

Urticaria and Angioedema Across the Ages



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Chronic urticaria (CU) and angioedema can occur at any age. Although most CU with or without angioedema occurs in adults, it can also present in children or the elderly and can complicate pregnancy and breast-feeding. The presentations of CU and angioedema are different in children, middle-aged adults, and older patients as are the differential diagnoses. Therefore, the management of CU and angioedema in these different age groups and special populations needs to take into account the age-specific features of urticaria and angioedema. Here, we describe the evaluation, diagnosis, and treatment of CU and angioedema in children, middle-aged adults, and older patients. This review focuses on CU with or without angioedema and does not discuss acute urticaria or bradykinin-mediated angioedema. © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1866-74)

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Chronic urticaria (CU), recurrent wheals, angioedema or both for more than 6 weeks, is a common clinical condition that places a significant health burden on patients by impairing their

quality of life. Our understanding of this condition is evolving. Better characterization of clinical features has improved our appreciation of CU phenotypes, which has enabled a more targeted investigation of relevant mechanistic pathways leading to novel treatments. Adopting standard terminology and definitions for different types of CU, such as chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), has been an integral part of the successful development of International Consensus guidelines.¹ Unfortunately, there are still gaps in knowledge regarding mechanistic pathways and treatment especially children, elderly patients, and women of childbearing age. The purpose of this review is to provide an up-to-date overview of CU pathogenesis, approach to diagnosis, and treatment with special focus on children, pregnant or lactating women, and the elderly (Table 1), which are more vulnerable populations where expert opinion often outweighs scientific evidence for making therapeutic recommendations as there are very few studies in children and almost none in elderly patients and women of childbearing age. The intent of this review is to illustrate the progress that is being made to better understand this often-frustrating condition while emphasizing the gaps in knowledge where more research is needed.

THE PATHOGENESIS OF CHRONIC URTICARIA

The clinical manifestations of CU are itchy wheals, angioedema, or both. Symptoms occurring on most days of the week for 6 weeks meet the definition of CU.¹ Approximately 20% of patients with CU have an identifiable physical or other stimulus for skin eruptions and are termed CIndU, whereas the remaining cases are without a clear trigger and are termed CSU.² It is worth noting that inducible urticaria may coexist in CSU, with the most common subtype being symptomatic dermographism (SD).³ A central event in the pathogenesis for both subtypes of CU is the degranulation of skin mast cells by a variety of proposed mechanisms. The resulting release of histamine, prostaglandin metabolites, leukotrienes, platelet activating factor, and other proinflammatory mediators causes vasodilation and extravasation, sensory nerve activation, and cellular infiltration, the underlying mechanisms for itch, wheals, and angioedema. For example, activation of the skin with a known stimulus in CIndU such as vibration in vibratory angioedema/urticaria leads to a measurable increase in plasma histamine and the occurrence of symptoms at sites of trigger exposure.⁴ In CSU, the accumulation of blood leukocytes such as lymphocytes, eosinophils, monocytes, and basophils in lesional sites has been noted in biopsies.⁵

Whereas some episodes of acute urticaria are triggered by specific IgE to a known offending allergen such as a food or drug, an identifiable external allergen is absent in CSU. Many theories have been forwarded to explain pathways for mast cell activation

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Abbreviations used

AAS- Angioedema activity score
Btk- Bruton tyrosine kinase
CIndU- Chronic inducible urticaria
CRTh2- Chemoattractant receptor homologous protein
CSU- Chronic spontaneous urticaria
CSU R- CSU responder
CSU NR- CSU nonresponder
CU- Chronic urticaria
EXPECT- Xolair Pregnancy Registry
FDA- Food and Drug Administration
GA²LEN- Global Allergy and Asthma European Network
MRGPRX2- Mas-related G-protein-coupled receptor X2
PUPP- Pruritic urticarial papules and plaques of pregnancy
SD- Symptomatic dermatographism
UAS- Urticaria activity score
UCT- Urticaria control test
UV- Urticarial vasculitis

and each has its own limitations. Among these are serologic factors such as IgG autoantibodies to either IgE or its receptor and autoreactive IgE to antigens such as IL-24 or thyroid peroxidase.^{6,7} The localized eruptions of urticaria remain difficult to explain on the basis of skin-based autoantigens as the responsible disease-promoting factors.⁸ To date, no single theory has been conclusively shown to explain the pathogenesis of disease.

Skin mast cells numbers have been reported as either normal⁹⁻¹¹ or increased with skin biopsy studies¹²⁻¹⁴ along with evidence for elevated serum tryptase relative to allergic and healthy controls, but still within the normal range for 90% of individuals.¹⁵ Patients with active CSU skin symptoms as well as those who report extracutaneous symptoms with hives have higher tryptase values.¹⁶ It is also recognized that skin mast cells in CSU have a hyper-releasing phenotype to stimuli that activate the Mas-related G-protein-coupled receptor X2 (MRGPRX2), a novel G coupled protein receptor whose ligands include 48/80, several drugs (eg, atracurium, icatibant) and mediators (eg, VIP, substance P).^{9,17} Expression of MRGPRX2 is increased in the skin mast cells of patients with CSU and may be involved in disease pathogenesis.¹¹ Toll-like receptors on mast cells may also respond to infections such as viruses and bacteria given the reports of infections resulting in exacerbation of CSU in some cases.¹⁸ Other pathways that may contribute to this disease include coagulation factors such as tissue factor.^{8,19}

Basophils have a unique phenotype in active CSU disease and are reduced in parallel with the degree of skin symptoms.²⁰ Approximately 50% of patients with CSU have basophils with a suppressed ability to release histamine *ex vivo* via IgE receptor activation and are termed CSU nonresponder (CSU NR) basophils.²¹ The other half of patients have intact *ex vivo* histamine release and are termed CSU responders (CSU R). A third cohort has extreme basopenia (<5000/basophils per mL blood).²² Longitudinal studies have revealed that these basophil phenotypes have unique disease consequences. Subjects with basopenia or CSU NR status basophils demonstrate more severe disease characteristics but of shorter duration than CSU R patients, who have a longer disease course but of a milder character.²² Patients in remission or under therapy with omalizumab have an improvement in basopenia, which may be explained by decreased

recruitment to the skin.^{23,24} The causes of basopenia and distinct IgE pathway basophil functional phenotypes in disease remain an active area of research. Recent advanced investigations of auto-antibody factors such as IgG to IgE or IgE receptors have been noted to occur in approximately 10% of CSU subjects, but do not explain the basophil functional phenotypes.^{24,25} Extreme eosinopenia has been noted in 10% of CSU cases, correlated with disease severity as well as with basopenia.²⁶ A few other features have emerged as potential biopredictors of disease course or therapeutic responses. Among these are total IgE, basophil IgE receptors, and basophil activation assays for treatment response to omalizumab.^{27,28}

OVERALL APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF CHRONIC URTICARIA

Differential diagnoses need to be excluded

Recurring wheals and angioedema are not specific for CU.^{29,30} Wheals, usually without angioedema, occur in urticarial vasculitis (UV) and autoinflammatory disorders such as Schnitzler syndrome or cryopyrin-associated periodic syndromes. Patients who exclusively develop recurrent angioedema, but not wheals, may have bradykinin-mediated angioedema, for example, angiotensin-converting-enzyme-inhibitor-induced angioedema, acquired angioedema, or hereditary angioedema.

Spontaneous, inducible, or both?

CU comes in 2 major types, CSU or CIndU, and the latter has 9 subtypes. Patients with CIndU can deliberately trigger whealing or angioedema development by exposing themselves to the relevant trigger, whereas patients with CSU cannot. Approximately 20% of patients with CSU have 1 or more comorbid CIndU conditions, most often cholinergic urticaria, cold urticaria, or SD and vice versa. Whether or not a patient has CIndU is best determined by asking the question, “can you make your wheals appear?”

What if it is CIndU?

Patients suspected to have CIndU should be provocation tested, by the use of relevant stimuli in controlled settings.³¹⁻³³ SD, for example, is tested by standardized scratching of the skin with a dermatographometer. Cold urticaria is confirmed by the application of a cold (4°C) temperature to the skin of patients. The underlying cause of CIndU is unknown as are prognostic or treatment markers. Comorbidities are poorly characterized. Therefore, further testing for underlying causes is not useful in most patients. When further tests are done, they should be driven by the patient history.

What if it is CSU?

History taking is indispensable in patients with CSU and should explore relevant drivers of disease activity and exacerbation, comorbidities, markers of disease course and activity, and predictors of treatment response. At the outset, erythrocyte sedimentation rate and/or C-reactive protein as well as a differential blood count should be done in all patients, to rule out severe systemic inflammation. Having a basophil phenotype and total IgE may be helpful to guide expectations on the outcome of treatment and on the duration and course of CSU, but are not currently recommended during an initial consultation. Specifically, total IgE and change pre- and post-omalizumab have been demonstrated to predict response to this treatment.³⁴ Based on

TABLE I. Recurrent urticaria and angioedema in children, elderly patients, and women of childbearing age—what is known and future needs

	Children	Elderly	Women of childbearing age
What is known	• Very few studies • CSU may be at least as common as in adults • Angioedema in patients with CSU may be less common than in adults • CSU treatment response may be better than in adults • Omalizumab is off label in children <12 y • Cryopyrin-associated periodic syndrome is important in the differential diagnosis	• Almost no studies • CSU may be more common than in younger adults • Treatment may be complicated by comorbid diseases, polypharmacy, organ insufficiency • Side effects of sedating antihistamines may be more pronounced • Urticarial vasculitis and Schmitzler syndrome are important in the differential diagnosis	• Almost no studies • Urticaria can complicate pregnancy and breast-feeding • Omalizumab is off label in pregnant and breast-feeding women • CSU must be distinguished from other urticarial dermatoses in pregnancy
Future needs	• New and existing treatments need to be studied and licensed • Patient-reported outcome measures need to be developed	• Efficacy and safety of treatments need to be characterized • True prevalence of CSU and CIndUs needs to be investigated	• Efficacy and safety of treatments need to be characterized • Clarify natural course of CSU during pregnancy

CIndU, Chronic inducible urticaria; CSU, chronic spontaneous urticaria.

the information provided by patients, further individualized tests should be considered and obtained if appropriate. Comprehensive general screening programs for causes of urticaria are not recommended nor is routine skin or serologic testing to foods or aeroallergens unless the history mandates this.

Patients with CU should be assessed for disease activity, impact, and control

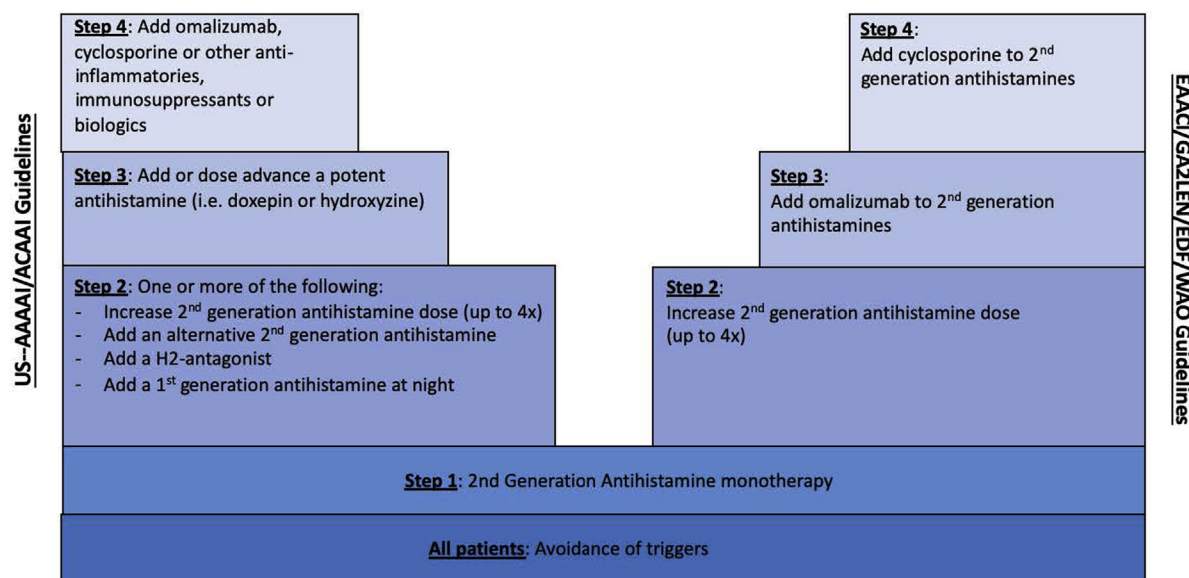
The use of patient-reported outcome measures in the diagnostic workup of CU is essential. Their results guide treatment decisions and help to understand the burden and impact of CU on patients’ lives. In patients with CSU, disease activity is assessed with the urticaria activity score (UAS)³⁵ in patients with wheals, and with the angioedema activity score (AAS) in patients with angioedema.³⁶ Patients record their signs and symptoms on a daily basis and determine their weekly scores, the UAS7 and the AAS7, by adding the values of the days of the week. Disease control is assessed by use of the urticaria control test (UCT) and the angioedema control test.^{37–49} Both tools measure disease control with 4 simple questions each. Quality of life impairment is determined with the CU quality of life questionnaire and the angioedema quality of life questionnaire.^{40,41}

In patients with CIndU, disease activity is assessed by trigger threshold testing. Patients with high disease activity have low trigger thresholds. In SD, for example, patients with high disease activity can be made to develop wheals by very mild scratching of the skin. Dermographometers such as FricTest allow for the application of graded defined shear forces to the skin to determine individual trigger thresholds. Patients with cold urticaria can be assessed for their individual critical temperature thresholds, that is, the warmest temperature that is cold enough to produce a wheal, with the help of TempTest. In addition to trigger threshold measurements, disease activity in patients with CIndU can also be assessed by disease-specific activity scores, such as the Cholinergic Urticaria Activity Score,⁴² which take into account the daily exposure of patients to relevant triggers as well as their avoidance behavior. Control of CIndU is measured with the UCT, and impact is assessed by disease-specific quality of life questionnaires such as the Cholinergic Urticaria Quality of Life Questionnaire.⁴³

Treat CU until it is gone

The goal of the treatment of CU is complete response and control; in most patients, it cannot be cured. No causal treatment is available as the primary pathogenic factors of disease remain elusive. The approach in CU, therefore, is the use of prophylactic symptomatic medication, until spontaneous remission occurs.

The first-line treatment for CU is the once daily use of a nonsedating second-generation H1-antihistamine.¹ Patients who continue to develop wheals or angioedema after 2 to 4 weeks of this treatment are recommended to increase the dose of their antihistamine to up to 4-fold the standard dose. Patients who fail to achieve control of their CU with a higher than standard-dosed nonsedating H1-antihistamine should be treated with add-on omalizumab, which is administered by subcutaneous injection at the standard dose of 300 mg every 4 weeks. If, after 6 months of treatment, omalizumab is not effective, off-label treatment with cyclosporine is suggested.¹ Patients who achieve complete control in response to treatment should be checked for spontaneous remission of their CU every 6 to 12 months.⁴⁴ Both the



***AAAAI – American Academy of Allergy Asthma and Immunology; ACAAI – American College of Allergy Asthma and Immunology; EAACI – European Academy of Allergology and Clinical Immunology; GA2LEN - Global Allergy and Asthma European Network; EDF – European Dermatology Forum; WAO – World Allergy Organization**

FIGURE 1. Comparison of the treatment algorithms for the CU US practice parameter and International guidelines (from Johal and Saini⁴⁵). CU, Chronic urticaria.

American Academy of Allergy, Asthma, and Immunology and International guidelines share some common steps, as depicted in Figure 1.

PREVALENCE OF CHRONIC SPONTANEOUS URTICARIA WORLDWIDE

A recent systematic review of the worldwide prevalence of CSU divided age groups into 0 to 19 years and >19 years of age as only 9 studies presented data stratified by age.⁴⁶ Only 1 study conducted a meta-analysis that reported data in children between 4 and 13 years.⁴⁶ Therefore, a traditional age range for CSU has not been established. Clinical trials have used the 18 to 65 years of age range likely based on historical precedence but have reduced the age to 12 and above if there are already significant safety data available for the investigational agent. This analysis found that the point prevalence estimate for CSU in children was slightly higher than adults. Furthermore, CSU was more common in adult women than adult men, but there were no sex-specific differences in children <15 years.⁴⁶

PREVALENCE, DISEASE CHARACTERISTICS, DIAGNOSTIC WORKUP, AND TREATMENT OF CHRONIC URTICARIA IN CHILDREN (0-19 YEARS)

The underlying causes of CU are held to be similar in children and adults. The international European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum/World Allergy Organization guidelines recommend applying the same approaches to the diagnostic workup and management in

pediatric patients as for adult patients,¹ and this is supported by a recent systematic review.⁴⁷ However, several studies have highlighted some interesting and important differences of CU in childhood as compared with adults.

The prevalence of CU may be higher in children than in adults

In a recent study, the CU prevalence in children varied from 1.1% to 1.5%, with the highest prevalence observed in France and lowest in Germany. The CU prevalence was numerically higher in older age groups (aged 7-11 and 12-17 years) as compared with the youngest age group (aged 0-6 years). The prevalence in the general population is 0.7, across all ages and geographical regions.⁴⁶ Kim et al⁴⁸ compared the prevalence of CU and CSU in different age groups and showed that children exhibit the highest rates, up to 7.5% (Figure 2).

Angioedema may be less common in children with CSU

Physicians reported that 5% to 14% of their pediatric patients with CSU had angioedema.⁴⁹ In adults, rates of angioedema are higher and the presence of angioedema is an important prognostic factor to predict the course of disease.⁵⁰ A study by Volonakis et al⁵¹ investigated 226 pediatric patients with CU aged 1 to 14 years for the presence of angioedema and reported that wheals along with angioedema were present in 15% of patients. Most studies found that around 30% to 50% of adult patients with CSU suffer from angioedema with or without wheals with angioedema rates ranging from 33% to 67% in different studies.^{52,53}

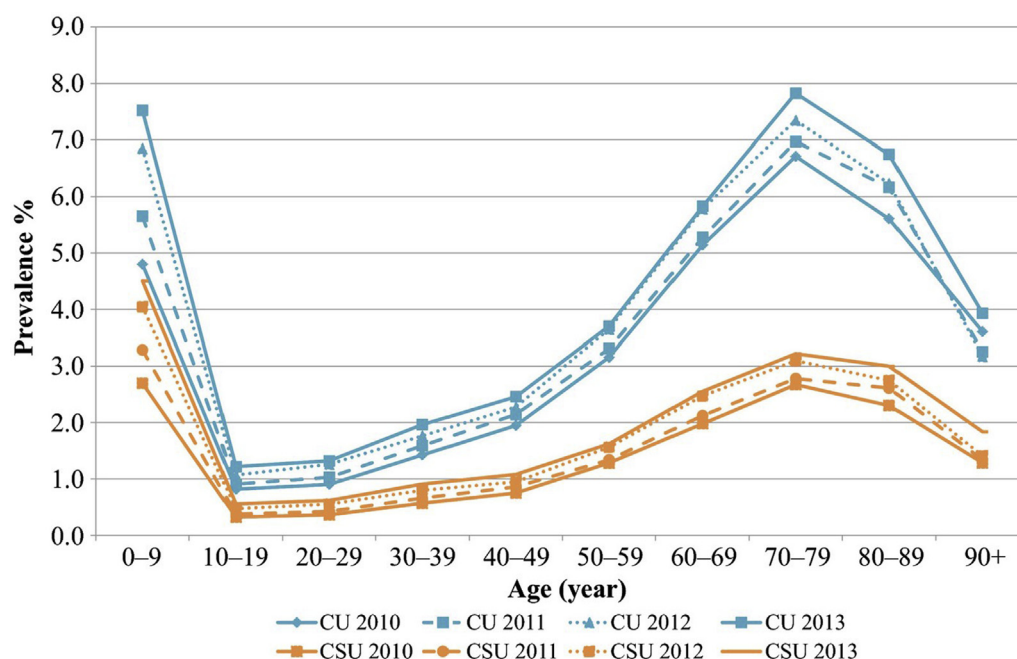


FIGURE 2. Prevalence of CU and CSU across the ages in Korea demonstrating a higher impact than expected in children and the elderly (from Kim et al⁴⁸). CSU, Chronic spontaneous urticaria; CU, chronic urticaria.

Children with CSU may show better treatment responses than adults

Ensina et al⁵⁴ reported that a third of pediatric patients with CSU received H1-antihistamines at approved doses, and half of the patients were treated with higher than approved doses. The study also found that a fourth of children with CSU showed insufficient responses to H1-antihistamine treatment at approved or higher doses. This is in line with the results of a recent European study in which one-third of pediatric patients with CSU remained uncontrolled with H1-antihistamines at approved or higher doses.⁴⁹ Adult patients with CSU show lower rates of treatment responses to H1-antihistamines. Most of the published results indicate that half or even less of adult patients with CSU show complete control of signs and symptoms to licensed doses of H1-antihistamines.⁵² In a recent study, 97 of 178 adult patients with CSU, that is 54%, had persisting symptoms despite standard-dosed or higher than standard-dosed H1-antihistamine treatment.⁵⁵ In another study from China, children with CSU also exhibited a significantly higher rate of response to second-generation antihistamines as compared with adults, that is 82% versus 62%.⁵⁶ This suggests that children with CSU show higher rates of treatment responses than adults, which is supported by a recent study from Korea reporting improvement rates at 6, 12, and 24 months of treatment of 61%, 78%, and 89% in children and 46%, 63%, and 75% in adults, respectively.⁵⁷ Of note, guideline treatment recommendations for pediatric patients with CU are largely extrapolated from findings obtained in adult patients,^{58,59} but this has limitations. The metabolism and excretion of H1-antihistamines, for example, can be different in children than in adults.⁶⁰

Unmet needs in the understanding of CU in children

CU in children remains ill-characterized. The global CU registry, CURE (www.urticaria-registry.com), may help to

change this. More than 2000 patients with CU, a third of which are children, have been included in CURE. All physicians who treat patients with CU are invited and encouraged to contribute to CURE. In addition, the GA²LEN UCARE network (www.ga2len-ucare.com) has recently launched a global project dedicated to the characterization of CU in children.

EVALUATION, DIAGNOSIS, AND TREATMENT OF CSU IN GERIATRICS (AGE ≥65)

Population demographics worldwide are changing with an increasing population of older adults. In 2015, 14.9% of the US population was over the age of 65 with estimates from US census bureau that this number will increase to 25% by 2060.⁶¹ As this segment of the population continues to grow, physicians should be aware of unique circumstances involved in elderly care. Wertenteil et al⁶² estimated the prevalence of CSU among adults in the United States as 0.23% (230 cases in 100,000 adults), with the greatest prevalence in patients over age 50. A Korean study detailing the clinical features of CSU in the elderly noted a higher prevalence of comorbid atopic dermatitis yet there was no significant difference in the prevalence of other atopic diseases, lab studies, or UAS.^{48,63}

The treatment of CSU in older adults follows the same treatment guidelines as other population ages yet the use of antihistamines and other medication may be complicated by potential concerns of comorbid disease, polypharmacy, and organ insufficiency.⁶⁴ Second-generation antihistamines are the preferred means of treatment although dosing may require adjustment for patients with comorbid renal and/or liver insufficiency.⁶⁴ If dose escalation does not resolve urticarial, then additional medication may be required. First-generation antihistamines are more lipophilic and subsequently are able to cross the blood-brain barrier causing impairment of cognition and memory, psychomotor function, and sedation.⁶⁴⁻⁶⁶ Furthermore,

first-generation antihistamines impair rapid eye movement sleep, learning, and work productivity as a result of their impact on circadian rhythm.^{65,66} First-generation antihistamines also affect other neurotransmitter functions as they have anticholinergic, antiserotonergic, and antidopaminergic function. Subsequently, the use of these medications may cause or worsen urinary retention, arrhythmias, peripheral vasodilation, postural hypotension, and mydriasis.⁶⁴ The 2010 GA²LEN position paper recommends avoiding the use of these agents in the general population but especially in the elderly as their effects are more pronounced.⁶⁶ The 2012 American Geriatric Society BEERS criteria list first-generation antihistamines as potentially inappropriate medications and subsequently strongly advise caution if used, to reduce or prevent medication-related adverse events.⁶⁷

In the management of elderly patients, physicians should be aware of the differential diagnosis especially in cases refractory to standard treatment. UV presents with painful, burning, tender urticarial lesions that persist longer than 24 to 48 hours and resolve with residual pigmentation.⁶⁵ Patients with UV may have reduced complement levels (C3, C4), and it can occur as a primary disorder or secondary to an underlying autoimmune disorder.⁶⁵ Diagnosis is ultimately made with biopsy demonstrating leukocytoclastic vasculitis.⁶⁵ However, studies have found that UV can occur even when lesions are evanescent coming and going over 24 to 48 hours. Therefore, a skin biopsy with routine hematoxylin and eosin staining should be obtained if there is high suspicion for UV. Although rare, lymphoproliferative disease and Schnitzler syndrome can also manifest with chronic urticarial lesions. These conditions should be considered when patients present with urticaria sparing the face, are refractory to standard treatment, and endorse systemic complaints of arthralgia, fever, neutrophilic leukocytosis in the presence of elevated inflammatory markers, and a monoclonal paraprotein.⁶⁵

SPECIAL POPULATIONS—WOMEN OF CHILDBEARING YEARS, PREGNANCY, AND BREAST-FEEDING

Although there is an increase in the prevalence of CSU in females, there is a paucity of literature regarding the management of urticaria in pregnant and lactating women, and the safety of treatments has not been rigorously studied. The treatment algorithms used in CSU apply to these groups with emphasis on the use of the lowest effective dose of medications possible.¹ Treatment begins with second-generation H1 antihistamines given their reduced side effect profile. Up to 4 times the Food and Drug Administration (FDA)-recommended dose can be used as needed for symptom control.¹ Updated FDA pregnancy and lactation labeling states that loratadine, cetirizine, levocetirizine, desloratadine, and fexofenadine “may be used during pregnancy as the risk of fetal harm is not expected based on limited human data.”^{65,68} Cetirizine and derivatives are generally preferred as first-line agent given the reported but not confirmed risk of hypospadias with the use of loratadine.⁶⁹ On occasion, first-generation antihistamines may be required for additional symptom control; however, International guidelines strongly recommend against the use of first-generation antihistamines given their high frequency of adverse effects including sedation, decrease in rapid eye movement sleep, and negative impact on learning and performance.⁷⁰ There are no studies that demonstrate greater clinical efficacy of first-generation when compared

with second-generation antihistamines, and labeling states that these agents should be used with caution in pregnancy given the risk of reported congenital anomalies.^{1,65,69,70}

All H1 antihistamines are excreted in breast milk in low concentrations, and therefore second-generation H1 antihistamines are preferred given the concern for neonatal sedation.¹ Most antihistamines are rated as L1 (safest) or L2 (safer) on Hale Lactation Risk Category.⁶⁹ Most first-generation agents are avoided during lactation given the concern for neonatal sedation, respiratory depression, and hypotonia.⁶⁹ First- and second-generation antihistamines may reduce serum prolactin, but this effect on breast milk production is of little consequence once breast milk production has been established and medication dose is considered low.⁶⁹

Approximately 40% to 50% of patients fail to improve with the use of antihistamines.^{71,72} Short courses of glucocorticoids are often required in antihistamine refractory urticaria or during severe flares but are not recommended for chronic use. Although glucocorticoids have been used in pregnancy for the management of a variety of inflammatory disorders, there are potential concerns for the development of pre-eclampsia, gestational diabetes, primary cleft palate, neonatal adrenal insufficiency, and low birth weight, and thus the benefit for use should outweigh the risk.^{71,73} Low levels of prednisone and prednisolone can also be expressed in breast milk with previous studies revealing that a nursing infant would ingest 0.1% of the mother’s daily dose.⁷³ It appears safe to use glucocorticoids during breast-feeding; however, mothers may delay breast-feeding for several hours after taking their glucocorticoid dose in attempts to minimize possible risk.⁷³

Several cases document the use of omalizumab during pregnancy. Cuervo-Pardo et al⁷¹ treated 4 females who failed high-dose first- and second-generation H1 antihistamines, H2 antihistamines, and leukotriene antagonists with omalizumab. Three patients also failed treatment with dapsone, hydroxychloroquine, and/or cyclosporine. All 4 women responded to omalizumab 300 mg every 28 days well with reduction in urticaria index scores. Three patients were treated with omalizumab for 1 year before becoming pregnant; 1 patient was on treatment for only 2 months before becoming pregnant. Once they became pregnant, each continued it through delivery at full term without gestational or fetal complications.⁷¹ Another case report documented the safe and effective use of omalizumab 150 mg every 2 weeks in a woman treated throughout 2 consecutive pregnancies who had previously failed high-dose cetirizine, azathioprine, and adalimumab.⁷⁴ She was on omalizumab therapy for 14 months before her first pregnancy, which she continued during pregnancy and postpartum.⁷⁴ During her second pregnancy as urticaria was in remission, her dose was modified to 300 mg every 4 weeks without reported gestational or fetal complications.⁷⁴ These reports are consistent with data from the EXPECT (Xolair Pregnancy Registry) study in which 191 females with asthma were treated with at least 1 dose of omalizumab 8 weeks before conception or anytime during pregnancy, majority of whom had their earliest exposure in the first trimester.⁷⁵ The results from EXPECT reported that there was no difference in the prevalence of congenital anomaly, prematurity, low birth weight, or gestational size in women treated with omalizumab.⁷⁵ Other medications used in the treatment of refractory CSU should be evaluated on a case by case basis with regard to risk of teratogenicity and embryotoxicity.¹

CSU must be distinguished from other urticarial dermatoses in pregnancy. Gestational pemphigoid is rare and begins with a sudden onset of pruritic papular urticarial eruptions on the trunk that becomes generalized with blisters.⁶⁵ Biopsy reveals subepidermal vesicles with a perivascular infiltrate of lymphocytes and eosinophils and C3 deposition along the dermoepidermal junction.⁶⁵ Treatment initially involves topical glucocorticoids, but oral glucocorticoids are necessary in refractory cases.⁶⁵ Prurigo of pregnancy (Prurigo Gestationis of Besnier) manifests as a pruritic eruption of papules and nodules on extensor surfaces after 20 weeks of gestation, occurring in 1 in 300 pregnancies.⁶⁵ Histopathology is nonspecific and lesions resolve after delivery. Topical glucocorticoids are the mainstays of treatment.^{65,73} Pruritic urticarial papules and plaques of pregnancy (PUPP) occurs in third trimester as pruritic urticarial plaques within abdominal striae sparing the umbilicus.^{65,73} The PUPP prevalence varies between 1 in 160 and 1 in 300 pregnancies. Lesions can involve the face, hands, and soles and can recur in subsequent pregnancies.⁶⁵ Histopathology reveals spongiosis of the epidermis, dermal edema between collagen fibers, parakeratosis, and infiltration of eosinophils. Pruritus typically resolves 2 weeks after delivery.^{65,73} However, treatment during pregnancy of PUPP involves oral antihistamines and topical glucocorticoids, but rarely oral glucocorticoids are required for severe pruritus.^{65,73}

CSU: NOVEL THERAPIES

Antihistamines and omalizumab are the only approved treatments for CU, yet many patients are refractory to these therapies (Figure 1). Omalizumab is approved for the treatment of CSU for those 12 years and older in comparison with its approval for asthma for those 6 years and older. New treatments are on the horizon and focus on the enhanced effect or novel targets including inhibition of IgE, Th2-cytokines, bruton-tyrosine kinases (Btk), and prostaglandin receptor antagonists.⁷⁶

Ligelizumab is a “next-generation high-affinity monoclonal anti-IgE antibody” under development for the treatment of CSU.⁷⁷ In comparison with omalizumab, ligelizumab has a 40 to 50 times greater affinity for IgE. Patients aged 18 to 75 years with antihistamine-resistant CSU treated with ligelizumab demonstrated a rapid onset of drug effect, dose-dependent efficacy, and superiority over omalizumab as more than 50% of patients taking the highest dose of ligelizumab were complete responders; more than double the response rate reported for omalizumab.⁷⁷ In addition, patients treated with a single dose of ligelizumab had suppression of symptoms for up to 8 weeks compared with the 4-week duration of omalizumab.⁷⁷ Another anti-IgE agent (UB-221) reported to have an 8-fold higher affinity for free IgE in comparison with omalizumab is currently under investigation.⁷⁶

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4 α receptor subunit and is currently approved for the treatment of moderate-to-severe atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis in patients older than 12 years. Dupilumab may be beneficial for patients with CU as levels of IL-4 and IL-13 are often elevated in the serum and skin of patients with CSU.⁷⁸ Lee and Simpson⁷⁸ documented a favorable response in 6 patients with CSU who previously failed antihistamines and high-dose omalizumab (600 mg q4weeks). Patients were treated with a

loading dose of 600 mg, followed by 300 mg every 2 weeks.⁷⁸ There are 2 ongoing randomized control trials evaluating the safety and efficacy of dupilumab in patients with CSU and cholinergic urticaria.⁷⁶ Isolated case reports show the effect of monoclonal antibodies targeting IL-5 and IL-5 receptor.^{79,80} Eosinophils and their products such as major basic protein have been reported to contribute to the pathogenesis of CSU because they are present in urticarial wheals and nonlesional skin.¹⁴ Patients with blood eosinopenia have been reported to have more severe and refractory disease.²⁶ Mast cells may recruit eosinophils through the release of IL-5, and thus the mechanism of action of reslizumab and mepolizumab may relate to their ability to inhibit eosinophil migration into the skin.^{79,80} The use of benralizumab also yielded favorable results in a patient with SD yet the mechanism of action is unknown. Unlike CSU, SD lesions are not characterized by infiltrating eosinophils.⁸¹ The efficacy of benralizumab and mepolizumab is currently under investigation in clinical studies (NTC01383024, NTC03494881).⁷⁶

Prostaglandin D2 is a product of activated mast cells and induces chemotaxis of eosinophils and basophils via its receptor CRTh2 (chemoattractant receptor homologous protein) on Th2 leukocytes.⁸² CRTh2 expression on basophils and eosinophils is decreased in patients with CSU.⁸³ AZD1981 is an oral, selective, and reversible CRTh2 antagonist that has been shown to reduce patient-reported itch, prostaglandin D2-induced eosinophil shape, and blood eosinophils in patients 18 to 65 years old with CSU refractory to antihistamine.⁸²

Btk is a cytoplasmic tyrosine kinase involved in cell signaling through B-cell receptors, toll-like receptors, and Fc ϵ RI-receptors and is essential for mast cell degranulation.^{45,76} Fenebrutinib (GDC-0853) is a highly selective, reversible, noncovalent oral BTK inhibitor undergoing clinical investigation for use in patients with antihistamine resistant CSU.⁷⁶ A highly selective BTK inhibitor is desirable to prevent side effects related to inhibition of “off-target” kinases.⁴⁵ Previous use of ibrutinib, a nonspecific oral Btk inhibitor, showed an effect in inhibition of IgE-mediated activation of mast cells and basophils yet its clinical use was limited due to nonselective inhibition of other kinases molecules.⁴⁵ LOU-064 is another Btk inhibitor currently under evaluation in a dose-finding study.⁷⁶ Other potential therapeutic targets in different stages of development include inhibitors of the JAK1/2 kinases, TNF- α , IL-1, MRGPRX2, histamine-4-receptor, C5a and C5aR, IL-33, IL-25, thymic stromal lymphopoietin, and stem cell factor.^{28,76}

CONCLUSIONS

CU affects all age spectrums of society. However, robust epidemiology is lacking in children, pregnant/lactating women, and the elderly. Recent advancements in CU terminology and guidelines represent progress that has provided clinicians with a common language that should improve our understanding of different phenotypes and facilitate ongoing research to better characterize their endotypes. The current algorithmic CU treatment steps 1 (monotherapy with a nonsedating H1-antihistamine) and 2 (2–4 times the recommended dose of a nonsedating H1-antihistamine) are known to be effective in controlling hives in 40% to 50% of patients. However, if patients fail to respond to these treatments, use of biologics such as omalizumab or immunosuppressants such as cyclosporin are step 3 and step 4 recommendations, respectively. Clinical trials

confirmed by real-world experience have demonstrated that only on average approximately 40% to 50% of omalizumab-treated patients are complete responders. Evidence supports that this biologic can be safely used in children and the elderly, and registries have also demonstrated safety of omalizumab in pregnant or lactating women. In contrast, cyclosporin has a significantly greater toxicity and is not appropriate in pregnant/lactating women, the elderly, young children, or other patients with comorbid conditions that could be worsened by this therapy. Thus, additional therapies that address the needs of these more difficult to manage and often vulnerable patients with CU are required. Fortunately, the future is bright for developing safe and effective therapies targeting novel pathways, which should lead to a better understanding of CU pathogenesis while improving clinical outcomes across the ages.

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