

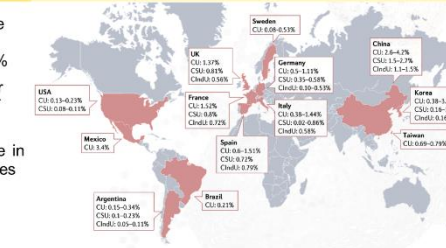
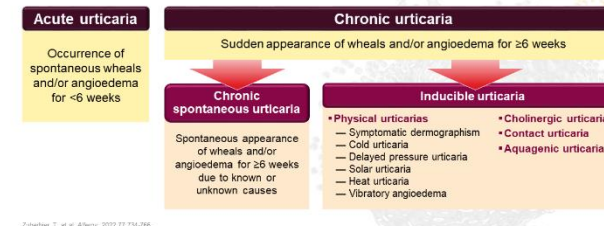
A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and Innovative Treatments on the Horizon

Recognizing and Diagnosing CU in Practice: How Well Do You Know Current Guidelines?

1	 <p>A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and Innovative Treatments on the Horizon</p>	<p>I'm Doctor Jonathan Bernstein, professor of medicine at the University of Cincinnati College of Medicine and partner at Bernstein Allergy Group and Clinical Research Center. And today, I'm going to talk to you about A New Dawn in Chronic Urticaria: Opportunities to Improve Patient Outcomes with Modern Diagnostic Principles and Innovative Treatments on the Horizon.</p>		
2	 <p>Recognizing and Diagnosing CU in Practice: How Well Do You Know Current Guidelines?</p> <p>Jonathan A. Bernstein, MD Professor of Clinical Medicine, University of Cincinnati Department of Internal Medicine Division of Rheumatology, Allergy and Immunology</p>	<p>The question we have to ask is: How well do you know your current guidelines? Can you recognize and diagnose chronic urticaria in practice?</p>		
3	 <p>Chronic Urticaria (CU)</p> <ul style="list-style-type: none"> Condition characterized by the development of wheals (hives) with or without angioedema <ul style="list-style-type: none"> Acute urticaria (<6-week duration and often gone within hours to days) CU (>6-week duration with daily or episodic wheals) <table border="1"> <tr> <td data-bbox="331 1205 596 1346"> <p>A wheal has 3 typical features:</p> <ol style="list-style-type: none"> A sharply circumscribed superficial central swelling of variable size and shape, 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 </td> <td data-bbox="619 1205 896 1346"> <p>Angioedema is characterized by:</p> <ol style="list-style-type: none"> A sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes Tingling, burning, tightness, and sometimes pain rather than itch A resolution slower than that of wheals (can take up to 72 hours) </td> </tr> </table> <p><small>Zuberbier T, et al. Allergy. 2022;77:161-166.</small></p>	<p>A wheal has 3 typical features:</p> <ol style="list-style-type: none"> A sharply circumscribed superficial central swelling of variable size and shape, 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 	<p>Angioedema is characterized by:</p> <ol style="list-style-type: none"> A sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes Tingling, burning, tightness, and sometimes pain rather than itch A resolution slower than that of wheals (can take up to 72 hours) 	<p>Chronic urticaria is characterized by the development of wheals with or without angioedema. And acute urticaria is defined as lasting less than 6 weeks, and often it goes away within hours to days, whereas chronic urticaria is persistent, it lasts greater than 6 weeks with daily or episodic wheals. A wheal has three typical features. First, it manifests as a sharply circumscribed, superficial central swelling of variable size and shape, almost invariably surrounded by reflex erythema. It's characterized by an itching or sometimes burning sensation; and they're fleeting in nature, with the skin returning to normal appearance, usually within 30 minutes to 24 hours. Angioedema can be associated with urticaria, and it is characterized as a sudden pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes. It may be associated with tingling, burning, tightness, and sometimes pain rather than itch, and resolution is slower than that of</p>
<p>A wheal has 3 typical features:</p> <ol style="list-style-type: none"> A sharply circumscribed superficial central swelling of variable size and shape, 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 	<p>Angioedema is characterized by:</p> <ol style="list-style-type: none"> A sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes Tingling, burning, tightness, and sometimes pain rather than itch A resolution slower than that of wheals (can take up to 72 hours) 			

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		<p>wheals, as it can take up to 72 hours to resolve.</p>
<p>4</p>	<h3>Global Prevalence</h3> <ul style="list-style-type: none"> Global prevalence estimated to be between 0.1%-4% CSU accounts for over two-thirds of cases Higher prevalence in females than males (2-4:1 ratio)  <p><small>CSU: chronic spontaneous urticaria; CIndU: chronic inducible urticaria. Gale P, et al. J Intern Med. 2018; 263(1):1-12. doi:10.1111/jim.14500. Sankaranarayanan M, et al. World Allergy Organ J. 2017; 10:100-103. Maurer M, et al. Allergy. 2011; 66:317-320. Cassano N, et al. J Allerg Clin Immunol. 2015; 135:104-107. Image reproduced for educational purposes only from Galbraith P, et al. J Allergy Clin Immunol. 2015; 135:104-107.</small></p>	<p>The global prevalence of chronic urticaria is estimated to be between 0.1% to 4%. Chronic spontaneous urticaria accounts for over two-thirds of cases. Higher prevalence occurs in females compared to males, with a 2:1 to 4:1 ratio. And here in this pictorial you can see the prevalence in different countries of chronic urticaria and chronic spontaneous urticaria and, in some cases, chronic inducible urticaria, which we'll talk about in a moment.</p>
<p>5</p>	<h3>Classifications and Subtypes</h3> <ul style="list-style-type: none"> CU can be further classified as CSU and CIndU based on the presence or absence of inducing stimuli  <p><small>Zuberbier T, et al. Allergy. 2022; 77:174-196.</small></p>	<p>Chronic urticaria can be further classified as chronic spontaneous urticaria and chronic inducible urticaria based on the presence or absence of inducing stimuli. So, we already defined acute and chronic urticaria. But it's important to note that in chronic spontaneous urticaria there is an appearance of wheals and/or angioedema that lasts 6 weeks or longer due to known or unknown causes. But it also can manifest as inducible urticaria and these are broken down into physical urticarias, which comprise of symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema. There are other forms of induced urticaria, including cholinergic urticaria, contact urticaria, and aquagenic urticaria.</p>

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Triggers and Prevalences of CIndU Subtypes

Subtype of CIndU	Trigger	Prevalence Among Patients With CIndUs
PHYSICAL URTICARIA		
Symptomatic dermographism (also called urticaria factitia)	Shear force acting on the skin (ie, friction)	Adults: 50%-78%; children: 38%
Cold urticaria (also called cold contact urticaria)	Cold exposure to the skin	Varies by climate. Adults: 8%-37%; children: 9%-14%
Delayed pressure urticaria	Application of sustained pressure to the skin	Adults: 3%-20%; children 3%-9%
Solar urticaria	Light (UV and/or visible light) exposure	Very rare; limited data
Heat contact urticaria	Heat exposure of the skin	Very rare; limited data
Vibratory angioedema	Exposure to vibration	Very rare; limited data
OTHER INDUCIBLE URTICARIA		
Cholinergic (including exercise induced)	Active or passive body warming	Adults: 6%-13%; children: 19%
Contact urticaria	Contact with eliciting agent	Very rare; limited data
Aquagenic urticaria	Skin contact with water	Very rare; limited data

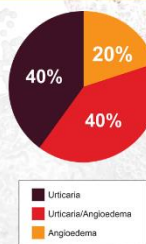
Urticaria
Maier M, et al. J Allergy Clin Immunol Pract. 2016;6:1119-1130.

The triggers and prevalences of chronic inducible urticaria subtypes are summarized in this table, again broken into physical versus inducible urticaria. You can see the different types of triggers that can elicit these forms of hives. For example, with symptomatic dermographism, also called urticaria factitia, a shear force is applied to the skin with friction, and there you can use the blunt edge of a tongue blade, an applicator, or something called a Frick test, which will elicit swelling after the physical shear force is applied. This is a common cause of chronic inducible urticaria, seen in 50% to 78% of adults and 38% of children. There are other ways of eliciting these inducible hives. With cold-induced urticaria, for example, there's something called an ice cube test. Or there is the "temp" test, which is a machine that can apply different temperatures precisely. And, again, you can see that it's not quite as common as symptomatic dermographism. Another common form of inducible urticaria is cholinergic urticaria, which is associated with active or passive body warming. And this can occur when people, when patients get emotional or exercise or go into a hot shower. And this is a condition that can be elicited using an apparatus called exercise ergometry. The other forms of inducible and physical urticaria can be referred to and are not as common, and we have much less data.

7

Course of Disease

- Onset of CU is typically between 20-40 years of age
 - Duration of CU can last for 3-10 years
 - CSU has a mean duration of 5 years
 - CIndUs tend to have a more protracted and severe course of disease
 - 33%-67% of patients with CU exhibit wheals and angioedema (≥ 1 /year)
 - 29%-65% of patients with CU exhibit only wheals
- Around 70% of patients with CU are expected to go into remission within 6 months, while 11% of patients will not experience remission even after 5 years


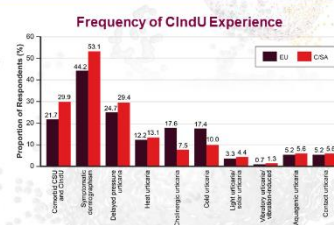


Goldstein T, et al. Allergy. 2010;73:1193-1194. Bernstein JA, et al. J Allergy Clin Immunol. 2014;133:1276-1277. Gang P, et al. J Allergy Clin Immunol. 2004;114:216-220.

So, what is the course of disease? The onset of chronic urticaria typically occurs between ages 20 to 40 years old. The duration can last 3 to 10 years and chronic spontaneous urticaria has a mean duration of about 5 years. Chronic inducible urticarias tend to have a more protracted and severe course of disease. It's estimated that anywhere

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		<p>between 33% to 67% of chronic urticaria patients exhibit wheals and angioedema at least once per year, whereas 29% to 65% exhibit only wheals. And around 70% of patients with chronic urticaria are expected to go into remission within 6 months, while 11% of patients will not experience remission even after 5 years. So, it is a variable course for many patients.</p>
8	<h3>Associated Symptoms</h3> <p>A study of CSU patients reported high frequency of systemic signs and symptoms, including:</p>  <p>Dong, JC, et al. J Allergy Clin Immunol Pract 2017;5(5):1314-1318</p>	<p>So, what are the associated symptoms? Well, patients can have joint pain or swelling, wheezing or breathlessness, headache, fatigue, gastrointestinal symptoms, flushing, and palpitations. This is not to be confused with anaphylaxis, which is a systemic condition involving many different organ systems.</p>
9	<h3>Differences in CSU Between Europe and Central/South America: The AWARE Study</h3> <ul style="list-style-type: none"> Global CU disease experience and management not well documented, but data are emerging AWARE: global prospective, non-interventional study: 4,224 CSU patients (C/SA 492; EU 3,732) Compared with patients in Europe, patients in C/SA were more likely to: <ul style="list-style-type: none"> Be younger Be female Have co-existing CIndU Have angioedema Have uncontrolled disease Differences in time since diagnosis, rates of controlled disease, health-related QOL, and treatment patterns also noted  <p>AWARE: A Worldwide Antihistamine-Resistant chronic urticaria patient Evaluation. CSA: Central/South America; EU: European Union. QOL: quality of life. Mazer M, et al. World Allergy Organ J. 2019;11:32. Reproduced for educational purposes only.</p>	<p>What are the differences in chronic spontaneous urticaria between Europe and Central or South America? This was actually studied in the AWARE study. The global chronic urticaria disease experience and management is not well documented, but data is emerging. The AWARE study was a global perspective, noninterventional study of over 4000 patients — from Central and South America 492 patients, and European Union 3732 patients. Compared to patients in Europe, patients in Central and South America were more likely to be younger, more likely to be female, more likely to have coexisting chronic inducible urticaria, more likely to have angioedema, and more likely to have uncontrolled disease. Differences in time since diagnosis, rates of controlled disease, health-related quality of life, and treatment patterns are also noted. The frequency of chronic inducible urticaria is summarized in the graph, showing that patients from Central and South America had more combined chronic spontaneous</p>

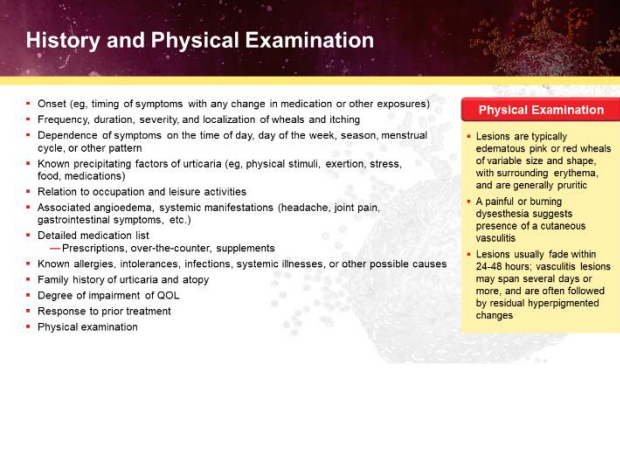
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		<p>urticaria and chronic inducible urticaria, as well as a higher prevalence proportion of respondents reporting symptomatic dermatographism, delayed urticaria, and, to some extent, heat urticaria.</p>
<p>10</p>	<p>Urticaria Guidelines</p> <ul style="list-style-type: none"> Multiple international guidelines have been published for CU diagnosis and management, including: <ul style="list-style-type: none"> JTFPP, representing AAAAI and ACAAI <ul style="list-style-type: none"> Bernstein JA, et al. <i>J Allergy Clin Immunol</i>. 2014;133:1270-1277. EAACI/GA'LEN/EuroGuiDerm/APAAACI <ul style="list-style-type: none"> Zuberbier T, et al. <i>Allergy</i>. 2022;77:734-766. While some differences in recommendations exist, core recommendations remain similar <ul style="list-style-type: none"> Generally share common criteria for diagnosis, including 6+ weeks of duration Generally agree that extensive investigations for CSU are typically not required unless other disorders are suspected based on history/examination <p><small>AAAAI: American Academy of Allergy, Asthma & Immunology; ACAAI: American College of Allergy, Asthma & Immunology; EAACI/GA'LEN/EuroGuiDerm/APAAACI: Dermatology Section of the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network and the Urticaria and Angioedema Clinical of Evidence and Consensus; the European Dermatology Forum; and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology; JTFPP: Joint Task Force on Practice Parameters.</small></p>	<p>Now there are multiple international guidelines that have been published for chronic urticaria diagnosis and management. The Joint Task Force Practice Parameter, which is represented by the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology, was published in 2014, and the international guidelines have been published most recently in 2022. While there are some differences in recommendations, the core recommendations remain similar. They generally share common criteria for diagnosis, including 6+ weeks duration for chronic spontaneous urticaria, and they generally agree that extensive investigations for chronic spontaneous urticaria are typically not required unless other disorders are suspected based on history and examination.</p>
<p>11</p>	<p>Diagnostic Algorithm for Patients Presenting With Wheals and/or Angioedema for ≥6 Weeks</p> <p><small>AAE: acquired angioedema due to C1-inhibitor deficiency; ACE-inh, angiotensin-converting enzyme inhibitor; AE: angioedema; AID: autoinflammatory disease; HAE: hereditary angioedema. Reproduced for educational purposes only from Zuberbier T, et al. <i>Allergy</i>. 2022;77:734-766.</small></p>	<p>This is the diagnostic algorithm published in the international guidelines for patients presenting with wheals and/or angioedema lasting 6 weeks or longer. And you can see it's broken down into patients presenting with wheals, angioedema, or both. And there's questions that are should be asked initially. For instance, with angioedema, is the patient taking an ACE inhibitor? If not, do they have any history of hereditary or acquired angioedema? If not, are symptoms inducible? If not, then they likely have chronic</p>

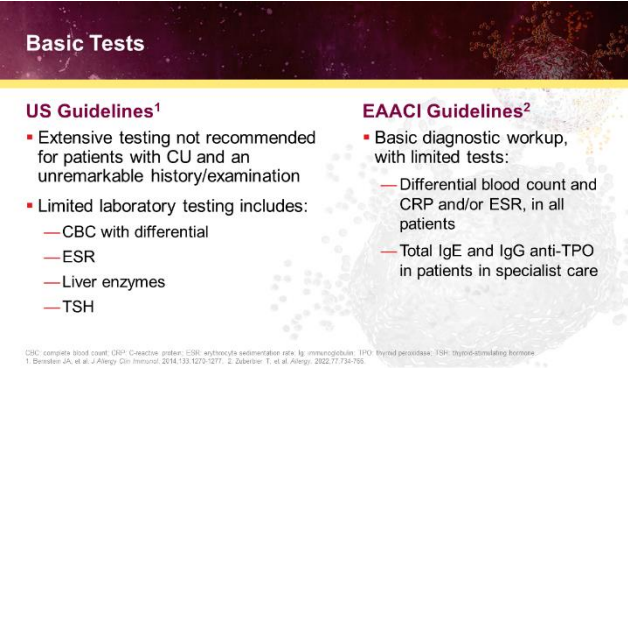
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		<p>spontaneous urticaria. However, if they answer yes to these questions, then there are other potential causes for the angioedema that should be addressed. Similarly, in patients with wheals, one should ask questions about systemic symptoms. If they are not present, one should ask about the average wheal duration. Again, if they are greater than 24 hours, one should think of other potential causes, such as urticarial vasculitis or acquired or hereditary angioedema. But if not, then one should ask questions about induced urticaria. And if they're not present, then one would arrive at the diagnosis of chronic spontaneous urticaria. But if they are present, one could have chronic inducible urticaria or a combination of chronic spontaneous urticaria and chronic inducible urticaria. It's important to note the difference between these conditions. Because mechanistically, chronic spontaneous urticaria and chronic inducible urticaria are mast cell-driven conditions where histamine and other mast cell mediators are involved in the pathogenesis; whereas for these other conditions, the mechanisms might include interleukin-one or bradykinin and these individuals will not respond well to the treatments that are advocated for chronic spontaneous urticaria.</p>
12	 <p>History and Physical Examination</p> <ul style="list-style-type: none"> Onset (eg, timing of symptoms with any change in medication or other exposures) Frequency, duration, severity, and localization of wheals and itching Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern Known precipitating factors of urticaria (eg, physical stimuli, exertion, stress, food, medications) Relation to occupation and leisure activities Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.) Detailed medication list <ul style="list-style-type: none"> Prescriptions, over-the-counter, supplements Known allergies, intolerances, infections, systemic illnesses, or other possible causes Family history of urticaria and atopy Degree of impairment of QOL Response to prior treatment Physical examination <p>Physical Examination</p> <ul style="list-style-type: none"> Lesions are typically edematous pink or red wheals of variable size and shape, with surrounding erythema, and are generally pruritic. A painful or burning dysesthesia suggests presence of a cutaneous vasculitis Lesions usually fade within 24-48 hours; vasculitis lesions may span several days or more, and are often followed by residual hyperpigmented changes 	<p>The history and physical exam is also very important. The onset of the hives; timing of symptoms with any change in medication or other exposures; the frequency, duration, severity, and localization of wheals and itching; dependence of symptoms on the time of day, day of week, season, menstrual cycle; or other patterns. Known precipitating factors of urticaria, physical stimuli, exertion, stress, food, medications, the relation to occupation and leisure activities. As mentioned, the</p>

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		<p>association with angioedema or other systemic manifestations. Detailed medication lists should be obtained; what patients used in terms of prescriptions and over-the-counter medications or supplements. Known allergies, intolerances, infections, systemic illnesses, or other possible causes that have been associated with hives. A family history of urticaria and atopy, the degree of impairment of quality of life, patient's response to prior treatment. And, of course, the physical examination, which shows the lesions are typically edematous pink or red wheals of variable size and shape with surrounding redness and are generally pruritic. A painful or burning dysesthesia suggests presence of cutaneous vasculitis; however, a skin biopsy would be necessary to confirm. Lesions usually fade within 24 or 48 hours, and this is also true of vasculitis lesions. However, they also maybe span several days or more, and often are followed by residual hyperpigmented changes.</p>
13	 <p>Basic Tests</p> <p>US Guidelines¹</p> <ul style="list-style-type: none"> ▪ Extensive testing not recommended for patients with CU and an unremarkable history/examination ▪ Limited laboratory testing includes: <ul style="list-style-type: none"> — CBC with differential — ESR — Liver enzymes — TSH <p>EAACI Guidelines²</p> <ul style="list-style-type: none"> ▪ Basic diagnostic workup, with limited tests: <ul style="list-style-type: none"> — Differential blood count and CRP and/or ESR, in all patients — Total IgE and IgG anti-TPO in patients in specialist care <p><small>CBC: complete blood count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Ig: immunoglobulin; TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone. 1. Bernstein JA, et al. J Allergy Clin Immunol. 2014;133:1079-1077. 2. Zuberbier T, et al. Allergy. 2022;77:724-730.</small></p>	<p>What are the tests that are recommended by the guidelines? Well, both guidelines recommend a limited workup. Extensive testing is not recommended for chronic urticaria with unremarkable history or physical exam. Both guidelines recommend a CBC with differential, sedimentation rate or C-reactive protein. And again, the US guidelines recommended liver enzymes and thyroid testing, whereas the European guidelines recommend possibly obtaining a total IgE level and antibodies against thyroid peroxidase, which may be prognosticators in terms of response to certain types of treatment.</p>

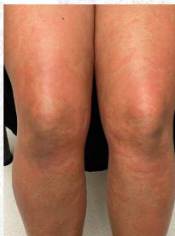
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14	<p>Extensive Tests</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>US Guidelines¹</p> <ul style="list-style-type: none"> ▪ Extended testing based on history and physical examination: <ul style="list-style-type: none"> — Skin biopsy — Physical challenge tests — Complement system (eg, C3, C4, and CH50) — Stool analysis for ova and parasites — Urinalysis — Hepatitis B and C serologies — Chest radiography, other imaging studies, or both — Antinuclear antibody — Rheumatoid factor, anti-citrullinated protein — Cryoglobulin levels — Serologic and/or skin testing for immediate hypersensitivity — Thyroid autoantibodies — Serum protein electrophoresis </div> <div style="width: 45%;"> <p>EAACI Guidelines²</p> <ul style="list-style-type: none"> ▪ Extended tests based on history: <ul style="list-style-type: none"> — Infectious diseases — Functional autoantibodies — Thyroid gland disorders — Allergy — Concomitant CINDU <ul style="list-style-type: none"> • Cold urticaria: differential blood count and ESR or CRP; rule out infection • Solar urticaria: rule out other light-induced dermatoses — Severe systemic diseases — Lesional skin biopsy </div> </div> <p><small>1. Bernstein JA, et al. J Allergy Clin Immunol. 2014;133:1270-1277. 2. Zuberbier T, et al. Allergy. 2002;57:734-756.</small></p>	<p>Extended testing based on history and physical exam for US guidelines might include these items listed, including skin biopsy especially if patients are unresponsive to high-dose antihistamines. And again, similarly, the extended test also may be based on history according to the international guidelines that are listed here.</p>
15	<p>Patient Case</p> <p>AB is a 26-year-old woman presenting with recurrent hives associated with angioedema that have been persistent for the past 6 months. During this time, she had been treated by her primary care physician with short courses of oral corticosteroids that resolved the hives temporarily.</p> <ul style="list-style-type: none"> ▪ She previously had hives from 2013-2014 that resolved after treatment with oral corticosteroids ▪ Her current episode has been much more severe: <ul style="list-style-type: none"> —It involves 95% of her body and includes severe itch that is also very painful —Hives are associated with chills and joint aching —She notes her skin welts when she scratches and when she gets anxious or upset ▪ No prior laboratory testing by her primary care physician 	<p>Now, let's turn to a case of a 26-year-old female presenting with recurrent hives associated with angioedema that have been persistent for the past 6 months. During this time, she has been treated by her primary care physician with short courses of oral corticosteroids that resolved the hives temporarily. She previously had hives from 2013, 2014 that resolved after treatment with oral corticosteroids. However, her current episode has been much more severe and involves 95% of her body and includes severe itch that is also very painful. Hives are associated with chills and joint aching, and she notes her skin welts when she scratches and when she gets anxious or upset. There's no prior laboratory testing performed</p>
16	<p>Patient Case Continued</p> <p>You take a detailed history from AB and find that:</p> <ul style="list-style-type: none"> ▪ She has no underlying chronic health issues; no history of allergies or asthma; no relationship to medications, foods, or underlying medical problems, or ▪ Family history is unremarkable ▪ Current medications: <ul style="list-style-type: none"> —Cetirizine 10 mg daily —Famotidine 20 mg twice a day —Prednisone 60 mg x 3 days, with a taper by 20 mg every 3 days <ul style="list-style-type: none"> • Prescribed recently at an urgent care center; on day 3 of this treatment course —Diphenhydramine 25 mg every 4 hours ▪ Social history: single, non-smoker, social drinker; works as a receptionist ▪ She notes the hives are very disruptive to her work and personal life; they interfere with her ability sleep, exercise, and have intimacy with her partner <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>Which of the following characteristics of AB's hives suggests a diagnosis of CU, rather than acute urticaria?</p> <p>A. Duration of hives between 3 and 24 hours</p> <p>B. Persistence of hives for >6 weeks</p> <p>C. Correlation of hives with menstrual cycle</p> <p>D. History of hives in 2013-2014</p> </div>	<p>by her primary care doctor. You take a detailed history from A.B. and find in the prior medical history there's no underlying chronic health issues, no history of allergies or asthma, no relationship to medications, foods, or underlying medical problems, her family history is unremarkable. Her current medications include cetirizine 10 mg a day, famotidine 20 mg twice a day. She is currently on a tapering dose of prednisone starting at 60 mg for 3 days and tapering by 20 mg every 3 days. This was prescribed recently at an urgent care center, and she was on day three of the treatment course. She was also using diphenhydramine, 25 mg every 4</p>

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		<p>hours. She was single, nonsmoker, social drinker, and worked as a receptionist. She notes that the hives are very disruptive to her work and personal life, and they actually interfere with her ability to sleep, exercise, and to have intimacy with her partner. So, which of the following characteristics of A.B.'s hives suggested diagnosis of chronic urticaria rather than acute urticaria: duration of hives between 3 and 24 hours; persistence of hives for more than 6 weeks; correlation of hives with the menstrual cycle; history of hives in 2013 and 2014. Well certainly, as we showed here, that persistence of hives more than 6 weeks is the correct answer.</p>
<p>17</p>	<p>Patient Case Continued</p> <p>You take a detailed history from AB and find that:</p> <ul style="list-style-type: none"> She has no underlying chronic health issues; no history of allergies or asthma; no relationship to medications, foods, or underlying medical problems Family history is unremarkable Current medications: <ul style="list-style-type: none"> Cetirizine 10 mg daily Famotidine 20 mg twice a day Prednisone 60 mg x 3 days, with a taper by 20 mg every 3 days <ul style="list-style-type: none"> Prescribed recently at an urgent care center; on day 3 of this treatment course Diphenhydramine 25 mg every 4 hours Social history: single, non-smoker, social drinker; works as a receptionist She notes the hives are very disruptive to her work and personal life; they interfere with her ability sleep, exercise, and have intimacy with her partner <p>What is the most appropriate next step in the diagnostic workup of AB's CU, given her history and symptoms?</p> <p>A. Skin biopsy B. Immediate hypersensitivity skin or serologic testing for food or other allergens C. CBC and thyroid function tests D. All of these</p>	<p>What is the most appropriate next step in the diagnostic workup of A.B.'s chronic urticaria given her history and symptoms: a skin biopsy; immediate hypersensitivity skin or serologic testing for food and other allergens; complete blood count and thyroid function tests; or all of these? Well, again, the correct answer would be C — a complete blood count and thyroid function test is advocated by both the US and international guidelines.</p>
<p>18</p>	<p>Patient Case Continued</p> <p>Physical examination:</p> <ul style="list-style-type: none"> Diffuse raised erythematous plaques with central pallor, ranging from 0.5-10 cm in size Edema involving her face, lips, tongue, and the back of her hands No dermatographism No signs of infection or systemic illness Limited laboratory assessment including CBC with differential, ESR, CRP, and TSH were all normal <p>What is the differential diagnosis for AB's CU?</p> <p>A. Contact dermatitis B. Atopic dermatitis C. Urticarial vasculitis D. Erythrodermic psoriasis</p>  <p><small>Image courtesy of Jonathan Bernstein, MD.</small></p>	<p>On physical exam, she has diffuse raised erythematous plaques with central pallor ranging between 0.5 to 10 cm in size; swelling involving her face, lips, tongue, and back of her hands is present. She has no evidence of dermatographism, even though she endorsed having this by history. There are no signs of infection or systemic illness. And the limited laboratory assessment, including a CBC with differential, sed. rate, C-reactive protein, and TSH levels were all normal. What is the differential diagnosis for A.B.'s chronic urticaria: contact dermatitis; atopic dermatitis; urticarial vasculitis; or erythrodermic</p>

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psoriasis? And the correct answer, of course, is C — urticarial vasculitis.

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CSU Diagnostic Workup: The 7 Cs

What to do in every patient with CSU

- Questions
- Physical examination^a
- Basic tests^b
- UCT

Confirm	Rule out differential diagnoses
Cause	Look for indicators of CSU ^{HTL} and CSU ^{HTL}
Cofactors	Identify potential triggers and aggravators
Comorbidities	Check for CIndU, autoimmunity, and mental health
Consequences	Identify problems with sleep, distress, sexual health, work, and social performance
Components	Assess potential biomarkers for predictors of treatment response
Course	Monitor CSU activity, impact, and control

^aIncluding review of patient photo documentation.
^bWheals: blood count (CBC/ESR, IgE, anti-TPO), and total IgG.
^cCSU^{HTL} Type 1 autoimmune pathologic CSU; CSU^{HTL} Type 1b autoimmune CSU; UCT: urticaria cases list.
Muller M, et al. *J Allergy Clin Immunol Pract*. 2021;9:2274-2283. | Jaber B, et al. *Allergy*. 2022;77:734-755.

So, when one looks at the diagnostic workup, once you consider the 7 Cs, and this is what to do in every CSU patient that you see, you should ask questions, get a physical exam, basic test, and you should assess a urticaria control test, which is a validated test that establishes whether patients' hives are controlled. So, the first is to confirm the diagnosis of chronic spontaneous urticaria, rule out other causes in the differential diagnosis. Once you try to identify an underlying cause at present, look for indicators for chronic spontaneous urticaria, different types. Cofactors — identify potential triggers or aggravators. Comorbidities — check for chronic inducible urticaria, autoimmunity, and patients' mental health. Consequences — identify problems with sleep, distress, sexual health, work, and social performance. Components — assess potential biomarkers for predictors of treatment response. And course, — monitor CSU activity, impact, and control.

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Confirm: Rule Out Differential Diagnoses

Condition/Issue to Be Considered	Questions and Aspects of the Physical Examination That Should Lead to Further Investigations	Diagnostic Tests That Should Be Done if Clues Are Obtained From History and Physical Examination
IN PATIENTS WITH WHEELS ONLY		
Urticarial vasculitis ^a	<ul style="list-style-type: none"> Do you have long-lasting wheals (ie, >24 hours)? Do your wheals leave hyperpigmented bruises? 	Skin biopsy, C3, C4, C1q
Schnitzler syndrome	<ul style="list-style-type: none"> Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, or malaise)? Are your wheals not itchy? 	Skin biopsy, serum immune fixation (monoclonal IgM/IgG), CRP, serum amyloid A, S100 A89 or A12
Cryopyrin-associated periodic syndrome	<ul style="list-style-type: none"> Have you had the symptoms since childhood? Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, or malaise)? Are your wheals not itchy? Do your symptoms exacerbate in cold temperatures? 	Skin biopsy, CRP, serum amyloid A, S100 A89 or A12, mutation analysis in the NALP3 receptor protein 3 gene
Still's disease (systemic juvenile idiopathic arthritis and adult-onset Still's disease)	<ul style="list-style-type: none"> Do you have extracutaneous symptoms (eg, fever, musculoskeletal pain, or malaise)? Skin inspection: macropapular rash(es) colored or urticarial rash? Physical examination: lymphadenopathy or hepatosplenomegaly? 	Skin biopsy, CRP, serum amyloid A, S100 A89 or A12, ferritin, liver enzymes
ChIdU	Can you make your wheals appear?	Provocation testing with respective trigger (ie, cold, friction, or exercise)
IN PATIENTS WITH ANGIOEDEMA ONLY		
ACE inhibitor-induced angioedema	Are you taking blood pressure medication?	Stop ACE inhibitor intake
Hereditary angioedema	Does or did anyone in the family have similar symptoms?	C4, C1-INH protein and function
Acquired angioedema	Did you ever have abdominal pain attacks?	C4, C1-INH protein and function, C1q and C1-INH antibodies

^aAngioedema: 20-25% of CSU.
^bC-ANCA: complement component 1-4 antibody; C3a1q: complement component 3a1q.
Muller M, et al. *J Allergy Clin Immunol Pract*. 2021;9:2274-2283. | Jaber B, et al. *Allergy*. 2022;77:734-755.

So, one confirms, you have to rule out the differential, and this is a table that lists the different potential causes that might be associated in patients with wheals only, which include urticaria vasculitis, Schnitzler syndrome, cryopyrin-associated periodic syndrome, Still's disease. And there are questions and aspects of the physical exam that should lead to further investigation and other diagnostic tests that could help rule in



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		<p>or rule out these conditions. Similarly, in patients with angioedema, only one should consider asking if they're taking an ACE inhibitor, which can be associated with angioedema, and if so, stop the ACE inhibitor and ask questions about hereditary angioedema, such as family history, and acquired angioedema should be also asked. And this typically occurs much later in life than patients with hereditary angioedema, which begins earlier in life. And again, ordering the appropriate tests to differentiate between these two conditions would be appropriate. However, if there's no family history, one would recommend starting with the screening C4 level to rule out bradykinin-mediated angioedema.</p>
21	<p>Cause: Look for Indicators of CSU or CInDU¹</p> <ul style="list-style-type: none"> ▪ Basic tests can distinguish CSU^{at1} from CSU^{at2}, with CRP often elevated and eosinophil and basophil levels reduced in CSU^{at2} <ul style="list-style-type: none"> – A subpopulation of patients with CSU has both types² ▪ Bio measures to assist with therapeutic response to omalizumab <ul style="list-style-type: none"> – Negative predictors are low IgE or elevated IgG anti-TPO ▪ Basophil activation testing can further help identify CSU^{at2} and should be guided by patient history and basic test results <p><small>1. Zuberien T, et al. Allergy. 2022;77:734-736. 2. Kolbits P, et al. J Allergy Clin Immunol. 2022;149:919-931.</small></p>	<p>Cause: One should look for indicators of these conditions. Basic tests can distinguish between CSU, different types of CSU autoallergy, which is type 1, or autoimmunity, which is type 2B, with CRPs, which are often elevated, and eosinophil and basophil levels, which are reduced in patients with autoimmune type 2B chronic spontaneous urticaria. A subpopulation of patients of chronic spontaneous urticaria has both types, meaning they have autoimmune type 1 and autoimmune type 2B urticaria. Bio measures to assist with therapeutic response to omalizumab, such as negative total IgE as patients with very low IgE levels less than 20 units tend not to be good responders to omalizumab and patients with elevated antibody against thyroid peroxidase may also be slow or poor responders to omalizumab. Basophil activation testing can further help identify patients with chronic spontaneous urticaria autoimmune type 2B types where patients produce antibodies against high-affinity IgE receptors on mast cells and should be</p>

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For instance, with aquagenic urticaria, one can use water compresses at 35 degrees applied to the skin of the upper body for 30 minutes and one should see urticaria at the challenge site. And for cold-induced urticaria, there are cold provocation testing where one can apply an ice cube at the forearm for 5 minutes and one would see urticaria at the challenge site during rewarming of the skin.</p>
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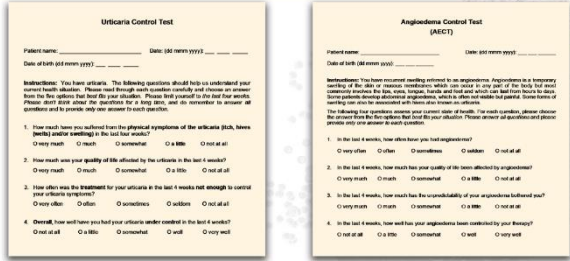
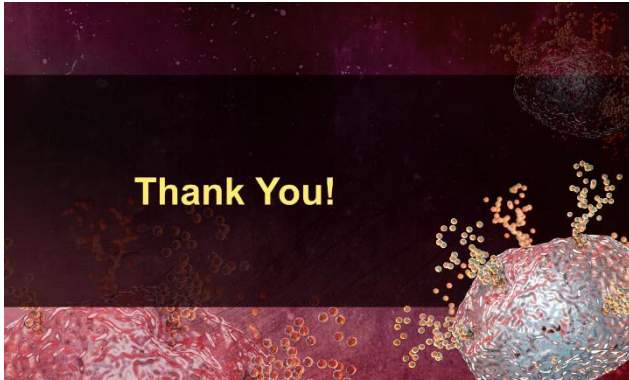
A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and Innovative Treatments on the Horizon

Recognizing and Diagnosing CU in Practice: How Well Do You Know Current Guidelines?

<p>26</p>	<p>Components and Course</p> <p>Assessment of CSU components associated with longer disease duration, higher disease activity, and response to treatment:</p> <ul style="list-style-type: none"> CSU activity and concomitant CInDU should be evaluated in all patients with CSU, and CRP and CBC with differential (giving an estimate for blood basophil and eosinophil counts) should be performed as recommended by international guidelines In addition, D-dimer and total IgE are recommended to be tested to help in counseling the patient in respect to disease duration and treatment response <p><small>Metz M, et al. J Allergy Clin Immunol Pract. 2021;9:2274-2283. Zuberik L, et al. Allergy. 2022;77:734-766.</small></p>	<p>Components and course: One could assess the CSU components associated with longer disease duration, higher disease activity, and response to treatment. And again, this should be evaluated in all patients with CSU, and CRP and CBC with differential should be performed as recommended by international guidelines. And in addition, D-dimer and total IgE are recommended to be tested to help counseling patients in respect to disease duration and treatment response.</p>																												
<p>27</p>	<p>Patient Case Continued</p> <ul style="list-style-type: none"> AB, a 26-year-old woman with recurrent hives associated with angioedema <ul style="list-style-type: none"> Persistent for the past 6 months and involves 95% of her body Hives associated with severe itch, painful welts when scratching, chills, and joint aching Physical examination found no dermatographism or any signs of infection or systemic illness Laboratory assessment, including CBC with differential, ESR, CRP, and TSH, were all normal No identifiable trigger After excluding any clinical signs indicative of vasculitis and further evaluating AB's symptoms and history, AB was ultimately diagnosed with CSU <p>What is the best way to assess the severity of AB's CSU?</p> <ol style="list-style-type: none"> Skin biopsy Blood tests for inflammatory markers Evaluation of response to antihistamines Patient-reported symptoms 	<p>So now we have our patient A.B. who has recurrent hives and angioedema. We found no dermatographia, no signs of infection or systemic illness. Laboratory tests, her screening laboratory tests were normal, she has no identifiable triggers. After excluding other clinical signs and taking her vasculitis and further evaluating A.B.'s symptoms and history, she was also ultimately diagnosed with chronic spontaneous urticaria. So, what is the best way to assess the severity of A.B.'s chronic urticaria: skin biopsy, blood test for inflammatory markers, evaluation of response to antihistamines, or patient-reported symptoms? And, of course, the correct answer is patient-reported symptoms.</p>																												
<p>28</p>	<p>Assessment of Disease Activity Impact: UAS/UAS7</p> <table border="1"> <thead> <tr> <th>Score</th> <th>Wheals</th> <th>Itch</th> </tr> </thead> <tbody> <tr> <td>0 — None</td> <td>None</td> <td>None</td> </tr> <tr> <td>1 — Mild</td> <td><20 wheals/24 hours</td> <td>Mild (present, but not annoying or troublesome)</td> </tr> <tr> <td>2 — Moderate</td> <td>20-50 wheals/24 hours</td> <td>Moderate (troublesome, but does not interfere with normal daily activity or sleep)</td> </tr> <tr> <td>3 — Intense</td> <td>>50 wheals/24 hours or large confluent areas of wheals</td> <td>Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)</td> </tr> </tbody> </table> <table border="1"> <tr> <td> Itch (severity) 0 = none 1 = mild 2 = moderate 3 = severe Once daily </td> <td>+</td> <td> Wheals (number) 0 = none 1 = 0-20 wheals 2 = 20-50 wheals 3 ≥50 wheals Once daily </td> <td>=</td> <td> Daily UAS (0-6) </td> <td>→</td> <td> Weekly UAS7 (0-42) </td> </tr> <tr> <td colspan="4"></td> <td colspan="2" style="text-align: center;">Sum for 7 Days</td> </tr> </table> <p><small>Chang WCH, et al. J Formos Med Assoc. 2016;115:398-398.</small></p>	Score	Wheals	Itch	0 — None	None	None	1 — Mild	<20 wheals/24 hours	Mild (present, but not annoying or troublesome)	2 — Moderate	20-50 wheals/24 hours	Moderate (troublesome, but does not interfere with normal daily activity or sleep)	3 — Intense	>50 wheals/24 hours or large confluent areas of wheals	Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)	Itch (severity) 0 = none 1 = mild 2 = moderate 3 = severe Once daily	+	Wheals (number) 0 = none 1 = 0-20 wheals 2 = 20-50 wheals 3 ≥50 wheals Once daily	=	Daily UAS (0-6)	→	Weekly UAS7 (0-42)					Sum for 7 Days		<p>Using certain validated instruments, such as the disease urticaria activity score, Urticaria Activity Score 7, and this is a score that is ranked based on a score of 0 to 3. Where you have no hives or itch. You have mild hives, which are less than 20 wheals for 24 hours and mild itch. Moderate is between 20 to 50 wheals for 24 hours with moderate itch that's troublesome but does not involve activity or sleep. And then intense hives, which is greater than 50 wheals for 24 hours, and again these are associated with intense itching that do affect normal daily activities or</p>
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		<p>sleep. And one can quantify these based on the itch, which is a once-daily score with a maximum score of 3 plus wheals, a maximum score of 3. And then this would be a daily UAS, which can range between 0 and 6 and then one can sum it up for 7 days and come up with the UAS7, which is a 0 to 42 score. So the maximum severity can be 7 times 6, which is 42.</p>
<p>29</p>	<p>Assessment of Disease Activity Impact: UCT/AECT</p>  <p><small>Reproduced for educational purposes only from Zuberbier T, et al. <i>Allergy</i>. 2022;77:731-756.</small></p>	<p>This is also the urticaria control test, which is very practical, and the angioedema control test, which is very practical to use in the clinical setting as there are four questions which ask about the different physical symptoms, quality of life, treatment response, and how well patients feel their lives are controlled. And again, this is validated to determine urticaria and angioedema control over time.</p>
<p>30</p>	<p>Key Take-Aways</p> <ul style="list-style-type: none"> CU is a spontaneous or inducible group of diseases characterized by the occurrence of wheals (and, in about 50% of cases, angioedema) for >6 weeks Multiple international guidelines exist for CU diagnosis and management, with core recommendations remaining similar History and physical examination are important for diagnosis, with limited laboratory testing typically required Assessment of disease impact and severity on patient QOL is crucial for effective management 	<p>So, what are the key takeaways? Chronic urticaria is a spontaneous or inducible group of diseases characterized by the occurrence of wheals and, in about half of cases, angioedema for more than 6 weeks. Multiple international guidelines exist for CU diagnosis and management, with core recommendations remaining similar. History and physical exam are important for diagnosis, with limited laboratory testing typically required. Assessment of disease impact and severity of patient quality of life is crucial for effective management.</p>
<p>31</p>	 <p>Thank You!</p>	<p>Thank you very much for your attention.</p>