REVIEW ARTICLE

Urticaria: Diagnosis and Treatment with Osteopathic Considerations

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KEYWORDS:

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ABSTRACT: Urticaria is a common benign dermatologic condition. It is primarily manifested by well-marginated pruritic wheals typically surrounded by erythema caused by the release of histamine into the skin. Urticaria may occur with or without angioedema and typically resolves within 24 hours. Urticaria that persists or recurs past six weeks is known as chronic urticaria. Urticaria may be caused by various medications and illnesses, though in most cases, a trigger cannot be identified. Certain forms of urticaria may be triggered by physical stimuli such as pressure, heat, cold, water, or sunlight. Antihistamines are the mainstay of pharmacotherapy for acute and chronic urticaria. Trigger avoidance should be emphasized when a trigger is identified. Other treatments include oral steroids, doxepin and omalizumab. Topical steroids are ineffective. This article reviews the presentation, diagnosis and treatment of acute and chronic urticaria.

Urticaria (also known as hives) is a common benign dermatologic condition caused by histamine released into the skin. It appears as well-demarcated, raised pruritic pale, pink or red wheals typically surrounded by erythema. Lesions can appear on any part of the skin and may range in size from millimeters to centimeters with well-demarcated, serpiginous borders. They may rapidly change size and coalesce or be separate. The lesions are blanching, are not tender and resolve without residual skin changes. *(Figures 1—4)*

The onset of urticaria to maximal spread usually takes from minutes to hours. They typically resolve without treatment in less than 24 hours. Lesions that recur within six weeks are considered recurrent acute urticaria.[1] Lesions that repeatedly occur over a period lasting more than six weeks are called chronic urticaria. Lesions that last longer than 24 hours, do not blanch or leave behind pigment changes following resolution are atypical and may be associated with urticarial vasculitis.[2,3]

Acute and chronic urticaria may occur with or without angioedema. Angioedema is swelling that occurs deeper in the tissues without any overlying skin changes. The discussion of urticaria in this paper includes both urticaria without angioedema as well as urticaria with angioedema. Angioedema occurring without urticaria is a separate clinical entity and is not addressed in this paper. This paper also does not discuss other conditions relating to the release of histamine, such as anaphylaxis.

EPIDEMIOLOGY

Urticaria is a common disorder, and the prevalence varies from 20% spontaneous acute urticaria, to 1% of the general population with chronic recurrent urticarial symptoms (depending on the which

FIGURE 1:

Urticaria on the flank of an adult male

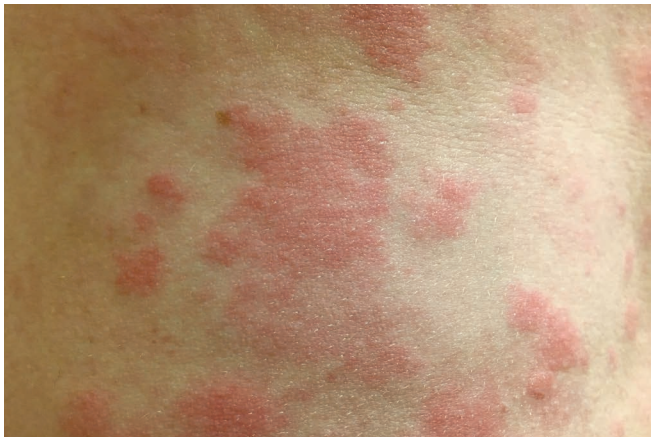

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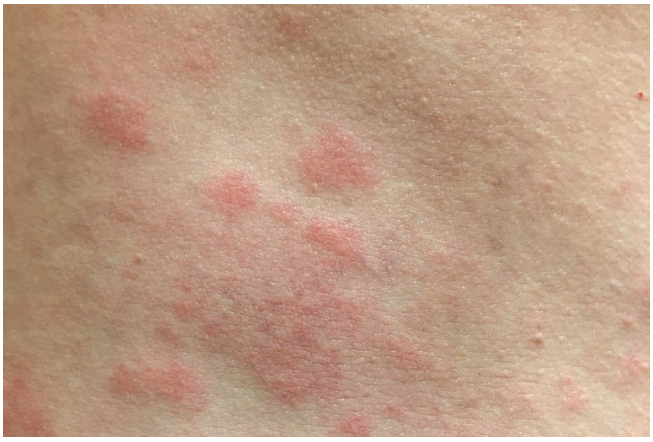
FIGURE 2:

Urticaria on the back of an adult male



Stephen K. Stacey, DO (Photographer)

FIGURE 3:

Urticaria on the arm of an adult female

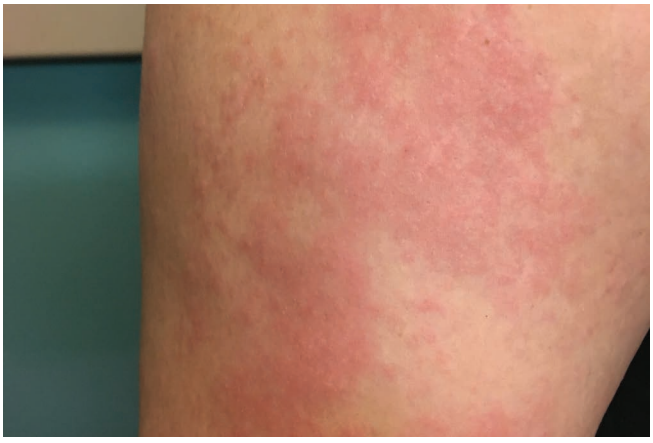


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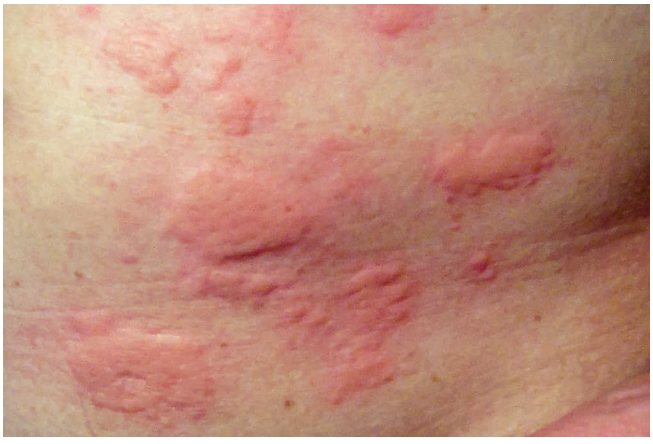
FIGURE 4:

Erythematous wheals of urticaria



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trigger the patient is susceptible).[3,4] Approximately 16-20% of those with recurrent acute urticaria will go on to develop the chronic form.[5] Chronic urticaria is noted in approximately 0.6-1% of the general population, with similar reports from multiple countries.[3,4,5,6] Prevalence is higher in women and adults in the third or fourth decade of life. Chronic urticaria may resolve spontaneously in up to 50% within the first year and in up to 80% by five years.

ETIOLOGY

The wheals of urticaria result from the release of histamine into the epidermis by mast cells and basophils. Histamine release into the deeper tissues such as the dermis and subcutis results in angioedema. This histamine release is typically IgE mediated in response to allergens that stimulate an immune response. However, non-IgE histamine release may result from proteases from aeroallergens, complement activation and autoantibodies to IgE. Systemic conditions are uncommon causes of urticaria and include mastocytosis, Hashimoto thyroiditis, hypothyroidism, Sjögren syndrome, SLE, RA, celiac, vasculitis, lymphoma, and viral infection such as hepatitis B and C. Medications may cause urticaria either through sensitization and IgE-mediated allergic response or direct stimulation of mast cell degranulation. Other common causes include insect bites, pruritic urticarial papules and plaques of pregnancy (PUPPP), physical urticaria and cholinergic urticaria.[7]

Acute urticaria typically results from exposure to a specific trigger. Patients may report a history of being exposed to drugs, environmental allergens, arthropod bite, food or specific contact allergen. Common offending drugs include penicillins, sulfonamides, NSAIDs, diuretics, muscle relaxants, and contrast dye. Common offending foods include milk, eggs, shellfish, peanuts, and tree nuts. They may also develop as a response to acute viral infection. Strong emotions are even purported to play a role in many cases. However, in approximately 30-50% of cases, no specific trigger is found.[8,9] The etiology of chronic urticaria is not well-understood. A specific trigger is rarely found even after a thorough search. It is likely caused by an autoimmune process involving IgG autoantibodies against IgG.[10]

Physical urticarias are a subset of urticaria caused by physical triggers. Physical triggers include physical pressure, heat, cold, water, or sunlight. Significant diagnostic uncertainty may exist in the diagnosis of physical urticarias because in certain patients the urticaria develops after a considerable delay following exposure to the offending process.[11,12,13]

WORKUP

The initial evaluation of urticaria involves a thorough history and general physical exam. The typical history of urticaria is of characteristic lesions that are very pruritic and arise over several hours and typically resolve within 24 hours without treatment. No labs or imaging are required to establish the diagnosis of urticaria but may help rule-out alternative diagnoses if indicated. Evaluation begins by establishing whether the urticaria are acute or chronic. Chronic urticaria are defined as recurring for over six weeks. History should also focus on identifying possible triggers

of urticaria as discussed above under "etiology".[14,15]

During the physical exam, lesions on any affected skin surface should be evaluated. The character and distribution of the lesions should be described. If the lesions have resolved before the evaluation, it can often be helpful to ask whether the patient has taken a picture of the lesions. In the case of recurrent urticaria, patients should be encouraged to take pictures of active lesions. Also note the presence of any excoriations in addition to the primary lesions. Urticaria should typically resolve without any residual skin changes, and the presence of remaining hyperpigmentation or other effects should prompt consideration of an alternate diagnosis such as urticaria pigmentosa.[16]

Several forms of physical urticaria can be elicited during the physical exam. The performance of each of these exam maneuvers is typically not indicated for acute urticaria. However, during the evaluation of chronic urticaria it can be helpful to evaluate whether a form of physical urticaria is the cause of the patient's symptoms. These are discussed in greater detail under "physical urticaria."

Laboratory evaluation and biopsies are not required to make the diagnosis of urticaria. They may be obtained to rule-out other diagnoses. No imaging is required. Skin prick testing is likewise not indicated as it has not been shown to improve outcomes or significantly alter management in either acute or chronic urticaria.[17,18] As part of their Choosing Wisely campaign, the American Academy of Allergy, Asthma & Immunology has stated: "Don't routinely do diagnostic testing in patients with chronic urticaria." They further state that "Routine extensive testing is neither cost effective nor associated with improved clinical outcomes. Skin or serum-specific IgE testing for inhalants or foods is not indicated, unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria."

PHYSICAL URTICARIA

Physical urticaria are a subset of urticaria caused by an identifiable physical trigger *(Table 1)*. Such triggers include physical pressure, heat, cold, water and sunlight. In general, physical urticaria may be evaluated by exposing the patient to the suspected trigger and observing the response. Care should be taken not to confound exposures, which may complicate the clinical assessment. For example, when assessing cold urticaria, if ice is placed directly on the skin then the patient has been exposed to both low temperature as well as water.[19] *(Table 2)*

Dermatographism is a condition in which physical pressure elicits the direct release of histamine, creating a wheal. It can be elicited by gently stroking the patient with a sharp object such as the wooden end of a cotton-tipped applicator. The wheals will typically appear within minutes over the area with or without pruritus. In delayed-pressure urticaria, the wheals may not appear until 6-12 or even 24 hours later, so the patient should be asked to continue to monitor the area for development of lesions if none are seen during exam.[20]

Cholinergic urticaria (sometimes known as generalized heat urticaria) is a condition in which hives develop diffusely in response to increased body temperature. Triggers may include exercise, hot water, ingestion of spicy foods, high ambient temperatures, or even strong emotions. The diagnosis can be clinical based off a history of suspicious lesions in the appropriate context. However, if the diagnosis is in question or requires confirmation, induced heat can be applied in the office. One method involves submerging the patient's arms in 40°C (104°F) hot water until the core temperature has elevated by at least 0.7 °C. The diagnosis is confirmed by the appearance of lesions in sites other than those directly exposed to the water.[21]

Local heat urticaria is a condition caused by heat applied to a focal area of skin. Unlike cholinergic urticaria, only the portions of skin exposed to the head manifest symptoms. This can be induced by applying a container of water heated to approximately 110 °F. Care should be taken to not accidentally burn the patient while still applying heat strong enough to induce symptoms.[22]

Cold urticaria may be elicited by conducting a cold stimulation test. One way to perform this test is to expose a portion of the patient's skin (such as the volar forearm) to ice in a plastic bag. The ice should be applied for five minutes. The skin should be observed after about ten minutes for the development of urticaria.[23]

Aquagenic urticaria may be elicited by placing one of the patient's extremities into a basin filled with water for 20–30 minutes. The water should be lukewarm to avoid confusion with local heat urticaria or cold-induced urticaria.[24]

Solar urticaria is a rare cause of urticaria. It is provoked by exposure to sunlight. Concerning clinical history with lesions of appropriate clinical appearance are enough to secure the diagnosis in most cases. If uncertainty exists, patients can be tested with controlled light exposure, which requires specialty equipment.[25]

TABLE 1:

Common urticaria treatments

TREATMENT	DESCRIPTION
Trigger avoidance	Indicated for all cases in which a trigger is identified.
Non-sedating H1 antihistamines	First-line therapy. Examples include loratadine, fexofenadine, cetirizine. May titrate dose to effect.
First-generation (sedating) H1 antihistamines	These agents possess a higher side-effect potential when compared with non-sedating antihistamines and should only be used at approved doses. Examples include diphenhydramine or hydroxyzine.
H2 antihistamines	Used in conjunction with H1 antihistamines as second-line therapy. Examples include ranitidine, cimetidine, famotidine.
Systemic steroids	May be used for refractory or severe cases. One sample regimen is prednisone 0.5—1 mg/kg as a single or divided dose daily for 3—5 days.
Topical steroids	Play no role in the management of urticaria.

TABLE 2:

Physical urticaria types

CONDITION	DESCRIPTION	EVALUATION
Dermatographism	Physical pressure elicits the direct release of histamine, creating a wheal.	Gently stroke the patient with a sharp object. Wheals typically appear within minutes.[20]
Cholinergic urticaria	Diffuse wheals develop in response to elevated body temperature.	Increase the patient's core temperature and observe for urticaria at sites not directly exposed to heat.[21]
Local heat urticaria	Wheals develop in areas of skin directly exposed to heat.	Apply dry heat (e.g., warm dry compress) to the patient's skin. Lesions are observed only at the area of exposure (contrast with cholinergic urticaria).[22]
Cold urticaria	Wheals develop in areas of skin directly exposed to cold.	Apply dry cold (e.g. ice covered in a bag) to the patient's skin. Lesions are observed at the area of exposure.[23]
Aquagenic urticaria	Wheals develop in areas of skin directly exposed to water.	Apply lukewarm water to patient's skin. Lesions are observed at the area of exposure.[24]
Solar urticaria	Wheals develop in areas of skin directly exposed to sunlight.	Clinical history with typical lesions in appropriate distribution. May attempt controlled exposure using specialty equipment.[25]

TREATMENT

Treatment options have variable efficacy and sometimes numerous agents may need to be tried to find the most efficacious plan. *(Table 1)* Avoidance of the inciting agent is fundamental as it is the single most effective therapy. It should be emphasized with all patients, but is sometimes difficult to accomplish. Many of the triggers for the various forms of physical urticaria such as sunlight, heat, cold, water, exercise and vibration can be avoided only to a limited extent.[26,27]

First-line pharmacotherapy for acute urticaria is to use a non-sedating H1-antihistamine such as fexofenadine, cetirizine, loratadine, or desloratadine. There is no evidence that any agent is superior to any other. Dosing can safely be titrated up to as high as four times the usual dose.[28] If symptoms are still not controlled, the addition of a histamine H2-receptor antagonist such as ranitidine, cimetidine, or famotidine may be attempted. A first-generation H1-antihistamine such as diphenhydramine or hydroxyzine may prove beneficial, especially if dosed at bedtime. Sometimes using a non-sedating antihistamine in the AM and a sedating antihistamine in the evening may prove effective.

For cases that do not respond to antihistamines, a short course of systemic corticosteroids (e.g. prednisone 0.5 to 1 mg/kg/d as a single or divided dose) may be attempted. Topical steroids are not an effective treatment for urticaria and should not be used.[29]

Treatment of chronic urticaria again focuses primarily on trigger identification and avoidance. Recurrent episodes may be treated individually as per treatment of acute urticaria above. If episodes are frequent, daily use of antihistamines may be required to reduce symptom burden. In these patients, steroids should be avoided if possible as the benefits of chronic steroid use may not outweigh the risks. Alternative treatments include doxepin, a tricyclic antidepressant with very potent antihistaminic effects. If all these treatment options are ineffective then omalizumab, cyclosporine and other anti-inflammatory/immunosuppressive agents have been advocated by many and found to be effective in select cases.[30]

FOLLOW-UP

Patients with acute urticaria typically do not require routine follow-up as the vast majority of cases resolve completely within 24–48 hours and do not recur. They should be advised that if lesions persist and become chronic, they should return for further evaluation. Patients with chronic urticaria should be monitored regularly for compliance and response to therapy.[31]

Lesions that do not blanch or leave behind pigment changes following resolution are atypical and may be associated with urticarial vasculitis. These lesions may require a biopsy.

OSTEOPATHIC CONSIDERATIONS

Lesions are distressing to the patient and often interrupt normal function. When patients experience severe pruritus, they naturally scratch the symptomatic area. The resultant structural changes (i.e. microtrauma from scratching) can interfere with the regulatory functions of the skin. This allows release of moisture and causes local irritation with inflammation. The resulting skin changes can cause a concomitant acute irritant dermatitis and, if continued, may even result in lichen simplex or other neurodermatoses. Understanding the psychological effects of the dermatologic disease is extremely important in providing whole-person healthcare. Urticarial lesions are temporarily disfiguring, and the patient's perception of a deteriorating appearance may contribute to or exacerbate underlying emotional stress or anxiety. Also, patients are often worried that the lesions may represent a severe condition, which can further exacerbate any mental condition.

CONCLUSION

For most cases of urticaria, the diagnosis is straightforward. Trigger identification should be attempted, and avoidance advised when able. Extensive diagnostic testing beyond a thorough history and physical is rarely indicated. In the cases where the diagnosis is in question, limited diagnostic testing should be performed to rule out alternative causes of the patient's symptoms. Treatment with antihistamines is usually successful. When needed, dosing may be safely titrated up to four times the typical level. Multiple forms of antihistamines may be attempted, beginning with non-sedating H1-antihistamines and adding H2-antihistamines or sedating (first-generation) H1-antihistamines as needed. Advise patients to avoid scratching the lesions. Cases of acute urticaria rarely need follow up as they typically resolve within 24–48 hours. Regularly monitor patients with chronic urticaria for response and adherence to treatment.

AUTHOR DISCLOSURES:
No relevant financial affiliations or conflicts of interest.

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