE

✓ Sarah would like to become pregnant in the near future and asks if there are any concerns

Antihistamine Use in Pregnant and Lactating Women¹

Use in Pregnant Women

No reports of birth defects in women using second-generation antihistamines during pregnancy

- Limited data: Small sample size studies available for cetirizine² and one large meta-analysis for loratadine³
- Widely used OTC for allergic rhinitis and urticaria; women may have used these drugs before pregnancy was confirmed

Recommendation

Loratadine with possible extrapolation to desloratadine
or
Cetirizine with possible extrapolation to levocetirizine

Use in Lactating Women

All H₁ antihistamines are excreted in breast milk in low concentrations

- Nursing infants occasionally develop sedation from first-generation H₁ antihistamines transmitted in breast milk

Recommendation

Second-generation H₁ antihistamines are preferred in nursing women

1. Zuberbier T et al. *Allergy*. 2018;73:1393-1414. 2. Weber-Schoendorfer C, Schaefer C. *Reprod Toxicol*. 2008;26:19-23. 3. Schwarz EBM et al. *Drug Saf*. 2008;31:775-788.

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Sarah^a

Discussion Points

- Pregnant women with urticaria should be treated with the least amount of medication possible
- No studies have evaluated the safety or efficacy of high-dose antihistamines in pregnancy
- Most patients can be treated with second-generation H₁ antihistamines alone, with occasional short courses of oral glucocorticoids for severe flares



^a Stock photo. Posed by model.

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So now we can inform Sarah that pregnant women with urticaria should be treated with the least amount of medication possible, and no studies have evaluated the safety or efficacy of high-dose antihistamines in pregnancy. Most patients can be treated with second-generation H₁ antihistamines alone, with occasional short courses of oral glucocorticoids for severe flares.

Dr. Bernstein: Sarah would like to become pregnant in the near future and asks if there are any concerns. There are no reports of birth defects in women who have used modern second-generation antihistamines during pregnancy reported to date. However, only small sample size studies are available for cetirizine and one large meta-analysis for loratadine. Furthermore, as several modern second-generation antihistamines are now prescription-free and used widely in both allergic rhinitis and urticaria, it must be assumed that many women have used these drugs, especially in the beginning of pregnancy, at least before the pregnancy was confirmed.

Nevertheless, as the highest safety is mandatory in pregnancy, the suggestion for the use of modern second-generation antihistamines is to prefer loratadine, with the possible extrapolation to desloratadine and cetirizine, with a possible extrapolation to levocetirizine. All H₁ antihistamines are excreted in breast milk in low concentrations. So use of second-generation H₁ antihistamines is advised, as nursing infants occasionally develop sedation from the old first-generation H₁ antihistamines transmitted in breast milk.

A Closer Look at the Therapeutic Approach to the Patient With Refractory CSU

MAKE A CASE: REFRACTORY CSU

Sarah*

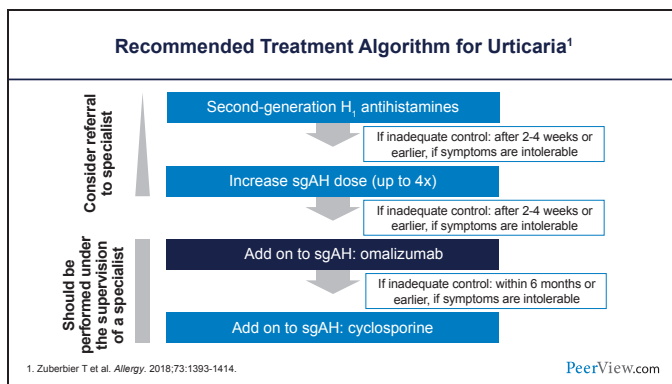
- Remains symptomatic despite 8 weeks of treatment with a second-generation H₁ antihistamine, which was escalated to 4 times the approved dose

~50% of patients with CSU continue to experience itch and hives, despite H₁ antihistamine treatment



* Stock photo. Posed by model.

Dr. Bernstein: Sarah remained symptomatic despite 8 weeks of treatment with a second-generation H₁ antihistamine, which was escalated to 4 times the approved dose. Actually, about 50% of patients with chronic spontaneous urticaria continue to experience itch and hives despite H₁ antihistamine treatment.



So, we come back to our treatment algorithm, and here we see that the next step, if there is no benefit from high-dose antihistamines, would be add on with a monoclonal antibody called omalizumab, which is an anti-IgE compound that has been approved for the treatment of chronic urticaria.

Omalizumab for Refractory CSU¹

- Anti-IgE monoclonal antibody approved in 2014 for patients aged ≥12 years with CSU who have not responded to antihistamines¹
- Phase 3 clinical trial program consisted of three randomized, double-blind, PBO-controlled studies in patients with moderate to severe H₁ antihistamine-refractory CIU/CSU

ASTERIA I² and ASTERIA II³

Efficacy and safety of omalizumab 75 mg, 150 mg, and 300 mg vs PBO in patients with CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines

GLACIAL⁴

Safety and efficacy of omalizumab 300 mg vs PBO in patients with CIU/CSU who remained symptomatic despite receiving up to four times the approved dosage of H₁ antihistamines and either an H₂ antihistamine or LTRA, or all three in combination

1. Xolair (omalizumab) Prescribing Information. https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed September 27, 2019. 2. <https://clinicaltrials.gov/ct2/show/NCT01287117>. Accessed September 27, 2019. 3. <https://clinicaltrials.gov/ct2/show/NCT01292473>. Accessed September 27, 2019. 4. <https://clinicaltrials.gov/ct2/show/NCT01264939>. Accessed September 27, 2019.

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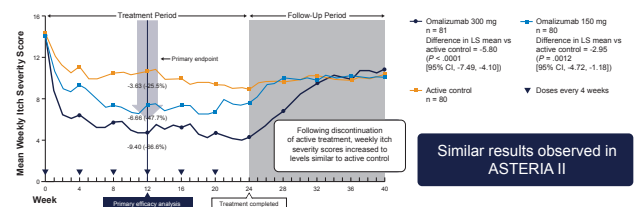
It was approved in 2014 for patients aged 12 years and older with chronic spontaneous urticaria who have not responded to antihistamines. The phase 3 clinical trial program for omalizumab consisted of three randomized, double-blind, placebo-controlled studies in patients with moderate to severe H₁ antihistamine-refractory hives, and they were termed ASTERIA I, ASTERIA II, and GLACIAL.

Both ASTERIA I and ASTERIA II evaluated the efficacy and safety of omalizumab 75-mg, 150-mg, and 300-mg doses versus placebo in patients with chronic spontaneous urticaria who remained symptomatic despite treatment with approved doses of H₁ antihistamines.

In contrast, the GLACIAL study was conducted to evaluate the safety and efficacy of omalizumab 300 mg versus placebo in patients with chronic spontaneous urticaria who remained symptomatic despite receiving up to four times the approved dosage of H₁ antihistamines and either an H₂ antihistamine or a leukotriene receptor antagonist, or all three in combination.

ASTERIA I: Change From Baseline and Percentage Reduction in Mean Weekly Itch Severity Score at Week 12 (N = 241)¹

- ASTERIA I:** 40-week, randomized, double-blind, PBO-controlled study to evaluate the efficacy and safety of subQ omalizumab as add-on therapy for 24 weeks in patients with CIU/CSU who remained symptomatic despite H₁ antihistamine treatment at licensed doses



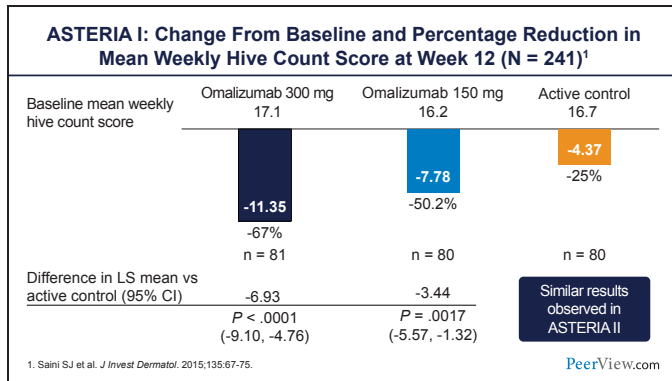
1. Saini SJ et al. *J Invest Dermatol*. 2015;135:67-75.

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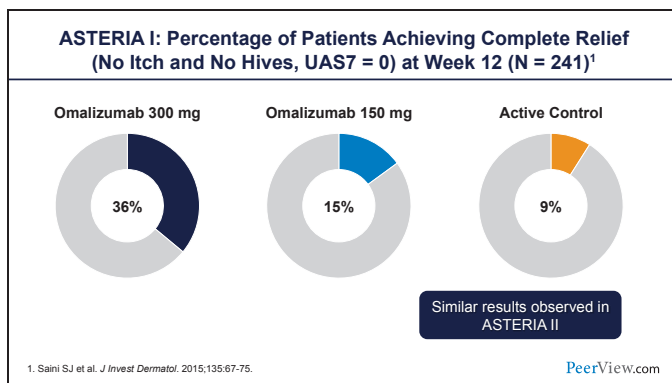
Now, these are the results of ASTERIA I, and the primary endpoint was the change from baseline and percentage reduction in mean weekly itch severity score at week 12; 241 patients were enrolled in this study. It was a 40-week randomized, double-blind, placebo-controlled study. And you can see at the endpoint, which is at 12 weeks, the primary efficacy analysis showed that both the 150- and 300-mg dose showed significant improvement compared with

the placebo, with the greatest improvement seen with the 300-mg dose. And these were both considered statistically significant and clinically meaningful.

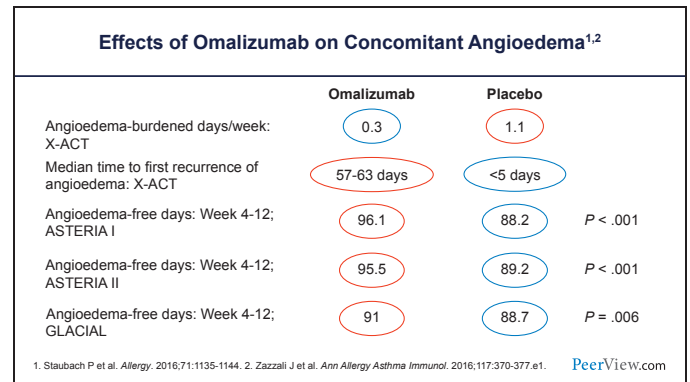
Now, following discontinuation of active treatment, the weekly itch severity scores increased to levels similar to the active control. Now, the results of this study are very similar to the results observed in ASTERIA II.



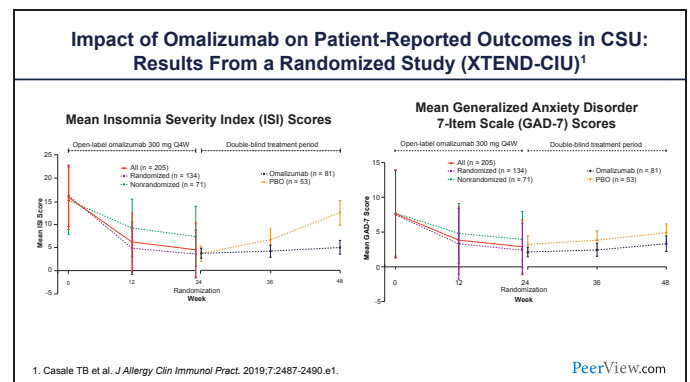
Now, this illustrates the significant reduction in mean weekly hive count, and you can see that in the patients who were receiving omalizumab 300 mg, there was a 67% reduction in the baseline mean weekly hive count. In patients receiving 150-mg omalizumab, there was a 50% reduction, and this was compared with 25% reduction in active control, which is not unusual, because in all studies we see that placebo has some effect.



So this slide illustrates the percentage of patients achieving complete relief, where they had no itching and no hives at week 12. And you can see in the 300-mg dose, 36% of patients had no itching, had no hives, and 15% of the patients receiving omalizumab 150 mg had no itching or no hives. And this is compared with the active control, where only 9% of patients at week 12 had no hives or no itching.



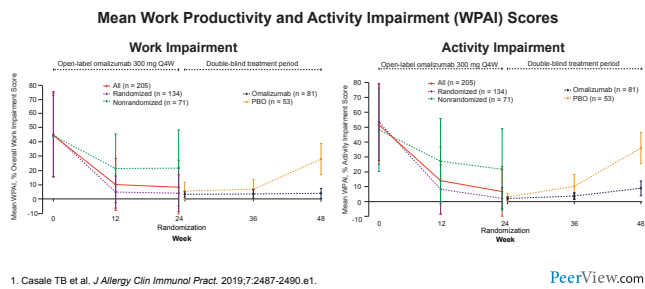
This slide illustrates the effects omalizumab had on concomitant angioedema, and one can see that overall the angioedema burdened days per week was significantly less compared with placebo. The median time to first recurrence of angioedema was 57 to 63 days, compared with less than 5 days for placebo. And if you look at each study—the ASTERIA I, the ASTERIA II, and the GLACIAL studies—in all of these studies, angioedema-free days at week 4 to 12 was significantly greater than the placebo.



So this slide illustrates the fact that omalizumab had a significant impact on patient-reported outcomes, as well. And these are the results of a randomized open-label study called XTEND. It was after the completion of the double-blind, placebo-controlled studies. And they used validated instrument scores—the mean Insomnia Severity Index and the mean Generalized Anxiety Disorder Scale—to look at these outcomes.

When you look at all patients in this study, there was a significant improvement in the mean Insomnia Severity Index scores in patients receiving omalizumab compared with placebo, and again, this was relevant in the patients who received omalizumab. And if you look at the Generalized Anxiety Disorder score, similarly, you see a significant improvement in anxiety in patients receiving omalizumab versus placebo.

Impact of Omalizumab on Patient-Reported Outcomes in CSU: Results From a Randomized Study (XTEND-CIU)¹ (Cont'd)



Omalizumab also had a significant impact on work impairment and activity impairment; patients receiving omalizumab had significant improvement in these scores compared with placebo.

Therapeutics Under Investigation in Clinical Trials for Treatment of CSU¹

Study Drug	Mechanism	Phase	ClinicalTrials.gov Identifier
Ligelizumab	Anti-IgE	3	NCT03580356
AK002	Anti-Siglec-8	2	NCT03436797
GSK2646264	Topical SYK inhibitor	1	NCT02424799
Fenebrutinib	BTK inhibitor	2	NCT03693625
Benralizumab	Anti-IL-5R	4	NCT03183024
Mepolizumab	Anti-IL-5	1	NCT03494881
Dupilumab	Anti-IL-4/-13	2	NCT03749135

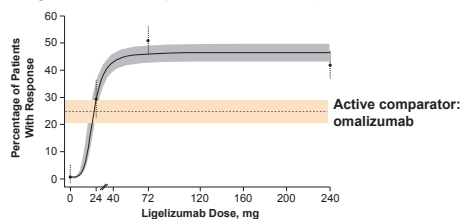
1. Johal KJ, Saini SS. *Ann Allergy Asthma Immunol.* 2019 Sep 5 [Epub ahead of print].

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It's important to note that there's a number of therapeutics that are currently under investigation in clinical trials for the treatment of chronic spontaneous urticaria.

Phase 2b Trial of Ligelizumab for CSU: Dose-Response Curve¹

- Ligelizumab is a next-generation high-affinity humanized monoclonal anti-IgE antibody
 - Currently being evaluated in two phase 3 clinical trials (PEARL 1 and PEARL 2)

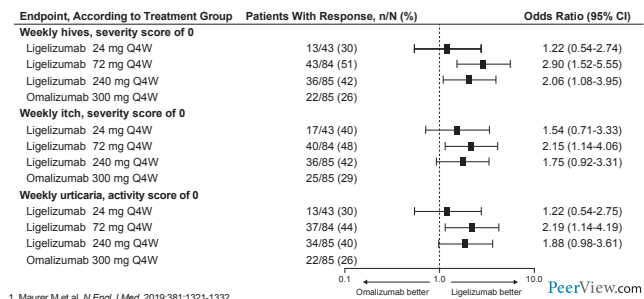


1. Maurer M et al. *N Engl J Med.* 2019;381:1321-1332.

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The one that's furthest along is ligelizumab, which is another anti-IgE compound that's in phase 3 trials. These trials are referred to as PEARL 1 and PEARL 2, and they are placebo and active-control trials. But based on phase 2B trials, we know that ligelizumab met the primary endpoint by demonstrating a clear dose response relationship and ...

Phase 2b Trial of Ligelizumab for CSU: Response at Week 12¹



... improvements over omalizumab in chronic spontaneous patients. Ligelizumab achieved rapid onset of action, and improved and sustained efficacy in patients with chronic spontaneous urticaria whose symptoms were not adequately controlled by H₁ antihistamines.

DECISION POINT

✓ Refractory CSU

COMPLICATING VARIABLE

✓ Sarah travels frequently for work and asks about treatment options that require minimal monitoring

Sarah^a

- Because of Sarah's work schedule, she is concerned about "stepping up" her treatment, as she has heard that biologic therapies require a lot of monitoring



No specific laboratory monitoring is required for patients receiving omalizumab for CSU

^a Stock photo. Posed by model.

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Dr. Bernstein: Now, a complicating variable is that Sarah travels frequently for work and asks about treatment options that require minimal monitoring. You inform her that no specific laboratory monitoring is required for patients receiving omalizumab for chronic spontaneous urticaria.

DECISION POINT

✓ Refractory CSU

COMPLICATING VARIABLE

✓ Sarah asks about what adverse events she can expect with recommended treatment options

Sarah^a

- Among all non-antihistamine therapies with proven efficacy for refractory CSU, omalizumab is the best studied, most widely used therapy and has a very low incidence of serious adverse events

Most Common Adverse Events in Patients Aged ≥12 Years From 3 PBO-Controlled CSU Studies (Day 1 to Week 12)^{1,2}

Adverse Event	Omalizumab 150 mg	Omalizumab 300 mg
Headache	12%	6%
Nasopharyngitis	9%	7%
Arthralgia	3%	3%
Viral upper respiratory infection	2%	1%
Nausea	1%	3%
Sinusitis	1%	5%
Upper respiratory tract infection	1%	3%
Cough	1%	2%

* Stock photo. Posed by model. ^a ≥2% omalizumab-treated patients and more frequent than in PBO.
1. Xolair (omalizumab) Prescribing Information. https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed September 27, 2019.



Dr. Bernstein: Sarah is very concerned about the about the side effects associated with biologic therapy. You inform her that, among all non-antihistamine therapies with proven efficacy for refractory chronic spontaneous urticaria, omalizumab is the best studied, most widely used therapy and has a very low incidence of serious adverse effects. In fact, in patients aged 12 years and older, the most commonly observed adverse reactions seen in patients receiving omalizumab, either the 150-mg or 300-mg doses, were headache, nasopharyngitis, arthralgia, viral upper respiratory infections, nausea, sinusitis, upper respiratory tract infection, and cough.

DECISION POINT

✓ Refractory CSU

COMPLICATING VARIABLE

✓ Sarah would like to become pregnant in the near future and asks if there are any concerns

Sarah^a

- Omalizumab has been used safely in pregnant women and is the treatment of choice for refractory CSU during pregnancy

EXPECT Study¹
Proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age are not inconsistent with findings from other studies in asthma population

- Small sample size available, but no apparent increased birth prevalence of major anomalies or patterns of major anomalies have been observed

Guideline Suggestion
"Using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated in pregnancy should not be used"²

* Stock photo. Posed by model.
1. Namazy J et al. *J Allergy Clin Immunol*. 2015;135:407-412. 2. Zuberbier T et al. *Allergy*. 2018;73:1393-1414.



Dr. Bernstein: So, Sarah would like to become pregnant within the next year, but she is concerned about taking a biologic therapy during pregnancy. She also wants to breastfeed and inquires about the safety of biologics while nursing. You inform her that omalizumab has been used safely in pregnant women and is the treatment of choice for refractory chronic spontaneous urticaria during pregnancy.

There were data from the EXPECT study. And again, to date, the proportions of major congenital anomalies, prematurity, low birth weight, and small size for gestational age observed in the EXPECT registry are not inconsistent with findings from other studies in this asthma population. Now, these are small sample sizes, but it does not appear that there's any increased birth prevalence of major anomalies or patterns of major anomalies observed in patients taking omalizumab.

Current guidelines suggest using the same treatment algorithm with caution both in pregnant and lactating women after risk-benefit assessment. Drugs contraindicated in pregnancy should not be used.

Narrator: This activity has been jointly provided by Medical Learning Institute, Inc. and PVI, PeerView Institute for Medical Education.

Diagnosing and Managing Chronic Spontaneous Urticaria in Primary Care: Examining the Latest Clinical Evidence for Improved Patient Outcomes and Quality of Life

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