Urticaria: A Brief Review

ABSTRACT

Urticaria is a common, mast cell-driven disorder that presents with transient wheals, angioedema, or both. Clinically, it is classified into acute or chronic, depending on the duration of symptoms, and further classified by the presence or absence of inducible stimuli. Although urticaria is rarely life-threatening, it can reduce quality of life and carry significant socioeconomic burden on patients. While there is no cure to the disease, the treatment algorithm for urticaria focusses on the control of symptoms with antihistamines as the mainstay of therapy and immunosuppressive/immunomodulating therapies for severe cases.

KEYWORDS: Urticaria; pediatric urticaria; angioedema; acute urticaria; chronic spontaneous urticaria

Introduction

Urticaria is a common pruritic skin condition characterized by erythematous wheals with or without angioedema.[1] Urticaria may be idiopathic or inducible and can be acute or chronic. Acute urticaria (AU) lasts less than six weeks and can be caused by contact with allergens, infection, drugs, food, or be idiopathic.[2] Chronic urticaria (CU) is defined as the occurrence of wheals for a total duration of six weeks or more and is most often idiopathic. It can be further classified as spontaneous when there is no definite trigger, known as chronic spontaneous urticaria (CSU), or inducible when a specific trigger is identified, known as chronic inducible urticaria (CIU).[2,3] Chronic inducible urticaria represents a subset of urticaria exclusively induced by specific stimuli and is further classified into physical urticaria (i.e. symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema) and non-physical urticaria (i.e. cholinergic urticaria, contact urticaria, and aquagenic urticaria).[2] Due to its pruritic nature, urticaria can be very uncomfortable. This paper provides an overview on the epidemiology, pathophysiology, clinical presentation, diagnosis, and current guidelines for management of acute and chronic urticaria.

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Epidemiology

The lifetime prevalence for any type of urticaria varies from <1% to 24%, with estimates of point prevalence ranging from 2.1-6.7% for AU and 0.1-0.3% for CU in children.[4-6] Prevalence of AU is higher in the first years of life and decreases with age.[7] Although most cases in children are thought to be triggered by infections and more than half of AU cases are idiopathic. Children with AU are more likely to have atopic diseases and have a parental history of asthma, allergic rhinitis and atopic dermatitis.[8] Seasonality of acute respiratory viral infections, the most prominent trigger of AU, coincides with AU seasonality.[9] CIU is much more frequent among first-degree relatives of affected individuals than the general population, suggesting a genetic basis for the disease.[10] In adults, there is female predominance in both AU and CU, whereas in children <15 years, there are no sex-specific differences in prevalence.[6,11,12] CU can occur at any age, but the chronic form is more common in adults, especially during the second and fourth decade of life.[1] Urticaria with angioedema is reported in 5-15% of pediatric patients with CU, which is lower than adult rates.[13,14] Over 70% of pediatric patients present with isolated urticaria, and around 10% present with isolated angioedema.[14] Whereas the majority of patients with AU have a self-limiting course within 3 weeks, pediatric CU has an average duration of 2 years with rates of resolution reported at 10.3% per year.[6] CIU is much more frequent among first-degree relatives of affected individuals than in the general population, suggesting a genetic basis for the disease. Along with a significant disease burden, CU is associated with high economic burden on both patients and health care system due to medication utilization and unnecessary laboratory testing.[15]

Pathophysiology

Urticaria is predominantly a mast-cell driven disease mediated by immunologic, non-immunologic, or idiopathic factors.[16] Mast cell activation leads to degranulation, cytokine and chemokine synthesis, and leukotrienes and prostaglandin synthesis.[17,18] Degranulation of mast cells leads to release of histamine, which results in local vasodilatation, increased capillary permeability and nerve activation. This manifests as intracutaneous (wheal) or subcutaneous (angioedema) edema. Activation of sensory nerves leads to pruritus and reflex erythema. Recruitment of inflammatory cells, such as basophils, eosinophils and T-cells, to the dermis creates a heterogenous immune landscape that contributes variably to the intensity of disease.[3]

Activation of mast cell can be categorized as immunologic and

non-immunologic processes.[18] Classically, type 1 hypersensitivity reactions present as acute urticaria. Sensitized patients produce IgE antibodies, which causes crosslinking of high-affinity receptors on mast cells and subsequent potent mast cell degranulation.[18] In chronic urticaria, the pathogenesis involves IgG autoantibodies targeting IgE and its receptors resulting in histamine release from basophils and mast cells.[19] This is supported by the increased prevalence of autoimmune disorders, such as hypothyroidism, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren syndrome, celiac disease, and type-1 diabetes mellitus among those with CU.[20] Mechanisms of nonimmunologic urticaria include degranulation of mast cells via direct stimulation, vasoactive stimuli, and metabolism of arachidonic acid.[18,21]

Triggers

Predisposing or aggravating factors of AU and CU include infections, medications, and food allergies, although the etiology can be idiopathic.[5,22] Viral infections, including post-viral illnesses, are the most frequent cause of AU in infants and children.[23] Aspirin, other non-steroidal anti-inflammatory drugs, beta-lactam antibiotics, and opiates are the most commonly reported drugs involved in exacerbating AU and CSU.[6] A specific identifiable trigger or aggravating factor can only be identified in 20-55% of cases, and most cases of pediatric CU occur spontaneously without a known trigger.[22,24,25]

When inducible, physical triggers are the most common precipitating factors for CU in childhood and are observed in approximately 20% of CU cases.[24,26] Among CIU cases, cold-induced urticaria is the most common subtype in children, followed by cholinergic, solar, and delayed pressure urticaria.[24] Other forms of physical urticarias include dermographism, aquagenic urticaria, heat urticaria, and vibration urticaria.[3]

Differential Diagnosis for Urticaria

- Anaphylaxis
- Urticarial vasculitis
- Cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis
- Mast cell activation syndrome
- Pre-bullous phase of bullous pemphigoid
- Bradykinin-mediated angioedema (hereditary angioedema)
- Early lesions of IgA vasculitis
- Allergic contact dermatitis
- Pruritic urticarial papules and plaques of pregnancy
- Serum sickness-like drug eruption
- Systemic juvenile idiopathic arthritis
- Cryopyrin-associated periodic fever syndromes
- Schnitzler syndrome
- Well's syndrome

History

A good history is essential when a patient presents with urticaria. Acute and chronic urticaria should be easily distinguishable based on the duration of the illness, with acute urticaria lasting for less than 6 weeks at a time. The history should also include questions on the age, frequency, and duration of onset, as well as size and distribution of lesions. For example, if a wheal lasts more than 24 hours without changing, other diagnoses should be considered. Patient's subjective skin symptoms, such as itching, burning, tingling, and deep swelling should be explored to ascertain for associated angioedema.[3] Of note, isolated angioedema that is more painful than pruritic should alert clinicians to consider hereditary angioedema, which is not associated with concurrent urticaria.[14] The history should focus on identifying potential triggers and exacerbating factors and to exclude items in the differential diagnosis.[27,28] The clinician should ask about history of previous anaphylaxis, recent respiratory infections, insect stings, food, physical triggers, psychosocial stress, medication changes, medication use, and personal care products.[29] AU should be differentiated from anaphylaxis, in which the urticaria occurs in the presence of systemic symptoms, such as respiratory difficulty, gastrointestinal upset, and tachycardia.[17]

Questioning about activities involving scratching, heat, and cold, recent travel relating to possible infections, relationship to menstrual cycle, and pregnancy may reveal potential triggers.[30,31] Temporal information about the time of exposure to the development of symptoms and time to resolution of symptoms is also helpful.[29] Relieving factors including over-the-counter medications should be asked about. It would be important to ask about the effect of urticaria on quality of life. Patients should also be asked about a family history of urticaria and angioedema.[3,32] Because many conditions can be associated with urticaria, clinicians should ask about systemic symptoms. Symptoms of periodic fever, conjunctivitis, arthritis, hearing loss, and fatigue can point to cryopyrin-associated periodic syndromes and Schnitzler syndrome.[27,28] Lesions in urticarial vasculitis are more painful than pruritic, last longer than 48 hours, and leave discoloration on the skin.[33] Additional symptoms, such as uveitis, fever, joint pain, cold intolerance and weight gain may point to an autoimmune disease, such as systemic lupus erythematosus, rheumatoid arthritis or hypothyroidism[32]

Physical Examination

Urticaria is characterized by pruritic pink-to-red papules and plaques that may have central pal-

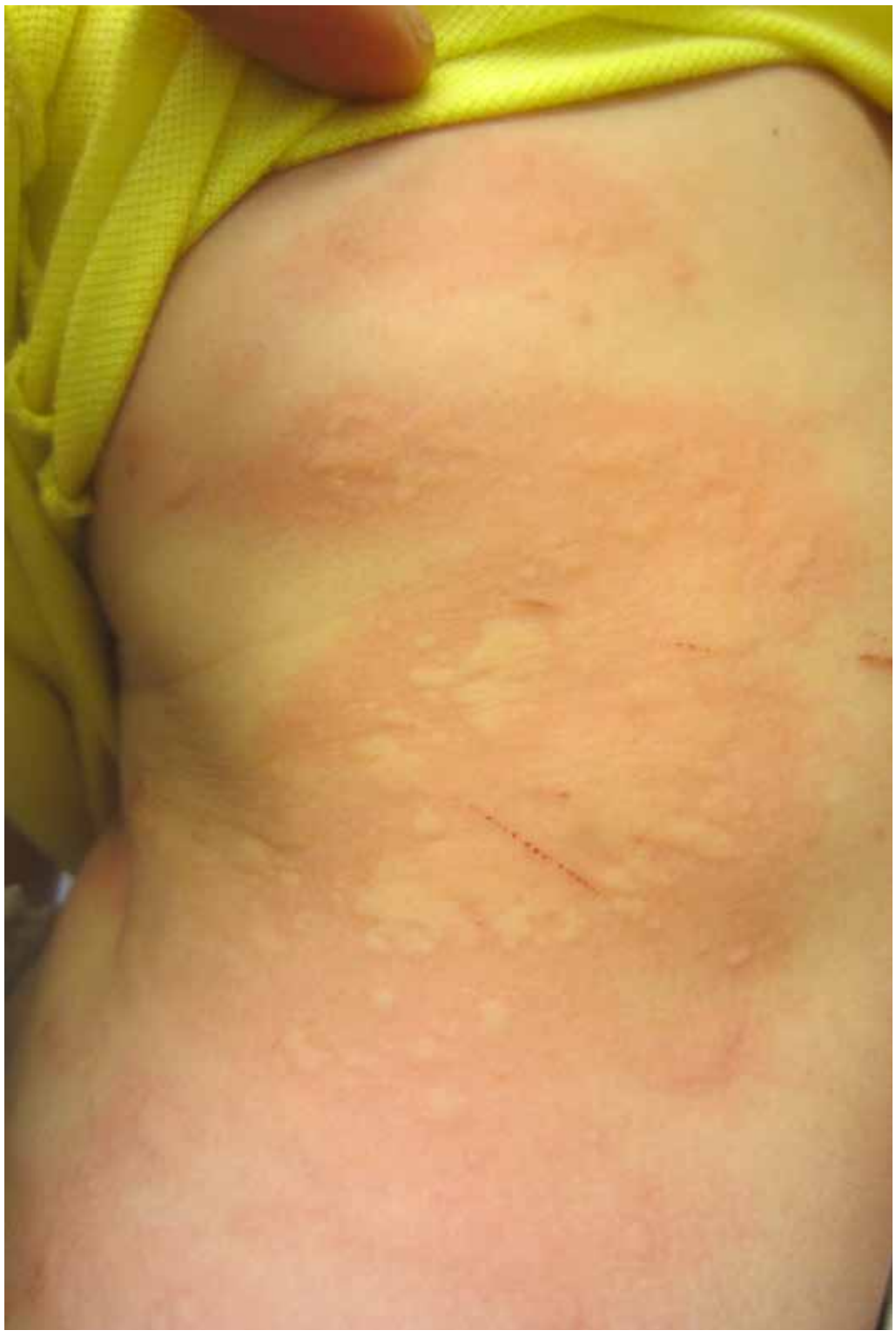

Figure 1a: Edematous wheals with background erythema over the trunk

lor (Figure 1a and b).[19] Urticaria can affect any part of the skin here but have a predilection for pressure-prone areas such as the waistline, axilla, and groin. Several other dermatoses can present with urticaria-like lesions. For example, erythema multiforme can mimic urticaria but is usually fixed, located over the acral skin and has a dusky or bullous centre. In urticaria, each wheal remains for less than 24 hours and typically fades or migrates without residual ecchymosis or pigmentation. If the patient cannot recall the time course of the wheals, drawing around an individual lesion with a skin-marking pen can document resolution or shifting of the plaques within a 24-hour time period. Concurrent angioedema can take up to 72 hours for resolution and is characterized by subcutaneous or submucosal edema affecting non-dependent areas, most commonly lips, peri-orbital, genitals, and extremities.[3,34] Secondary changes from scratching may be evident including excoriations, erosions, and hemorrhagic crust. Darier's sign, which refers to the development of urticarial wheals and flares in response to scratching or rubbing of fixed lesion on the skin, is pathognomonic for cutaneous mastocytosis (Figure 2).[35] This is in contrast to dermatographism, which is formation of linear urticarial plaques following scratching of uninvolved skin (Figure 3).[19]

Investigations

The diagnosis of urticaria is made clinically. Given its self-limiting course, AU does not typically require investigations, unless there is a history of anaphylaxis. In CSU patients, routine laboratory testing is not recommended in patients with otherwise unremarkable history and physical examinations.[36] In fact, Choosing Wisely, a partnership

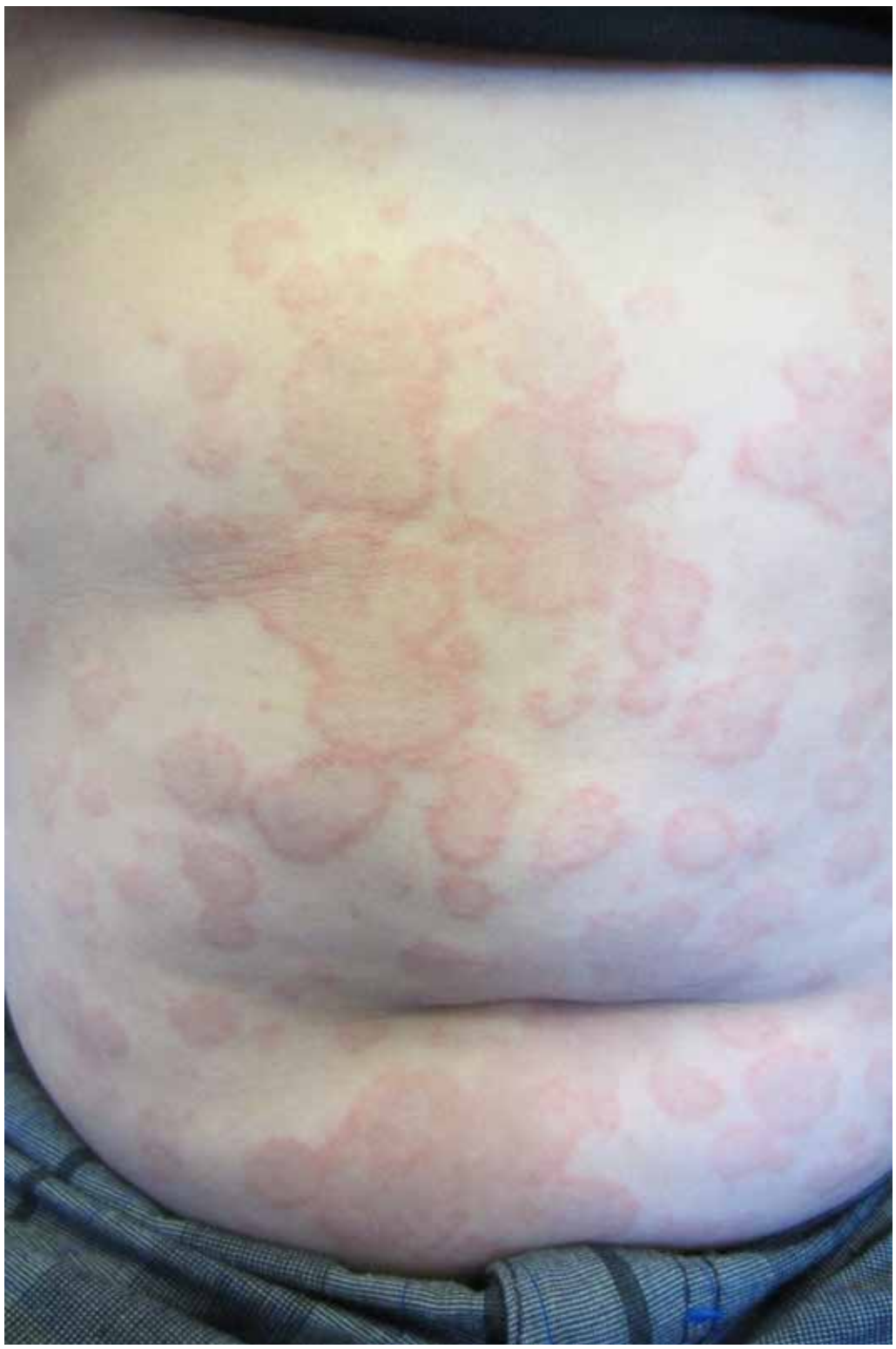

Figure 1b: Annular urticarial plaques over the chest and abdomen

between American Board of Internal Medicine Foundation and specialty societies for reducing unnecessary tests and treatments, recommends against routine testing for patients with CU, unless clinical suspicion warrants targeted laboratory testing. If clinically appropriate, basic tests include complete blood cell count with differential and biomarkers, such as C-reactive protein (CRP) and/or erythrocyte sedimentation rate, to establish baseline disease activity.[3] In addition, specialists can include total IgE and IgG anti-TPO in the CSU workup. The diagnostic yield of biomarkers, however, is variable. Previous studies have reported CRP levels were significantly higher in CSU patients and correlated with disease activity; whereas others have found limited correlation between CRP levels and disease resolution and severity in children.[24] Therefore, diagnostic results should be interpreted in the context of a pertinent patient history and physical examination.[12] Patients should be regularly assessed for disease activity, impact, and control with validated patient-reported outcome measures, such as the Urticaria Activity Score and Angioedema Activity Score.[3] In patients with a suggestive history, autologous serum skin test, *H.pylori* screening, thyroid hormones and autoantibodies, or skin biopsy can be also considered in the workup for CSU.[3,37] Provocation and threshold testing can be used to reproduce response to a suspected stimulus and monitor treatment responses when subtypes of inducible urticaria are in question. These tests should be done in a supervised clinical setting.[17] Examples of provocation tests include a TempTest for cold-induced urticaria, Demographic Test or FricTest for symptomatic dermographism, and passive heat challenge with exercise or hot bath for cholinergic urticaria.[38]

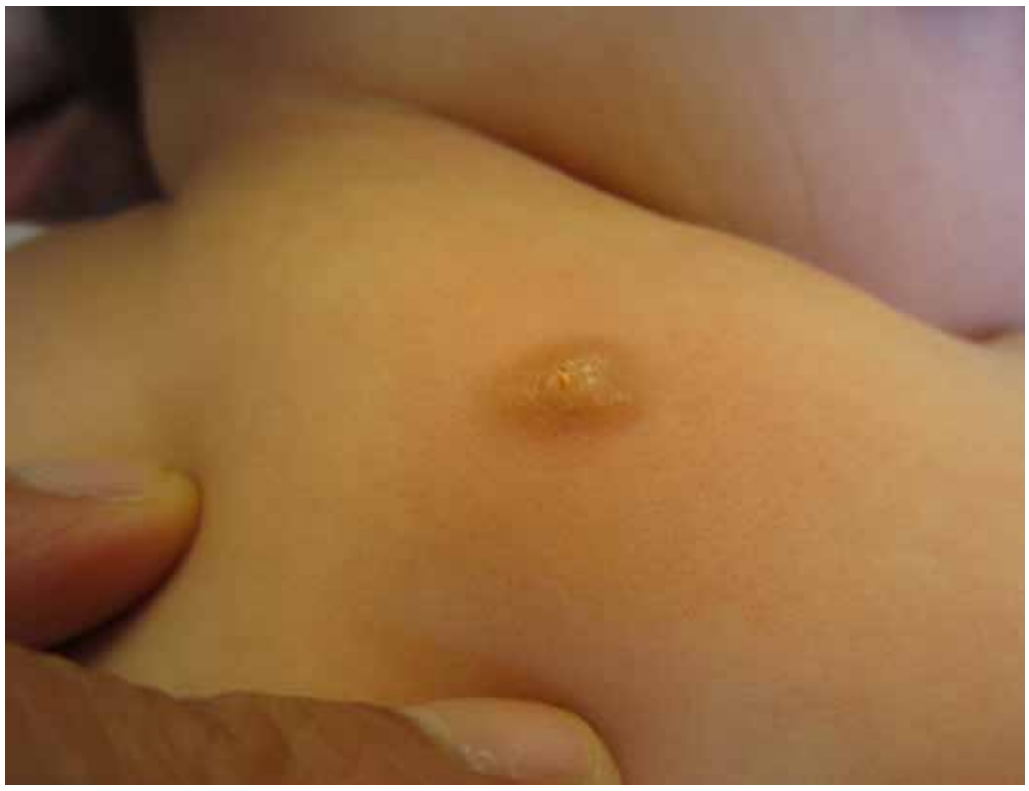

Figure 2: Urticarial plaque overlying a brown patch after rubbing indicating a positive Darier sign in a child with a solitary mastocytoma

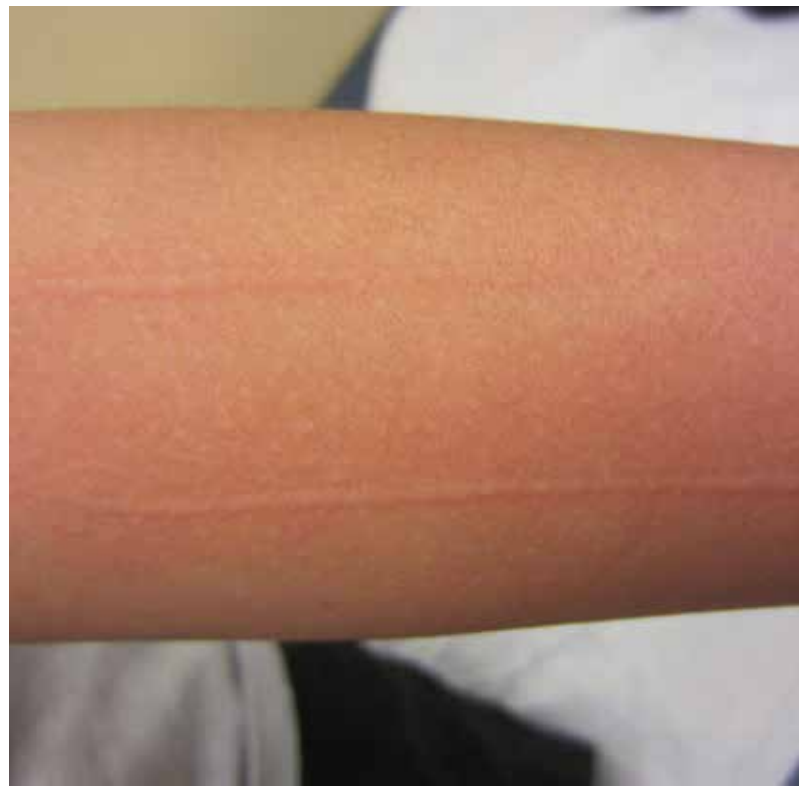

Figure 3: Linear urticarial plaques over the arm following scratching of the skin with a tongue depressor

Management

The therapeutic approach to urticaria involves identification of underlying cause of disease, avoidance of any identified triggers, tolerance induction, and pharmacological treatment for symptom management.

The mainstay of treatment for AU is elimination and avoidance of trigger. In AU, most cases are self-limiting and resolve within days to weeks. Even if a trigger cannot be identified and avoidance is not possible, 2nd- generation H_1-antihistamines can be used as first line pharmacotherapy for symptom relief.[3] Presence of systemic symptoms (e.g. hypotension, respiratory distress, dysphagia, gastrointestinal upset) associated with urticaria suggest anaphylaxis, in which case immediate intervention with epinephrine is first line. In severe cases of AU that are unresponsive to antihistamines, a short course of oral corticosteroids with prednisone 20-50mg/day for up to 10 days can reduce disease severity.

Similarly in CU, elimination or avoidance of the underlying cause is the cornerstone of management; however, the etiology often remains unknown in most patients. In CSU, in which causes are non-specific, relevant or aggravating factors, such as psychological stress and intake of medications, such as NSAIDs, should be avoided to reduce disease exacerbations.[3,39] Infections and subsequent inflammatory processes, such nasopharyngeal and gastrointestinal infections, do not consistently correlate with CSU disease activity. However, *Helicobacter pylori* infections should be treated because

SUMMARY OF KEY POINTS

- Urticaria is a common pruritic condition that is divided into acute or chronic forms. It can be idiopathic or inducible by triggers that including foods, medications, infections, environmental factors, physical stimuli, and medications.
- Acute and chronic urticaria are clinical diagnoses guided by a detailed history and physical examination, and diagnostic testing is not routinely indicated, unless clinical suspicion warrants exclusion of underlying causes.
- Pathogenesis of urticaria involves mast cells and subsequent release of histamines and proinflammatory mediators that result in sensory nerve activation, vasodilatation, and plasma extravasation with leukocyte recruitment to lesions.
- Second-generation, non-sedating H1-antihistamines are the mainstay of treatment for all types of urticaria and dosed up to fourfold to achieve adequate control.

of their association with malignancies.[40] Some evidence for symptom improvement in patients following a pseudoallergen-free diet has been suggested in a non-blinded study.[41] Omission of specific food allergen and a trial of pseudoallergen-free diet limited to 3-4 weeks can be considered in appropriate patients with caution.[42] In most patients, CSU is a self-limiting condition with spontaneous remission seen in 21% to 47% of patients within 1 year.[43] In CIU, inducing tolerance through consistent daily exposure to stimulus can be useful in some subtypes of CIU if complete avoidance is not possible for patients.[3]

The step-wise pharmacotherapy algorithm for urticaria aims to reduce symptoms and signs until spontaneous remission is achieved. Standard-dosed oral 2nd- generation H_1-antihistamines are recommended as first-line treatment for all types of urticaria in adults and children.[3] Options include bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and rupatadine. In general, these agents are not licensed for use in children less than 6 months of age, and the age indications differ by country. Second- generation H_1-antihistamines are preferred as they are non-sedating and free of anticholinergic effects. In patients with AU, they should be taken when symptomatic and on an as-needed basis. In patients with CU, they should be taken regularly and daily. In those who show insufficient response to standard dosing, 2nd- generation H_1-antihistamines can be increased to twofold and fourfold before other treatments are considered. Patients should be informed that updosing is off-label and higher than fourfold dosing is not recommended. It is not recommended to mix different 2nd- generation H_1-antihistamines at the same time.

Omalizumab can be used as an add-on treatment in patients with CSU and CIU who are unre-

sponsive to antihistamines after 2-4 weeks of use.[3,44] The licensed doses are 150 mg and 300 mg administered subcutaneously every 4 weeks and is approved in children 12 years of age and older.[12] Although updosing is off-label, it can be dosed up to 600mg, can be used at intervals of 2 weeks, and can be both updosed and used more frequently in patients who show insufficient response. If adequate control is not achieved within 6 months or earlier, cyclosporin 3.5-5mg/kg per day can be considered as an add-on treatment.[3,45] It should only be recommended in patients with severe disease refractory to any dose of antihistamine and omalizumab in combination, given its profile of adverse effects.

Other symptomatic treatments outside of the treatment algorithm have not shown consistent evidence for efficacy. Leukotriene receptor antagonists, such as montelukast, have not been sufficiently assessed in validated trials.[3] Topical steroids have not demonstrated clinical efficacy. Systemic corticosteroids are strongly not recommended for long-term use in CU, given the high doses needed (i.e. prednisone 20-50mg/day) and side effects profile. However, rescue systemic corticosteroids for up to 10 days may be considered to reduce disease symptomatology in AU and acute exacerbation of CSU. Oral dapsone, H_2-antagonists (i.e. ranitidine), methotrexate, intravenous immunoglobulins, and phototherapy have low-quality evidence and should only be considered in appropriate clinical contexts.

CLINICAL PEARLS

Individual wheals typically resolve within 24 hours without leaving residual changes on the skin. If the duration of wheals is unclear, patients or clinicians can draw a line around the lesion to observe for changes or resolution.

In addition to the physical stimuli in chronic inducible urticaria, other triggers of chronic urticaria include psychosocial stress, work exposures, surgical implants, and menses.

Investigations are not needed to make a diagnosis. However, a limited work-up can be considered for potential comorbidities (e.g. thyroid hormones and autoantibodies for active thyroid disease) or to exclude other diagnoses in the appropriate clinical context (e.g. skin biopsy for urticarial vasculitis).

With the exception of avoiding alcohol consumption, pseudoallergen-free or other food elimination diets should not be routinely recommended to patients for symptom control. In fact, IgE-mediated food allergy is rarely an underlying cause of urticaria.

Conclusion

Urticaria is a common pruritic skin condition that can be acute or chronic and is characterized by development of wheals (hives), angioedema, or both. The disease is mainly driven by mast cells via immunologic, non-immunologic or idiopathic processes with involvement of various mediators, such as histamines, prostaglandins, and proinflammatory markers. Triggers of urticaria are diverse and include food, medications, physical stimuli, and other environmental factors. Acute urticaria is a clinical diagnosis, while chronic urticaria can include a diagnostic workup, if suggested by a good history and physical exam, with basic tests to identify triggers or rule out other diagnoses. Management of urticaria is tailored to the acuity of disease and associated symptoms with the ultimate goal of optimizing patients' quality of life. The first-line treatment, after avoidance of known triggers, is the use of 2nd- generation H_1-antihistamines, which can be updosed to 4 times the recommended daily limit.

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Urticaria Key Points for the Practitioner

History (key points to cover)

- Classify acute vs. chronic by frequency of occurrence of wheals (≤6 weeks vs. >6 weeks) and spontaneous vs. inducible by presence of a definite trigger
- Evaluate the duration of time each urticarial lesion lasts for (<24 hrs)
- If acute and angioedema is present, make sure to rule out anaphylaxis (vomiting, facial swelling, abdominal pain, diarrhea, wheezing)
- Assess impact on quality of life (frequency, associated subjective symptoms, like itching, tingling, swelling and burning, psychological impact)
- Identify eliciting factors (i.e. food, insects, scratching, temperature, exercise, medication changes, personal care products, household products, psychosocial stress, pregnancy)
- Document response to previous therapies
- If chronic, ask about systemic symptoms (i.e. uveitis, fever, joint pain, cold intolerance)

Physical Examination (key things to note)

- Note any secondary changes (i.e. excoriations from scratching)
- Note shape, size, site and distribution of lesions (i.e. annular or plaque morphology, pressure-prone areas)
- Note concurrent angioedema

Selected DDx (key entities to consider and differentiating features)

- Urticarial vasculitis (more painful than pruritic and can leave residual bruising or discolouration on skin)
- Systemic mastocytosis (involvement of liver, spleen, lymph nodes, and bone marrow in addition to skin)
- Contact dermatitis (lesions develop over hours to days after contact with offending agent)
- Bullous pemphigoid (chronic, autoimmune blistering skin disease)
- Schnitzler's syndrome (monoclonal gammopathy, recurrent fever, bone and muscle pain, arthralgia, lymphadenopathy)
- Erythema multiforme (fixed, targetoid lesions, predilection for palms and soles, preceding HSV infection, symptoms of pain and burning more than pruritus)

Urticaria Information for the Patient and Family

What is urticaria?

Urticaria, also known as hives, is a skin reaction that causes itchy, pink or red, raised rashes. These usually go away or change shape in 24 hours or less. Sometimes, there may be deeper skin swelling and this is known as angioedema. This can take up to 72 hours to resolve.

If you stop getting new spots within 6 weeks, this is called “acute urticaria”. If you keep getting new spots for over 6 week, this is called “chronic urticaria”.

Because of how itchy urticaria is, it can cause a lot of problems for patients.

What causes urticaria?

Urticaria is caused by “allergic cells” in the body called mast cells that get too excited. These cells release histamine, which causes itchiness and the rash. Many things can trigger urticaria, but in lots of patients, the urticaria just pops up without any known trigger. Common triggers include infections like the cold, medications like antibiotics and painkillers and food allergies.

Sometimes, the rash is caused by physical triggers. Some of these triggers include scratching, cold, heat, sun, exercise, vibration or pressure.

How can I treat it?

Most urticaria gets better within a few days or weeks without any treatment. However, there are things that can be done to help control the disease and make it less bothersome.

The first step of treatment is to look for and to avoid any obvious the triggers. For example, in chronic urticaria (urticaria that lasts for more than 6 weeks), it may be helpful to look for and avoid any physical causes. It can be helpful to avoid known triggers like psychosocial stress and painkiller medications like ibuprofen.

For all patients, it is helpfu to use a non-drowsy antihistamine on an as-needed basis to control your symptoms. In Canada, the children’s version of cetirizine, desloratadine, fexofenadine and loratadine are approved for children 2 years of age and older, and the adult version is safe in children 12 years of age or older. These can be found over the counter.

In chronic urticaria, you should take a non-drowsy antihistamine regularly and daily to prevent symptoms. In more severe cases, you can increase the dose of antihistamines or add other treatments to your regimen, such as immunosuppressive agents, immunomodulating injections and other oral agents. Topical steroid creams are not helpful in urticaria and should not be used, but oral steroids may be used in severe situations. It is important to discuss with your doctor which option is best suited for your health.

Urticaria is rarely dangerous. However, it can be a sign of a severe allergic reaction when it is accompanied with other symptoms, such as gastrointestinal upset, breathing problems, and throat swelling. In such cases, an epinephrine autoinjector should be used immediately.