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The complexity of urticaria

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The complexity of urticaria

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Editorial: The complexity of urticaria

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urticaria, comorbidity, pregnancy, anaphylaxis, urticarial vasculitis

Editorial on the Research Topic
The complexity of urticaria

Urticaria is a common condition that presents with transient, pruritic wheals, angioedema or both. It often leads to a reduced quality of life and significant socioeconomic burden. Although the definition is clear, characterizing the lesions may be challenging for the health-care provider and an incorrect diagnosis may directly impact in treatment outcomes. Goméz et al. discuss the urgency in improving the diagnostic criteria, and the importance of identifying and managing properly the disease to reduce its burden.

Distinguishing between wheals and urticarial lesions is the first step to provide a correct diagnosis. As important as the characterization of the lesions is the presence of systemic symptoms such as fever, malaise, and arthralgia. Matos et al. propose two interesting diagnostic algorithms and a practical review of acute and chronic urticaria differential diagnosis. Not limited to skin lesions, the authors also review the main features and differences of histaminergic and bradykinin-mediated angioedema, highlighting the importance of an early diagnosis of hereditary angioedema.

Furthermore, according to the international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline the prevalence of acute urticaria in a lifetime is around 20% (1). The underlying mechanism is associated with degranulation of skin mast cells while the generalized mast cell and basophil degranulation causes anaphylaxis. Besides, acute urticaria and angioedema present as the most prevalent symptoms from the skin in anaphylaxis; thus, in Emergencies and in primary health care setting the differential diagnosis among anaphylaxis and acute urticaria/angioedema is confusing and puzzling in many cases, leading to errors and delayed treatment as adrenaline is the first-line treatment for anaphylaxis, but not for acute urticaria, where H1-antihistamines are the first choice. Ensina et al. provide a comprehensive review on main aspects, similarities and differences regarding definitions, mechanisms, causes, diagnosis and treatment of acute urticaria and anaphylaxis.

Chronic urticaria is not only more common but is also more severe in females, and although it is a relatively common disease, there is not enough information about the effects of hormonal conditions on the disease. Publications from the PREG-CU project showed that urticaria gets better during pregnancy in half of women while one third of the patients experience symptoms' worsening and 10% reported visits to emergency departments due to urticaria exacerbations (2). Almost 60% of pregnant women used medication for urticaria regardless of the trimester they were. Globally, patients with chronic urticaria did not have an increased risk for preterm birth or neonatal problems, except for increased cesarean section frequency,

which is most probably associated with the comorbidities of the patients. However, emergency referrals for urticaria exacerbations increased preterm birth risk which emphasizes the importance of keeping urticaria under control during pregnancy. Kocatürk et al. review the reported effects of sex hormones and pregnancy-specific immunological changes on urticaria, the impact of pregnancy on urticaria, and current information and guidance on the management of urticaria during pregnancy and lactation.

The prevalent fear of patients suffering from chronic urticaria and a major concern of treating physicians is the possible co-existence of other severe diseases, especially malignancies and systemic autoimmune disorders. Accordingly, extensive laboratory testing is being performed in many cases in contrary to current evidence and international guidelines (1). Autoimmune, psychiatric, and atopic diseases are the most frequently reported comorbidities among CU patients, while malignancies, cardiovascular and other diseases have also been reported as associated diseases in patients with chronic urticaria although existing data refers to specific populations (3). Papapostolou et al. overview current data on comorbidities of CU, and furthermore comment on the potential linked pathways underlying these diseases. In the era of tailored made intervention, CU patients should be recognized and treated as a multimorbid group with treatment interventions targeting the comorbidities and the urticaria management *per se* until the complete unravelling of the underlying pathophysiology of chronic urticaria.

Despite the fact, that chronic urticaria is a common disease, some inducible forms of chronic urticaria are rare and their diagnosis is often delayed. In a survey conducted in german speaking countries Altrichter et al. reported a marked average diagnostic delay of almost 3 years. Diagnostic provocations and/or laboratory tests were performed in a small minority of patients. Despite several physician contacts 90% of the patients stated to have an uncontrolled disease, resulting in a strong impact on their everyday activities, sleep, and QoL.

Omalizumab is recommended as second-line therapy in chronic spontaneous urticaria. In a Colombian study conducted by Garcia-Gomez et al. 123 patients were followed upon their treatment response. The percentage of patients with controlled CSU at 3 months on omalizumab treatment was 80% and at 6 months 87% respectively, while the safety profile was almost excellent. On the other hand, omalizumab is a comparatively high-cost medicine and access to this treatment can be challenging. Ridge et al. report a dramatic reduction in unplanned healthcare interactions at primary care and emergency departments in Ireland when patients are treated with omalizumab; thus, the increased cost of omalizumab may at least partly counter-balanced by the reduced use of health system resources.

Urticarial vasculitis is a small-vessel leukocytoclastic vasculitis characterized by different clinical manifestations ranging from long-lasting urticarial lesions to severe and potentially life-threatening multi-organ involvement. Petrelli et al. report their experience on 6 patients with refractory normocomplementemic urticarial vasculitis successfully treated with omalizumab suggesting that this biological therapy may be a safe and effective therapeutic option in urticarial vasculitis.

In conclusion, the scientific works of this Research Topic cover different aspects of urticaria and provides state-of-the-art knowledge in the field of urticaria that could be implemented in both recearch projects and clinical practice.

Author contributions

All authors contributed equally to the article and approved the submitted version. All authors contributed to the article and approved the submitted version.

Conflict of interest

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BRIEF RESEARCH REPORT
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Omalizumab Reduces Unplanned Healthcare Interactions in Irish Patients With Chronic Spontaneous Urticaria

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Chronic spontaneous urticaria (CSU) is a common, debilitating skin disorder associated with impaired quality of life and psychological comorbidity. Symptoms can be difficult to control and many individuals will not respond to first line treatment. Due to the chronic and unpredictable nature of the disorder, patients frequently have repeated healthcare attendances. Despite this, little is known about healthcare resource utilization internationally. Furthermore, there is no Irish data to inform fundholding decision makers. Omalizumab is an anti IgE monoclonal antibody used in refractory urticaria. It is a comparatively high cost medicine and access to this treatment can be challenging. Recent assessments of omalizumab compared with usual care suggest that omalizumab is a cost-effective treatment for refractory urticaria. We carried out a retrospective review of 47 patients commenced on omalizumab. We evaluated unplanned primary and secondary care attendances and urticaria symptomatology before and after treatment. As expected, patients with refractory disease that were commenced on omalizumab had objective improvements in urticaria symptoms. Importantly, we show that this is reflected in a dramatic reduction in unplanned healthcare interactions at primary care and emergency departments. These data suggest that omalizumab may benefit these patients by reducing disease activity and thereby reducing the need for unplanned healthcare interactions.

Keywords: chronic spontaneous urticaria, omalizumab, healthcare economics, dermatology specialty medicine, medicines access

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a condition characterized by recurring episodes of wheals lasting longer than 6 weeks. Angioedema can also be a feature. CSU has a major impact upon health-related quality of life, sleep, and daily activities (1). Psychological comorbidity is common and the persistent and unpredictable nature of the disorder results in significant health care access often with repeat attendances (2, 3). Time to diagnosis is prolonged. In Europe, the mean time to diagnosis is 2–4 years (4). The first-line symptomatic treatment for CSU is second generation antihistamines (5). However, up to 40% of patients will not respond to first-line treatment even when prescribed up to four times per day (6). Omalizumab is a safe and effective anti IgE monoclonal antibody that is recommended in CSU that is unresponsive to high dose second

generation antihistamines (5). It is a high cost medicine that typically requires high level funding approval often with in-hospital administration and monitoring, thus demanding administrative and clinical support. In Ireland, access to omalizumab remains challenging with funding allocated on a case by case basis.

A recent study in the Netherlands which compared omalizumab for CSU with usual care found that omalizumab was a cost effective treatment in the Dutch setting (7). Among Dutch patients, indirect healthcare costs, particularly productivity costs, significantly contributed toward the drugs cost effectiveness. However, the transferability of cost effectiveness evaluations between countries is challenging and therefore local data is vital.

The aim of this study was to perform a retrospective single site review of patients commenced on omalizumab for refractory urticaria. We investigated unplanned healthcare attendances at primary and secondary care before and after treatment with omalizumab. We also assessed urticaria symptomatology before and after treatment with omalizumab.

TABLE 1 | Baseline characteristics, $n = 47$.

Mean age	45.13 (SD 11.5)
Female gender	78.7%
CSUA	42/47 (89.3%)
Rescue steroid use in 12 months prior	37/47 (76%)
High dose antihistamine use	47/47 (100%)
Other immunosuppressant use	2/47 (4.3%)
Leukotriene antagonist use	33/47 (70.2%)
UAS7 at inclusion ($n = 42$)	35.4 (SD 5.05)
UCT at inclusion ($n = 42$)	2.5 (SD 1.8)
Unplanned ED attendances in 24 months, % participants	55.3%
Average number of ED attendances related to urticaria/angioedema per participant	1.3
Unplanned GP attendances in 24 months, % participants	91.5%
Average number of GP attendances related to urticaria/angioedema per participant	3.9

METHODS

Design

This retrospective single site study sought to assess the effectiveness of omalizumab treatment in CSU in relation to urticaria symptomatology and unplanned healthcare visits at a large teaching hospital in Ireland. Data was collected in the pre-pandemic era. Participants gave their informed consent to be involved in the study. The study dataset was collected by one clinical team member from patient clinical records; both written and electronic. Institutional ethics committee approval was in place from the SJH/TUH JREC approval number JREC 2017(03)CA17.

Outcomes

We collected baseline data on participants including age, clinical diagnosis and current medication use.

Healthcare Attendances

Participants were asked whether they had made unplanned visits to the emergency department as a result of their urticaria or angioedema within the last 24 months and how many times they attended. Participants were also asked whether they had had any unplanned visits to their GP in the last 24 months. An unplanned GP visit was defined as an appointment sought for urgent or immediate management of the patient's urticaria or angioedema. Follow up data were collected between four and six months after initiation of omalizumab.

Urticaria Symptomatology

Participants receiving omalizumab for CSU ($n = 42$) completed the Urticaria Activity Score 7 which assesses wheals and itch over one week prior to commencing omalizumab (8). In addition, the urticaria control test (UCT) was used as a measure of urticaria symptomatology (9). This is a four item questionnaire whereby lower scores are indicative of higher symptom burden and was completed both pre and post initiation of omalizumab.

Adverse Effects and Subjective Improvement

Participants were asked to report any adverse effects 6 months after initiation of omalizumab. Participants were also asked whether or not they experienced a subjective improvement in their urticaria since commencing omalizumab.

RESULTS

Baseline characteristics are shown in **Table 1**. Females accounted for 78.7% (37/47) of participants. Chronic spontaneous urticaria that was refractory to high dose antihistamines was the most frequent indication for omalizumab (89.3%). Other indications for omalizumab included delayed pressure angioedema, recurrent spontaneous angioedema and symptomatic dermographism. The mean UAS7 score for patients with CSU was 35.4 (SD 5.05) whereby scores >28 suggest severe urticaria. The mean UCT score for patients with CSU prior to omalizumab was 2.5 (SD 1.8) where scores <12 suggest high disease activity and poor disease control.

Management of CSU

All participants were taking high dose antihistamines prior to commencing omalizumab. Leukotriene receptor antagonists were prescribed for 33 participants. The majority of patients had used rescue oral steroid therapy in the 12 months prior to commencing omalizumab. Two participants were taking other immunosuppressants (hydroxychloroquine, and methotrexate).

Healthcare Attendances

The majority of participants (26/47) had attended the emergency department on at least one occasion in the preceding 24 months

TABLE 2 | Pre and post omalizumab assessments.

Measure	Pre omalizumab	Post omalizumab (6 months)
UCT score ($n = 42$)	2.5	13.1 ($p < 0.00001$)
Unplanned ED attendance, % of participants	55.3%	2%
Unplanned ED attendance, cumulative number of visits	62	1
Unplanned GP attendance, % of participants	91.5%	8.5%
Unplanned GP attendance, cumulative number of visits	181	4
Adverse effects	6.4%	
Subjective improvement in symptoms	97.9%	

for urgent management of their symptoms. The majority of participants (43/47) had also attended their general practitioner (GP) for urgent management of their symptoms and the average number of GP attendances related to urticaria or angioedema per participant was 3.9.

Pre and Post Omalizumab Assessments

As detailed in **Table 2**, unplanned hospital attendances related to urticaria or angioedema occurred in 26/47 participants in the preceding 24 months, with a cumulative total of 62 unplanned emergency department visits across all participants. After initiation of omalizumab, one participant out of 47 reported a single unplanned ED attendance. A comparison of unplanned hospital attendances before and after omalizumab showed that visits fell from 2.58 per month to 0.17 per month.

Unplanned GP attendances related to urticaria or angioedema occurred in 43/47 participants in the preceding 24 months, with a cumulative total of 181 unplanned GP visits across all participants. After initiation of omalizumab, four participants out of 47 reported a cumulative eight GP attendances. Unplanned GP attendances before and after omalizumab fell from 7.54 visits per month to 1.33 visits per month.

The mean UCT score prior to the initiation of omalizumab was 2.5 (SD 1.8) suggestive of poorly controlled urticaria. Symptoms of urticaria reduced after initiation of omalizumab with a mean UCT score of 13.1 (SD 2.6) suggestive of low disease activity and good symptomatic control.

An adverse effect attributed to omalizumab was recorded for three participants. The adverse effects were subjective fluid retention, post injection headache and burning at injection site. A subjective improvement in symptoms after initiation of omalizumab was reported by 46/47 participants.

DISCUSSION

CSU is a common disease that affects all age groups (10). Patients with CSU frequently wait prolonged periods of time for an accurate diagnosis and refractory disease is frequent (4). Direct costs from CSU are high and are primarily related to pharmacological treatments as well as cost of hospitalization (1, 11). In addition, loss of productivity, absenteeism and impaired quality of life are well acknowledged in this cohort and represent indirect costs of disease management (1).

This retrospective review sought to describe unplanned healthcare interactions and urticaria symptomatology in patients with CSU before and after treatment with omalizumab. The demographics and characteristics of Irish patients included in our analysis were comparable to the data for the global cohort and from other studies (10). Results indicate that Irish patients with chronic spontaneous urticaria had more unplanned healthcare visits when their urticaria was symptomatic. In addition, the majority of patients reported rescue use of oral steroids. Six months after treatment with omalizumab, urticaria symptomatology improved and the number of unplanned healthcare visits fell. Reported adverse events were rare and almost all participants reported a subjective improvement in their symptoms upon initiation of omalizumab.

Calculation of primary care costs for this cohort is challenging in an Irish setting as universal primary care is not established. However, this study observed a 97.8% decrease in unplanned primary care attendance after omalizumab was initiated. With regards to secondary care, the unit cost of an emergency department visit in Ireland is €298 (12). The cost of secondary care as quantified by unplanned ED attendances fell from a cumulative figure of €18,476 to €298 after the initiation of omalizumab.

The cost of omalizumab includes drug acquisition at approximately €372.58 per month, as well as drug administration and monitoring in an ambulatory care setting (13). While it is apparent that patients' clinical improvement may lead to savings in indirect costs as observed in other cohorts, the cost effectiveness of omalizumab in an Irish setting remains unclear (7). A recent move toward self-administration of omalizumab offers an interesting approach toward streamlining services for CSU patients (14, 15).

It is noteworthy that the number of emergency department visits among CSU patients in the current study appear high, when compared with those reported in other countries (11). This suggests high direct costs of CSU management in Ireland. Recent data from the Netherlands propose that omalizumab is a cost effective treatment for the management of CSU when compared with usual care (7). In the Dutch setting, productivity costs, which comprised reduced numbers of hours at work and reduced efficiency at work were found to be key contributors to the cost effectiveness of omalizumab. Further characterization of healthcare use in CSU patients in Ireland will enable a rigorous assessment of cost-effective treatments.

The reduction of healthcare interactions in this study may be attributable to multiple factors. Omalizumab is an effective treatment for refractory urticaria that reduces symptom burden (5). However, patients commenced on omalizumab may also benefit from being linked into a specialist service, leading to targeted disease management and a more direct pathway to expert care. Patients who undergo specialist review are more

likely to have been prescribed treatments that are in keeping with international urticaria guidelines (16). Furthermore, patients with access to specialist services may have the opportunity to contact a member of their clinical team when required, as opposed to making unscheduled visits to the emergency department or their GP. The natural course of CSU can have a relapsing and remitting pattern therefore spontaneous resolution of symptoms may also occur. Despite these points, we propose that the decrease in healthcare attendances and improvement in urticaria symptomatology in this patient group is noteworthy.

Our study is of value in that it is the first assessment of healthcare utilization in patients with CSU in Ireland. Findings are particularly useful to funding bodies who continue to evaluate the cost effectiveness of omalizumab for CSU. However, the sample size of the current study is small, and data were collected retrospectively. In addition, this study did not assess indirect costs of CSU management in Ireland which warrants further investigation.

CONCLUSION

Although chronic spontaneous urticaria represents the most common cause for referral to clinical immunologists in Ireland, the prevalence and burden of this disease in the Irish setting is not well understood (17). This study demonstrates the high frequency of unplanned healthcare interaction when patients' CSU is active. Treatment with omalizumab resulted in a fall in urticaria symptomatology and reduced unplanned healthcare attendance. Patients who experience a clinical improvement in their CSU may indeed have improved productivity leading to reduced indirect costs of their disease. However, the direct cost of omalizumab is considerable and typically requires monitoring in ambulatory care. The transition toward self-administration of omalizumab provides an opportunity for understanding how the delivery of this treatment can be optimized in an Irish setting (15). While these data will be useful in informing funding decisions, further information on healthcare utilization in cohorts of patients with CSU across international jurisdictions is required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by St. James's Hospital and Tallaght University Hospital Joint Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KR wrote the manuscript. VR collected the data. NC conceived the analysis. All authors contributed to the article and approved the submitted version.

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REVIEW
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Acute Urticaria and Anaphylaxis: Differences and Similarities in Clinical Management

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Acute urticaria is a common condition that presents with wheals and/or angioedema. However, these symptoms are also frequent in anaphylaxis, a life-threatening reaction that should be immediately diagnosed and treated. In both, mast cells play a central role in the physiopathology. Causes and triggers of acute urticaria and anaphylaxis are similar in general, but some peculiarities can be observed. The diagnostic approach may differ, accordingly to the condition, suspicious causes, age groups and regions. Adrenaline is the first-line treatment for anaphylaxis, but not for acute urticaria, where H1-antihistamines are the first choice. In this paper, we review the main aspects, similarities and differences regarding definitions, mechanisms, causes, diagnosis and treatment of acute urticaria and anaphylaxis.

Keywords: urticaria, angioedema, anaphylaxis, diagnosis, treatment

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INTRODUCTION

Urticaria is a condition with a lifetime prevalence rate of up to 20% and characterized by the development of wheals, angioedema, or both (**Table 1**) (1, 2). Acute urticaria, which is defined by the occurrence of symptoms for up to 6 weeks, can be the only manifestation of a hypersensitivity reaction but can also be associated with other systemic symptoms, indicating an anaphylactic reaction (1, 3). This paper aims to review the mechanisms, triggers, diagnosis, and treatment of acute urticaria and anaphylaxis, highlighting the differences in managing both conditions.

THE MAST CELL AND ITS ROLE IN URTICARIA AND ANAPHYLAXIS

Urticaria and anaphylaxis are often but not always related to mast cell activation from multiple triggers, including IgE-mediated and non–IgE-mediated mechanisms. Mast cell plays a broad critical role in the innate and acquired immune response because they express multiple receptors responding to specific antigens, as well as circulating complement components and fragments,

TABLE 1 | Clinical characteristics of urticaria [adapted from (1)].

Typical features of a wheal:
1. A sharply circumscribed superficial central swelling of variable size and shape, amost invariably surrounded by reflex erythema
2. An itching or sometimes burning sensation
3. A fleeting nature, with the skin returning to its normal appearance, usually within 30 min to 24 h
Angioedema is characterized by
1. A sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes
2. Tingling, burning, tightness, and sometimes pain rather than itch
3. A resolution slower than that of wheals (can take up to 72 h)

immune complexes binding IgG and IgM, cytokines, changes in blood pressure, and immunologic activation (4, 5). Therefore, mast cell activation in patients with urticaria and anaphylaxis is more likely to occur through multiple pathways in addition to IgE.

Mature mast cells are primarily found in tissues where external pathogens enter the body, including the skin, gastrointestinal tract, and airway. Immunological staining of tissues has revealed two types of human mast cells characterized by their neutral protease content: mast cells which are tryptase-positive but chymase-negative (MCT), and mast cells which are both tryptase- and chymase-positive (MCTC) (6). MCT are found typically at mucosal tissues, such as the intestine, lung and nose, are T-lymphocyte dependent and are increased in number in allergic disease (7). In contrast, the development of MCTC is independent of lymphocytes, and they are located primarily in the skin and gastrointestinal submucosa. MCTC account for more than 99% of the mast cells in the dermis of both lesional skin and non-lesional skin of patients with chronic spontaneous urticaria (CSU) (8). Immunoglobulin E (IgE)-dependent stimulation leads to degranulation of both subtypes, but MCTC can also be activated by IgE-independent mechanisms.

Activation of mast cells occurs when allergen-specific IgE is bound by allergen and interacts with high-affinity IgE receptor (FcεRI) on their surfaces (9). In addition to FcεRI, human mast cells express receptors for IgG (FcγRII/III), complement (C3a/C5a), drugs [Mas-related G protein-coupled receptor X2 (MRGPRX2)], opioids, neuropeptides, nerve growth factor, stem cell factor and cytokines, ligation of which modify mast cell function-survival, maturation, differentiation, growth, apoptosis, and degranulation (5, 10). Mast cells can be activated through newly identified MRGPRX2 by fluoroquinolones such as ciprofloxacin, icatibant and general anesthetics such as atracurium, rocuronium, tubocurarine, independent of the IgE-FcεRI pathway (11, 12). In this pathway, binding of these drugs and drugs expressing the THIQ (tetrahydroisoquinoline) motif directly to MRGPRX2 results in protein kinase A and phosphoinositide 3-kinase pathway activation, calcium release and degranulation (5, 11, 12). Also, activation of mast cells through MRGPRX2 may contribute to neurogenic inflammation, pain, itch, and pruritic skin diseases, including CSU (13). Increased MRGPRX2 protein expression has been reported in the skin of patients with CSU (14).

CAUSES AND TRIGGERS OF ACUTE URTICARIA AND ANAPHYLAXIS

Acute Urticaria

Common causes or triggers of acute urticaria include infections (viruses, bacteria, and parasites), food and medicines and less frequently latex, Hymenoptera venom, vaccines, physical stimuli, which a detailed history should identify. The prevalence of different etiologies varies among different age groups. In half of the cases, it is not possible to identify a specific cause for acute urticaria, being classified as idiopathic (15–17).

Respiratory infections, mainly of viral etiology, are considered the most related trigger to acute urticaria in all age groups (about 40% in adults and 60% in children) in different populations (16, 18–23). Gastrointestinal and urinary tract infections are also associated. In a study with children, infection was the most frequently documented cause for acute urticaria (48.6%), followed by drugs (5.4%), and food allergies (2.7%) (24). In the pediatric age, herpes virus (especially cytomegalovirus, Epstein-Barr virus, and herpes virus type 6) was the principal agent responsible for acute and recurrent flares of urticaria. Other viruses, including adenovirus, rotavirus, parvovirus B19, respiratory syncytial virus, and recently SARS-Cov2, have also been described as potential triggers (25). *Mycoplasma pneumoniae* and *Streptococcus spp* are frequent, while Chlamydia is less reported as an acute cause. Parasites may also induce acute urticaria with eosinophilia (15). In adults, hepatitis viruses (A, B and C) are most frequently implicated in acute urticaria (25).

However, the prevalence of infectious causes tends to reduce with age, and drug therapy with antibiotics (beta-lactams) and non-steroidal anti-inflammatory drugs (NSAIDs) often trigger urticaria in infants and children. At the same time, NSAIDs, angiotensin-converting enzyme inhibitors and neuromuscular blockers are more implicated as potential triggers of acute urticaria in adults (26).

Food allergies are minor causes of acute urticaria (16, 24, 27). The most implicated food allergens are cow milk, eggs, peanuts, tree nuts, wheat, and seafood (16, 18–23). Certain foods such as some types of fish (tuna, sardines, anchovies), cheeses (Emmental and gouda), salami, sausage, fruits (strawberry), vegetables (especially tomatoes) and beverages (wine and beer) have been described as triggers of recurrent urticarias, especially in patients intolerant to histamine or with deficiency of the enzyme diamine oxidase, responsible for histamine degradation. However, predicting the benefit of low histamine diets is practically impossible due to different dietary habits worldwide, and more studies on the subject are needed (28, 29).

Urticaria caused by latex, Hymenoptera venom and vaccines are less frequent. However, hypersensitivity to insect bites in Latin America countries is described as the main inducer of urticaria in children (30). Physical stimuli (dermographism, increased body temperature and cold) rarely cause acute urticaria, especially in children (15).

Anaphylaxis

Similar to urticaria, the profile of anaphylaxis triggers depends on age and different geographic areas. Moreover, in up to 35% of

anaphylaxis cases, a specific trigger may not be identified during the acute event or in subsequent evaluations, characterizing an idiopathic picture (31–39).

Worldwide, food, insect venom and drugs are the most frequent triggers (40–44). Food is the most common trigger for severe anaphylactic reactions in children, while drugs and insect venom are common triggers in adults (40, 42, 44–46).

In young children, due to the greater need for hospitalization, anaphylaxis from food and drugs is notably greater. In infants and young children, food, especially cow milk, eggs, peanuts, tree nuts, sesame and wheat, are the most common causes of anaphylaxis (41–44, 46, 47). Nuts, cashews, and hazelnuts are also causes of anaphylaxis in school children. Food dyes are not a common cause of food allergy (18).

Food-induced anaphylaxis in adults varies by region and food exposure. In North America and Australia, peanuts and nuts are the main triggers for anaphylaxis, while shellfish are most often associated in Asia. In central Europe, the foods most associated with anaphylaxis are peanuts, tree nuts, sesame, wheat, and shellfish. However, in southern Europe, it is lipid transfer proteins (pan-allergens responsible for cross-reactivity between fruits, vegetables, and pollens) associated with cofactors that are the most frequent food allergens. Sesame seed and buckwheat are common causes of anaphylaxis in the Middle East and Korea, respectively (3, 41–47).

Less common allergens that can trigger late anaphylaxis reactions such as alpha-gal should also be investigated (3).

Medications are also a cause of anaphylaxis, and reactions usually appear in school-age children and adolescents. They are found to be the most common cause of anaphylaxis-related deaths both in adults and in children in different countries, but this may vary depending on the method of the study and database searched (18, 31, 48–50).

Antibiotics, particularly beta-lactams, are described as the main triggers of drug-induced anaphylaxis in childhood, with few reports of anaphylaxis to other non-beta-lactam antibiotics, such as macrolides. In adults, penicillin, cephalosporins, and sulfonamides are the most implicated antibiotics (48, 51–58).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the second leading cause of drug-induced anaphylaxis in children worldwide. However, in Latin America, NSAIDs are the first cause in both children and adults (56, 59). In addition to antibiotics and NSAIDs, neuromuscular blockers, anesthetics, opioids, hypnotics, ethylene oxide, plasma expanders, and dyes (patent blue and methylene blue) have been frequently involved in perioperative anaphylaxis (3, 22). In some countries latex allergens remain a significant trigger of perioperative anaphylaxis (60, 61). But the incidence of latex allergy has decreased in many places due to primary prevention measures such as wearing powder-free latex gloves and latex-free surgical material in the operating room (62–64). Reactions to radiographic contrast media have occurred less frequently with the use of non-ionic and low osmolality contrasts rather than with monomeric ionic (65).

New triggers have been identified as a cause of anaphylaxis and include immunobiological drugs, chemotherapeutics, chlorhexidine, polyethylene glycol, and methylcellulose. In general, medications are the leading cause of fatal anaphylaxis in adults and children (3).

In the United States, antibiotics, NSAIDs, immunomodulators and biologic agents are the most implicated agents in drug-induced anaphylaxis, whereas, in the United Kingdom, general anesthetics are frequently associated with fatal drug-induced anaphylaxis (32).

Insect venom-induced anaphylaxis also exhibits regional patterns. Bee venom is the most frequent trigger in South Korea, and it is also more frequent in children. While in central Europe, the wasp is the insect that induces the most anaphylaxis. In other regions, such as America, Asia and parts of Australia, and venom is an important trigger of anaphylaxis. Fatal cases of anaphylaxis from insect venom are most associated with adults (3).

Exercise-induced anaphylaxis and anaphylaxis induced by food-dependent exercise are two rare but significant entities. Various activities such as yard work, walking and running can trigger an exercise-induced anaphylaxis condition. Symptoms can occur during or after physical activity, but it is usually challenging to predict crises. In induced anaphylaxis by food-dependent exercise, symptoms occur when the causative food, such as seafood, dairy products, and wheat, is consumed minutes to several hours before exercise. In these cases, patients should avoid eating these foods 4–6 h before exercise (18).

Some external cofactors or associated conditions play an important role in the development of allergic reactions, including anaphylaxis. In the presence of cofactors such as physical exercise, drugs (e.g., nonsteroidal anti-inflammatory drugs, proton pump inhibitors), acute infections, alcohol and menstruation, allergic reactions may be elicited at lower doses or there may be more severe or life-threatening clinical reactions (40). There are associated conditions that work as cofactors jeopardizing patients, or increasing mortality (e.g., unstable asthma, mast cell disorders, cardiovascular diseases). However, the mechanism of action of such cofactors have not been fully identified yet, but increased bioavailability of allergen due to increased intestinal permeability and intestinal allergen absorption, decreased activation threshold on the cellular level and transient plasma hyperosmolality, are among the potential mechanisms proposed (40, 66, 67).

Supposedly, cofactors play a role in approximately 14–30% of anaphylactic reactions. Therefore, in a given patient these cofactors should always be considered in the clinical history and eliminated when possible, to reduce the risk of a future severe reaction (66, 68).

DIAGNOSTIC APPROACH FOR ACUTE URTICARIA AND ANAPHYLAXIS

Urticaria as a Manifestation of Anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and can be fatal. Skin and mucosal manifestations are frequent but not always present (69). Anaphylaxis is highly likely when any one of three criteria are fulfilled (**Table 2**) (3, 32, 70, 71).

Therefore, anaphylaxis may occur without skin involvement, resulting in delays in recognition of anaphylaxis. Cutaneous

TABLE 2 | Clinical criteria for diagnosing anaphylaxis [adapted from (67)].

Anaphylaxis is highly likely when any of the following three criteria is fulfilled:
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both and at least one of the following
a. Respiratory compromise
b. Reduced BP or associated symptoms of end-organ dysfunction
Two or more of the following that occur rapidly after ex-posure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin–mucosal tissue
b. Respiratory compromise
c. Reduced BP or associated symptoms
d. Persistent gastrointestinal symptoms
Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or >30% decrease in systolic BP {Low sys-tolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years and <90 mmHg from 11 to 17 years}.
b. Adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline. PEF, peak expiratory flow; BP, blood pressure.

findings of urticaria and angioedema are the most frequent manifestations (about 80–90% of anaphylaxis cases) and usually last for <24 h (72). It is important to note that urticaria is not directly related to anaphylaxis severity. Severe anaphylaxis can present without urticaria, as in some cases reports of fatal anaphylaxis (73).

Anaphylaxis, urticaria, and angioedema have similar pathogenic mechanisms, including vasodilation and increased capillary permeability. Anaphylaxis symptoms may differ according to age group. For example, children younger than 6 years are more likely to experience vomiting and cough, while older children are more likely to experience chest tightness, dizziness, hypotension, and cardiovascular collapse (18).

Different elicitors can cause distinct clinical manifestations. In perioperative anaphylaxis, cutaneous signs may not be easily seen. Urticaria and angioedema may only become apparent when the perfusion is restored, or the surgical drapes are removed (74). A study on perioperative anaphylaxis reviewed 266 reports of Grades 3–5 anaphylaxis over 1 year from all NHS hospitals in the UK. They found that the most typical presenting features were hypotension (46%), bronchospasm (18%), tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%), and reduced/absent capnography trace (2.3%) (75).

When to Investigate Acute Urticaria

Current guidelines recommend that acute urticaria usually does not require a diagnostic workup because it is usually self-limiting (1, 76). Although viral or other infectious illnesses cause many cases of acute urticaria, extensive evaluation for specific viral pathogens or antiviral therapy is not indicated unless suggested by the clinical history.

The recent international European Academy of Allergology and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EuroGuiDerm)/Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) guideline state that the only exception is the suspicion of acute urticaria due to a type I food allergy in sensitized patients or the existence of other eliciting factors such as non-steroidal anti-inflammatory drugs (NSAIDs) (1).

An allergic cause is possible if the clinical history suggests a specific trigger to which the patient was exposed shortly before the onset of symptoms (usually within 1–2 h after exposure). If the history does suggest a possible allergy, skin testing, serum tests for allergen-specific immunoglobulin E (IgE) antibodies are appropriate. However, the interpretation of allergy tests can require some expertise. A positive result is suggestive, although not diagnostic of allergy, and a negative result does not exclude allergy. Allergy tests and educating the patients may be helpful to allow patients to avoid re-exposure to relevant causative factors. Occasionally, it is essential to confirm a diagnosis of allergy in acute urticaria with confirmatory tests to avoid mislabeling patients as allergic. Although skin biopsy is not indicated in most cases of acute urticaria, it might occasionally help differentiate this condition from other inflammatory disorders (76).

The Importance of Tryptase When Investigating Anaphylaxis

Tryptase is a marker of mast cell activation. It is a serine protease expressed in mast cells, and to a lesser degree, in basophils. There are four isoforms, but only α and β are considered biologically important (77).

During anaphylaxis, tryptase can be detected in serum 30 min after the onset of symptoms, peaks within 60 to 90 min, begins to decline after 2 h, and returns to normal levels within 24 to 48 h. Therefore, blood samples must be collected within 1–4 h of the reaction. Immunoassays allow detection of both total (baseline release) and mature (released only at the time of activation) tryptase. Another blood sample to measure the basal level of tryptase is needed 24 to 48 h after anaphylaxis (69, 78). In general, baseline tryptase levels >8 ng/ml are considered elevated, but this is not always a sign of mast cell activation. It is difficult to establish a cut-off point for the diagnosis. There are no special levels to confirm mast cell activation (hence anaphylactic episodes) as it must be calculated according to individual baseline tryptase levels with the formula: 1.2 x baseline + 2 ng/ml (79).

Tryptase levels are typically higher and more persistently elevated in anaphylactic reactions to intravenous drugs and insect venom than oral triggers such as food. Furthermore, elevations correlate with hypotension (69).

However, normal tryptase levels do not rule out anaphylaxis because the sensitivity is not optimal. This is explained by the fact that about 27% of the population does not have α-tryptase genes, affecting serum tryptase levels. Several studies use an equation with tryptase increasing at least 20% above baseline plus two ng/ml within 4 h of the allergic reaction (79–82). Tryptase levels $\geq$2 ng / mL + 1.2 × baseline is significantly increased for patients with low baseline tryptase (72, 79, 81).

Unfortunately, tryptase is not available everywhere. In a study by Jares et al. whose aim was to investigate the clinical features and management of drug-induced anaphylaxis (DIA) in Latin

America, only 8 of 264 patients (3%) had tryptase levels accessed (56). In an online survey promoted by the Latin American Society of Allergy and Immunology to assess the current resources available in Latin American countries for the diagnosis and treatment of anaphylaxis, they found that the determination of serum tryptase was possible only in some health centers, often private, in five of the ten countries surveyed (83).

Differential diagnoses of elevated total tryptase levels include patients with systemic mastocytosis (SM), acute myelocytic leukemia, myelodysplastic syndromes, immunologic disorders (hypereosinophilic syndrome), severe renal failure, or familial tryptasemia – a disease associated with cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, due to the expression of more than two α-tryptase genes (69, 78).

Challenges in Finding the Cause of Anaphylactic Reactions

The diagnoses of anaphylaxis should be based on relevant clinical history and a combination of available tests, i.e., skin tests, *in vitro* tests (serum tryptase, specific IgE serum levels, basophil activation test or histamine release tests) and/or provocation tests (3). However, the investigation of precipitating agents can become challenging given the complex variability in clinical presentation, multiple concurrent exposures, and many differential diagnoses, such as in the context of perioperative anaphylaxis (84).

Acute serum tryptase levels is an important tool during the diagnostic evaluation of anaphylaxis but it is not worldwide available. Moreover, it has high specificity, but low sensitivity and results should be carefully interpreted (84).

IgE-mediated anaphylactic reactions can be assessed by *in vivo* (skin tests to foods, venom, drugs, latex) and/or *in vitro* tests (serum specific IgE to foods, venom, and some drugs) (3). It is worth noting that, in the context of anaphylaxis, their detection facilitates guidance as to the allergen to be used in provocation tests. However, a positive skin test or elevated specific IgE are useful to confirm the etiology of an allergic reaction only when the clinical history is suggestive, otherwise they just reveal sensitization (84).

Most skin tests are considered safe and rapid but not free of systemic reactions. The perfect timing for performing skin tests may vary among different allergens. In general, a period of at least 4 weeks after the anaphylactic episode is suggested but could be longer for drug-induced anaphylaxis and each patient should be individually assessed. Comorbidities (e.g., asthma) must be controlled, and medications (antihistamines, high-dose corticosteroids, antidepressants, and antipsychotics with an antihistamine effect) paused prior to testing (84).

An obstacle faced when performing skin tests and determining serum specific IgE levels is to obtain cut-off values that could confirm the diagnosis and avoid provocation tests. In addition, specificity and sensitivity vary according to the trigger involved in the reaction, not being possible to accurately determine universal values of specific IgE (84).

The determination of molecular biology-based components has enabled advances in precision medicine by conferring greater specificity to diagnosis, allowing the identification of discriminative co-sensitization vs. cross-sensitization phenomena, stratifying the clinical risk associated with a specific sensitization pattern, and a better indication to the provocation test in cases of anaphylaxis by food (85–87). Molecular allergy diagnostics yielded best results in peanut and tree nut allergies (88, 89).

Despite all the scientific advancement in recent years, the provocation test is still considered the gold standard in diagnosing hypersensitivity to foods and drugs, regardless of the pathophysiological mechanism involved (85, 90). They are used to confirm, exclude, or prove tolerance to a particular food or drug and test a safe alternative (84). A significant disadvantage is a risk of inducing anaphylaxis, making provocation a high-risk procedure. The decision on its execution is influenced by clinical history, age, type of symptom, time of the last reaction, results of skin testing and/or serum levels of specific IgE, and the joint decision between physician and patient, carefully evaluating risk vs. benefit. Those with a convincing history of anaphylaxis from a specific allergen and proven evidence of specific IgE sensitization should not undergo provocation tests (87, 90).

Complementary tests, such as basophil activation test (BAT) with food, drugs, Hymenoptera venoms and latex, reflect tissue mast cell sensitization and activation. Due to the lack of standardized kits for most allergens is employed mainly in clinical research. However, BAT should be considered a diagnostic tool in selected patients, especially those with severe and high-risk anaphylaxis related to drugs (3, 90).

Further elucidation of the underlying mechanisms of anaphylaxis is needed to better characterize the phenotypes and endotypes of anaphylaxis and decrease the number of cases labeled as idiopathic anaphylaxis (3, 78).

ACUTE URTICARIA AND ANAPHYLAXIS TREATMENT

Adrenaline and Beyond in Anaphylaxis Treatment

Epinephrine (adrenaline) is the first-line drug recommended by the American, European and World Allergy Organization guidelines for treating anaphylaxis, although its use remains suboptimal. The recommended dose is 0.01 mg/kg, maximum 0.5 mg, given intramuscularly in the mid-anterolateral region of the thigh, which can be repeated every 5–15 min as needed (3, 32, 71).

The vasodilatory effect on skeletal muscles facilitates the rapid absorption of adrenaline into the central circulation, in contrast to its vasoconstrictor effect when injected into the subcutaneous tissue, delaying its absorption and onset of action. Intravenous administration is also not recommended for initial treatment, as potentially fatal arrhythmias can occur within bolus administration of epinephrine (3, 32). However, in special circumstances such as severe hypotension, intravenous administration appears to be more effective and should be used with caution (71).

There is no absolute contraindication to the administration of epinephrine, and delays in its administration are associated with progression to severe anaphylaxis and potential death (3, 32).

As it is a non-selective agonist of all adrenergic receptors present in all organ systems affected by anaphylaxis, it exerts effects on α1 receptors causing peripheral vasoconstriction, reversing hypotension and mucosal edema; on β1 receptors increasing cardiac output, thus reversing hypotension; and on β2 receptors reversing bronchoconstriction and inhibiting the additional release of histamine and other mediators by mast cells and basophils, also preventing worsening of symptoms (3, 32, 71).

A self-injectable adrenaline device is highly recommended among experts for patients at risk of anaphylaxis (71). But despite its critical role, the self-injectable form of adrenaline is not available in most countries, being limited to only 32% of all 195 countries in the world, mainly in developed countries. The high cost is one of the main limiting factors (3).

In Brazil, for example, there is neither the manufacture nor the marketing of these devices, requiring their importation. This fact dramatically hinders the management, implementation of the "action plan," and self-management of anaphylactic reactions outside the hospital environment (71).

Another issue that is also relevant is the expired validity of the injectors. Because they remain unused for long periods, there is a high probability that patients carry this medication with its expiration date (71). All these aspects, notably the high cost, unavailability and expired validity are barriers to the use of adrenaline autoinjectors (91).

Second-line interventions include removing the trigger when possible, calling for help, correct positioning of the patient, offering high flow oxygen, administration of intravenous fluids (crystalloids) associated with the first dose of adrenaline in patients with cardiovascular involvement and severe pictures of anaphylaxis, should also be considered. However, no robust evidence is available (3, 71).

Additionally, in cases of bronchial obstruction, inhaled short-acting beta-2 adrenergic agonists (e.g., salbutamol) can be administered. When laryngeal/pharyngeal edema has been suspected, inhaled adrenaline administration by nebulizer, as a supplement to intramuscular adrenaline, and oxygen are recommended (3, 71).

Several other drugs can be used in the additional treatment of anaphylaxis, but never in isolation since they do not have a global effect capable of reversing the systemic symptoms of anaphylaxis. The need for any additional medication should be individualized and depend on the adrenaline response (3).

Systemic antihistamines have only been shown to relieve cutaneous symptoms, and a possible effect on non-cutaneous symptoms remains unconfirmed (71). It is noteworthy that antihistamines are now a third-line treatment in some guidelines due to concerns that their administration may delay more urgent measures, such as repeated administration of adrenaline (3, 32).

Glucocorticoids are commonly used in anaphylaxis, as they are believed to prevent prolonged symptoms and possibly biphasic reactions, but there is limited evidence of their efficacy, and they may be deleterious in children; their routine use is becoming controversial (3, 71).

Parenteral administration of glucagon may be helpful in the treatment of patients with anaphylaxis refractory to adrenaline use, particularly those on beta-blocker therapy, although evidence is very limited. The dose for adults is 1–5 mg in a slow bolus, intravenously, followed by a titrated infusion of 5–15 mcg/min (3, 71).

Patients with anaphylaxis are at risk of prolonged reactions and developing biphasic reactions, although the likelihood is low. In these cases, there is a recurrence of symptoms 8 to 10 h after the initial reaction, without a new exposure to the triggering antigen, and should be treated as any anaphylaxis. Thus, more prolonged monitoring should be considered in patients with asthma, those with a history of severe anaphylaxis, biphasic reactions, and/or a need for multiple doses of adrenaline (3, 32, 71).

Education and management of anaphylaxis should be customized according to the patient's clinical history and presentation, considering their age, concomitant diseases, concomitant medications, and triggering factors (3).

Acute Urticaria Treatment: Which Drugs and for How Long

Initial treatment of acute urticaria should focus on the short-term alleviation of pruritus and reduction of wheals. The literature on the management of acute urticaria is rare, probably because the condition is too often self-limited. Current guidelines recommend modern second-generation H1-antihistamines (such as bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine) as a first-line symptomatic treatment for acute urticaria (1, 76). The newer, second-generation H1-antihistamines are minimally or non-sedating and free of anticholinergic effects that can complicate the use of first-generation agents (92). These medications have been mostly evaluated in treating chronic urticaria (CU), and in some cases, their use in acute urticaria is extrapolated from those researches. In current guidelines, there is no recommendation on which to choose for the treatment of acute urticaria, although a few studies in patients with CU suggest that cetirizine and levocetirizine may be modestly more effective than other agents (93). Some patients require higher than standard doses to control urticaria and may experience drowsiness at those higher doses. The higher doses may have better efficacy in some adults, although this has not been conclusively demonstrated in patients with acute urticaria. Current guidelines have no specific recommendation on how long H1-antihistamines should be used in acute urticaria, but it might be required until complete symptoms are controlled (1).

First-generation antihistamines available in parenteral presentation, such as diphenhydramine and promethazine, are rapidly acting and effective in emergency units for acute urticaria treatment. However, they can be associated with sedation and impaired motor skills because of their ability to cross the blood-brain barrier in both pediatric and adult patients besides other frequent prominent anticholinergic effects, including dryness

of the mouth and eyes, constipation, inhibition of micturition, and potential provocation of narrow-angle glaucoma. Thus, its use should be limited, and non-sedating 2nd generation oral antihistamines preferred as first-line treatment for most patients, especially for those with mild and moderate disease (94).

In patients with poor response to antihistamines, a brief course of oral corticosteroids might also be required while attempting to eliminate suspected triggers and develop an effective treatment plan (76). The recent international guideline recommends that for acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids limited to 10 days might be necessary to some patients (1, 23, 95). H1-antihistamine therapy should be continued during and after the course of glucocorticoids because some patients experience an exacerbation as the glucocorticoids are tapered or discontinued. If symptoms do not recur for several days after stopping glucocorticoids, then antihistamines could also be discontinued.

ANAPHYLAXIS PREVENTION - VENOM IMMUNOTHERAPY, DESENSITIZATION FOR DRUGS AND FOODS

Prevention of anaphylaxis includes education based on the known trigger of anaphylaxis. Thus, current management relies on allergen avoidance and treatment of severe reactions with epinephrine (3). In cases of anaphylaxis by stinging insects, this can be very difficult. Also, for food allergy, avoidance of the trigger is currently the only approved therapy, and while effective, diets can be difficult to carry out (96). For drug allergies, the most common situation is to avoid the drug that caused the reaction. Food allergy and insect venom allergy present a high risk of anaphylaxis, which is unpredictable in occurrence and severity. The unpredictable nature of these allergies can affect the patient and family's psychosocial functioning and quality of life (73).

Venom Immunotherapy (VIT)

In patients with a history of Hymenoptera sting, anaphylaxis and positive skin or *in vitro* tests (serum specific IgE) to Hymenoptera venom, venom immunotherapy (VIT) should be considered, especially in those patients with mastocytosis (97, 98).

To select VIT, it is essential to take a good clinical history. Initially, collect information about the stinging insect (i.e., number of stings, previous and subsequent re-stings, nest, extraction of the sting, death of offending insect). It is important to take information on occupational or activities linked to a higher likelihood of sting (e.g., farmers, beekeepers, outdoor sports). Furthermore, discriminate if the reaction was local or systemic. Local large reactions (LLR) are edema exceeding 10 cm, increasing within 24/48 h, and lasting longer than 72 h. Although worrisome for some patients, they have a low risk of evolution into systemic reactions (99). VIT indications are enumerated in **Table 3**.

TABLE 3 | Indications of venom immunotherapy [adapted from (92)].

History of systemic reaction involving organs other than the skin in children and adults
In adults, systemic skin reactions with high risk of re-sting and/or compromised quality of life.
In children, VIT is generally not recommended when only skin involvement is present, due to the low risk of RS after a re-sting (10%), unless the subject is at high risk for a re-sting and/or distant of emergency care facilities, and/or impaired quality of life for the patient and/or parents
Clonal mast cell disorders with a history of systemic reaction

TABLE 4 | Drug desensitization indications [adapted from (51)].

1. When no alternative drug is available
2. When the drug involved in DHR is more effective (better quality of life; better survival) or associated with fewer adverse effects than alternative drugs
3. When the drug involved in DHR has a unique mechanism of action, like aspirin in Aspirin Exacerbated Respiratory Disease (AERD)

Desensitization for Drugs (DS)

For patients with proven or highly suspected drug hypersensitivity reaction (DHR), drug desensitization (DS) is a procedure designed to safely reintroduce drugs into patients who have had IgE/non-IgE Type I reactions (100–102).

DS is defined as the induction of a temporary state of tolerance of a drug for a hypersensitivity reaction. It is indicated in some specific situations, as shown in **Table 4** (101). It is performed by administering increasing doses of the medication over a short period (from several hours to a few days) until the total cumulative therapeutic dose is achieved and tolerated (100, 102). It is a procedure that helps to prevent anaphylaxis, keeping patients in the first-line treatment and, therefore, representing an important advance in their prognosis (69). Although several protocols have been proposed to desensitize patients to different drugs, the 12-steps rapid desensitization protocol has been demonstrated to be safe and efficient and can be adapted to be used with any parenteral drug (103, 104).

Immunotherapy for Foods

Immunotherapy has several routes of administration and has been performed subcutaneously, sublingually, epicutaneously and orally. The subcutaneous approach was abandoned many years ago due to safety concerns. The sublingual and epicutaneous approaches have both been shown to be safe, but efficacy is limited by a restricted dose capacity, that is the amount that can be absorbed through the skin or under the tongue. Oral immunotherapy (OIT) is more effective than the other routes, in part because much larger doses can be administered (105).

Cow's milk, hen's egg, wheat, soy, peanut, tree nut, fish, and shellfish are most often associated with food allergies. Oral immunotherapy (OIT) is an option for individuals who do not naturally tolerate these foods by late childhood or adulthood (96).

OIT for foods involves introducing an allergenic food mixed with a vehicle in gradually increasing doses. OIT protocols include an initial escalation phase, followed by a dose build-up phase and maintenance phases. The efficacy of the OIT depends on the chosen outcomes, including the ability to tolerate the treatment, induction of a state of desensitization, and/or the development of a more durable state of clinical tolerance,

what is often referred to as lack of sustained response. Adverse reactions during OIT are common. Reactions are usually mild, with local symptoms such as oral itching. However, moderate and even severe reactions may also occur, and patients may require treatment with epinephrine, especially during dose escalation (96). Recently, a death from baked milf OIT was reported in Canada, as well as an exercise-induced anaphylaxis to wheat OIT in Japan (106, 107). Eosinophilic esophagitis occurs in some patients undergoing OIT, and it is not clear how often the disease was already present before the start of OIT and could complicate the procedure (108).

In cases of idiopathic anaphylaxis, when the trigger is not known, the anti-IgE monoclonal antibody omalizumab demonstrated to be a successful treatment, effectively reducing the number of episodes, and improving quality of life (109). In addition, omalizumab has been shown to be effective as an adjunct to treatment in patients who experience episodes of anaphylaxis during immunotherapy with food (OIT) or with Hymenoptera venom (VIT). Some studies showed more safety using omalizumab in groups of patients with OIT (milk and peanut). These patients were able to tolerate a higher amount of protein with fewer reactions (110).

DISCUSSION

Anaphylaxis is a life-threatening reaction that requires immediate diagnosis and treatment. Anaphylactic reactions can present with a variety of symptoms, and hives and angioedema are often observed (3). On the other hand, acute urticaria is limited to the skin and mucosa and, although not potentially lethal, may impact patients' quality of life (1).

Mast cells have a central role in the pathophysiology of the two conditions, and their activation can be triggered by allergic and non-allergic mechanisms (4, 5). Many of these triggers can cause both acute urticaria and anaphylaxis, but some are more frequent in a determined region, age group or type of reaction - NSAIDs, for example, is the leading cause of drug-induced anaphylaxis in Latin America but not in the United States, and viral infections are an important cause of acute urticaria in children but not anaphylaxis (28, 56). So, it is of extreme importance to understand the potential triggers for each condition and perform an adequate investigation when recommended. In general, an extensive investigation is not necessary for acute urticaria but mandatory to search for a cause in anaphylaxis, especially to prevent future and more severe reactions (1, 3).

Acute urticaria and anaphylaxis are treated differently, at least regarding first-line therapy. Whereas H1-antihistamines are the preferred therapy in acute urticaria, their effect in anaphylaxis is limited to skin symptoms. In addition, parenteral use of antihistamines may cause hypotension as a potential side effect (111). On the other hand, adrenaline is the first drug to be administered during an anaphylactic reaction, but its use in acute urticaria should be limited for patients with moderate to severe laryngeal angioedema (1, 3).

Finally, avoiding the trigger responsible for the reaction is the best way to prevent further episodes of anaphylaxis or acute urticaria. Of course, anaphylaxis prevention is mandatory because of the risk of a severe reaction. Desensitization to drugs and foods can be an option in selected patients, as well as venom immunotherapy. In acute urticaria, preventive measures are not always possible, mainly when it is caused by virus infections or in those cases where no specific trigger can be identified.

In conclusion, reactions presenting with hives and/or angioedema must be carefully assessed to distinguish between acute urticaria or anaphylaxis, as the diagnostic investigation, treatment and preventive measures are different and can directly impact in patient's survival and quality of life.

AUTHOR CONTRIBUTIONS

All authors contributed to manuscript conception, design, revision, read, and approved the submitted version.

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Multicentric and Observational Study of Omalizumab for Chronic Spontaneous Urticaria in Real-Life in Colombia

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Background: Although chronic urticaria (CU) is a common, cause of medical consulting both in general practitioners and allergist specialists worldwide, there is little information about its behavior and management in Latin America. Currently, national and international guidelines recommend using Omalizumab for cases refractory to management with antihistamines. Despite advances in the knowledge of Omalizumab for the management of CU, although there are few studies in underdeveloped countries, there are many studies evaluating the impact of Omalizumab treatment. There is not clinical information related with CSU-Omalizumab in patient settled in the Caribbean area. This research aims to evaluate the management of CU with Omalizumab in a real-life scenario in Colombia.

Methodology: We conducted an observational, descriptive, and retrospective study with patient recruitment between 2014 and 2017 of individuals diagnosed with Chronic Urticaria (CU) treating allergology specialists in five Colombian cities. We included patients with CU who failed to achieve disease control after treatment for 4 weeks with fourfold doses of second-generation H1-antihistamines, as recommended by the EAACI/GA²LEN/EDF/WAO guidelines and who received treatment with Omalizumab.

Results: We included 123 patients, 73.1% ($n = 90$) were women. The mean age was 47.1 years (Standard Deviation, SD: 16.2). The median of the total months of disease evolution was 30 (IQR = 13–58). 81.3 % ($n = 100$) of patients were diagnosed with chronic spontaneous urticarial (CSU). 4.8% ($n = 6$) had inducible CU (CIndU), and 13.8% ($n = 17$) reported mixed urticaria (spontaneous CU with at least one inducible component). Regarding emotional factors, 34.9% ($n = 43$) of subjects indicated anxiety symptoms, 34.1% ($n = 42$) had exacerbations associated with stress, and 14.6% ($n = 18$) manifested episodes of sadness. The percentage of patients with CSU controlled according to medical criteria at 3 months with Omalizumab were 80% ($n = 80/100$) and

at 6 months 87% ($n = 87/100$). The frequency of adverse events was 29.2% ($n = 36$), with headache being the most frequent adverse event.

Conclusions: This real-life study with Omalizumab at CU describes percentages of effectiveness and safety similar to those observed in pivotal and real-life studies conducted in other regions around the world.

Keywords: urticaria, angioedema, Omalizumab, inducible, antihistamines

INTRODUCTION

Urticaria is a disease characterized by the sudden appearance of hives, pruritus. Angioedema appears in about 40% of patients. Secondary to releasing inflammatory mediators such as histamine by mast cells present in the skin. It is chronic when the symptoms occur for at least 6 weeks (1). Chronic Urticaria (CU) is classified in Chronic Spontaneous Urticaria (CSU) and Chronic Inducible Urticaria (CIndU) (2). CSU was previously known as idiopathic urticarial.The triggering factor is not identified in most case of CSU, and the onset of symptoms is unpredictable (3). In CIndU, generally, a physical stimulus is consistently recognized that initiates lesions (4).

The exact prevalence of CU is currently unknown. Zuberbier et al. (5) reported a lifetime prevalence of 1.8% (95% CI 1.4–2.3%) in German adults surveyed over 3 years. A recent study with 3,538,540 Germans during 2017 reported 17,524 patients (0.5%) diagnosed with CU; chronic spontaneous urticaria (CSU: 71.2%), chronic inducible urticaria (CIndU: 19.7%), and CSU+CIndU [9.1%; (6)]. In another study, the prevalence in children was 0.1–0.3% (7). About CU duration is variable; however, it has been reported 6 to 12 weeks in 52.8% of patients, 3–6 months in 18.7%, 7–12 months in 9.4%, 1–5 years in 8.7%, and more than 5 years in 11.3% (8).

Several etiological factors have been associated with CU, including autoimmune diseases, allergens, pseudo-allergens, and infections, but it is challenging to identify the specific trigger in most patients (9, 10). Autoimmune and inducible conditions may be more resistant to treatment and have a prolonged course (11).

CU affects the quality of life of those who suffer from it, causing a significant commitment to work and school activities, anxiety, and depression, with negative consequences on health services and society (12–14).

One of the treatments used in clinical practice for disease control is Omalizumab. A humanized anti-IgE monoclonal antibody approved as an adjunct treatment for CU in people over 12 years of age with inadequate responses to antihistamine anti-H1 treatment (1, 9, 15–17).

In underdeveloped countries and the Latin American region, little is known about the clinical features of CU in patients receiving Omalizumab (18–22). This study aims to describe the characteristics and clinical response to treatment with Omalizumab in patients with CU in real life in Colombia.

MATERIALS AND METHODS

Study Design

This is an observational, descriptive, and retrospective study. Between the years 2014 and 2017, we recruited patients that meet the following criteria: (i) older than 12 years of age; (ii) clinical diagnosis of CU; (iii) disease duration >6 weeks; (iv) being under symptomatic pharmacological treatment according to EAACI/GA²LEN/EDF/WAO guidelines (23); (v) failed disease control and be refractory to fourfold doses of second-generation H1-antihistamine therapy after 4 weeks; and (vi) received Omalizumab therapy. Patients weighing <20 kg, known hypersensitivity to Omalizumab or pregnancy were excluded. We retrieved clinical information on these patients from clinical allergologist in five Colombian cities (Bogotá, Cali, Medellín, Barranquilla, and Cúcuta).

This study was endorsed by the Ethics and Biomedical Research Committees of Fundación Santa Fe de Bogotá (Bogotá—Colombia), Fundación Valle del Lili (Cali—Colombia), and Fundación Universidad del Norte (Barranquilla—Colombia). All participants gave their informed consent before being included in the study.

Study Variables

We reviewed the medical record looking for sociodemographic variables, family history of autoimmune disease, and atopic state of the patient. We also took into account the reports of laboratory test such as antinuclear antibodies (ANA), anti-DNA antibodies, anti-phospholipid antibodies, rheumatoid factor, anti-thyroperoxidase antibody (anti-TPO), anti-myeloperoxidase antibodies (anti-MPO), autologous serum skin test (ASST), rapid plasma reagin test (RPR), and skin biopsy. We consider the criteria of the EAACI/GA²LEN/EDF/WAO guidelines for definition, classification, diagnosis, and management of urticaria (23).

In addition, we recovered from medical records information about the activity of the disease and emotional alterations associated with the diagnosis of CU registered prior to treatment with the clinical allergologist researchers in this study. We reviewed the time in years from the diagnosis of urticaria to its implementation, dose, duration, outcomes, and adverse events of treatment about Omalizumab therapy.

Statistical Analysis

The present study is descriptive, with no hypothesis or comparison/intervention under consideration. The variables

TABLE 1 | Demographic and clinical characteristics of patients with chronic urticaria.

	n = 123	
	N	**%**
Sex		
Female	90	73.1
Age—Mean (SD)	47.1 (16.2)	
Months of evolution of the UC—Median (p25–p75)	30 (13–58)	
Type of chronic urticaria		
Spontaneous	100	81.3
Mixed	17	13.8
Inducible	6	4.8
Angioedema	49	39,8
Comorbidities		
Respiratory allergy	20	16.2
Drug allergy	7	5.6
Atopic dermatitis	4	3.2
Other allergic disease	3	2.4
Systemic lupus erythematosus	1	0.8
Autoimmune thyroiditis	9	7.3
Rheumatoid arthritis	2	1.6
Sjogren's syndrome	2	1.6
Vitiligo	1	0.8

SD, standard deviation.

were measured standardized, and these do not have subjectivity regarding their occurrence. Therefore, we do not consider a significant risk of bias in this study. A complete descriptive analysis was performed with absolute and relative frequencies for the qualitative variables and parameters of central tendency together with the maximum and minimum values for quantitative variables according to the nature of the variable. Additionally, a stratified analysis was performed by age group, sex, and socioeconomic stratum of the study subjects. For statistical analysis, we used Stata v14 software.

RESULTS

Demographic and Clinical Characteristics of Patients With CU

One hundred twenty-three patients diagnosed with CU were included in the analysis. The mean age was 47.1 ± 16.2 years. 73.1% ($n = 90$) of the patients were women. The duration of the disease at the time of inclusion in the study showed a median of 30 months (IQR 13–58 months) (**Table 1**).

81.3% ($n = 100$) of patients were diagnosed with chronic spontaneous urticarial—CSU. 4.8% ($n = 6$) of the individual showed chronic inducible urticaria (CIndU). Heat ($n = 3$), cold ($n = 2$), and cholinergic urticaria ($n = 1$) were identified as triggering factors. 13.8% ($n = 17$) of patients reported mixed urticaria, i.e., CSU with at least one inducible component; dermographism being the most frequent ($n = 12$) (**Table 1**).

Angioedema was observed in 39.8% ($n = 49$) of study subjects. We observed respiratory allergies (16.2%; $n = 20$), autoimmune thyroiditis (7.32%; $n = 9$), drug allergy (5.6%; $n = 7$), among other comorbidities in these patients (**Table 1**).

TABLE 2 | Paraclinical tests recorded in the study.

	Tests performed (*n*%)	**Positive tests (n)**	**Positivity (%)**
Antinuclear antibodies (ANA)	80 (65%)	12	15.0
Anti-DNA antibodies	57 (46.3%)	1	1.7
Anti-phospholipids antibodies	40 (32.5%)	2	5.0
Rapid plasma reagin test (RPR)	31 (25.2%)	3	9.6
Rheumatoid factor	48 (39%)	3	6.2
Anti-thyroperoxidase antibody (anti-TPO)	61 (49.6%)	9	14.7
Anti-myeloperoxidase antibodies (anti-MPO)	45 (36.6%)	5	11.1
Autologous serum skin test (ASST)	16 (13%)	4	25.0
Biopsy	15 (12.2%)	4	26.6

Paraclinical Findings Observed in Patients With CU

Antinuclear antibodies (anti-ANA) were the most requested laboratory test (65%; $n = 80$); however, it only showed 15% ($n = 12/80$) positivity among patients tested. Other tests of markers related to autoimmunity were also requested. In contrast, the autologous serum test (AST) was performed on only 13% ($n = 16$) of patients; however, it showed a positivity of 25% ($n = 4/16$; **Table 2**). Regarding serum total IgE concentrations, this test was performed on 34.1% ($n = 42$) of patients showing an average of 244.7 IU/ml (SD: 397 IU/ml), with a minimum value of 6.5 IU/ml and a maximum of 2,500 IU/ml.

Disease Activity and Emotional Alterations Associated With the Diagnosis of CU

The disease activity was measured and recorded in the medical records of only 89.4% ($n = 110$) of the subjects; in 56.3% ($n = 62/110$) of patients, the activity of the disease was measured by clinical interview. The implementation of a *"patient-reported outcome measures"* (PROMs) questionnaire was observed in 57.3% ($n = 63/110$) of subjects employing the urticarial control test (UCT) questionnaire.

Before first interview with the allergology specialist, and previously to starting treatment with Omalizumab, 82.1% ($n = 101$) of patients were being treated according to the EAACI/GA²LEN/EDF/WAO guideline (23). 16.3% ($n = 20$) of participants had prescribed at least two drugs combination. 45.5% ($n = 56$) of subjects were treated with first-line of treatment (standard doses of second-generation H1-antihistamines for 2 weeks); however, symptoms persisted and the dose was increased four-fold for 4 weeks (second-line of treatment). 21.9% ($n = 27$) of patients were treated with fourfold dose of 2nd generation H1-antihistamines (second-line of treatment); however, symptoms persisted after 4 weeks of treatment. We observed that 4.88% ($n = 6$) of patients were

being treated with a therapy that combined fourfold dose of 2nd generation H1-antihistamines accompanied with short course of oral corticosteroids, antileukotrienes and immunomodulators (Ciclosporin) drugs (Third-line of treatment); nevertheless, symptoms persisted.

Chronic urticaria is a disease that affects the quality of life of those who suffer from it. Of the total number of subjects evaluated, 34.9% ($n = 43$) indicated anxiety symptoms, 34.1% ($n = 42$) had exacerbations of symptoms associated with stress, 14.6% ($n = 18$) of the subjects described episodes of sadness, up to suicidal ideation in 0.8% (**Table 3**).

Findings Observed During Treatment With Omalizumab

All patients received Omalizumab for being refractory to four-fold doses of second-generation H1-antihistamine therapy after 4 weeks. 37.4% ($n = 46$) of patients received Omalizumab between 6 and 12 months. 86.9% ($n = 107$) received a dose of 300 mg every 4 weeks. 6.5% ($n = 8$) received 150 mg of Omalizumab, and 6.5% ($n = 8$) of patients were treated with 600 mg of Omalizumab every 4 weeks.

Forty-seven (38.21%; $n = 47$) patients showed disease control after the 1st month of treatment with Omalizumab. This quantity increased to 83.74% ($n = 103$) at 6 months of therapy. Participants with Chronic Spontaneous Urticaria presented the highest percentage of improvement (87%; $n = 87/100$) at 6 months of treatment. A very similar finding in patients with CIndU who reported an improvement of 83.3% ($n = 5/6$) from the third month of treatment. In contrast, only 64.7% ($n = 11/17$) of patients with mixed urticaria reported improvement at 6 months of Omalizumab therapy (**Figure 1**).

Regarding the safety of Omalizumab, 29.2% ($n = 36$) of patients reported at least one adverse event associated with the drug; However, this was not a reason to discontinue treatment. Headache being the most frequent (36.1%; $n = 13/36$), followed by myalgia 19.4% ($n = 7/36$), local pain and inflammation at the administration site (11.1%; $n = 4$), arthralgias (8.3%; $n = 3$), among other side effects (**Table 4**).

TABLE 3 | Emotional alterations associated with the diagnosis of CU.

	n: 123	%
Anxiety	43	34.9
Stress-associated exacerbations	42	34.1
Sadness	18	14.6
Sleep disturbance	17	13.8
ideas of handicap	3	2.4
Suicidal thoughts	1	0.8

DISCUSSION

This is the first study conducted in Colombia that sought to characterize CU patients managed with Omalizumab providing data on the response and safety of this drug in real-life. Of the

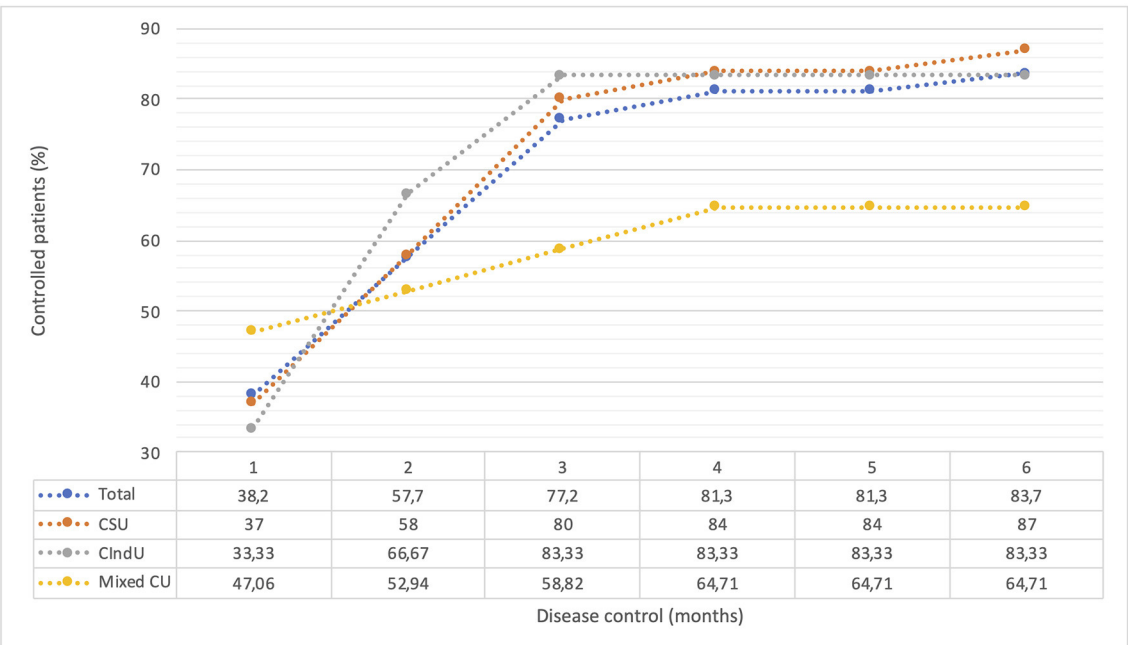

FIGURE 1 | Control of the disease with the use of Omalizumab stratified by type of Chronic Urticaria. Disease control was defined according to the presence of symptoms of urticaria in last 4 weeks of treatment with Omalizumab. Some patients were evaluated using the UCT; those patient with a UCT-score ≥12 was considered as "well-controlled disease" (56%; $n = 69$), while others were evaluated using the clinical interview employing questions comparable to the UCT (57%; $n = 70$). CU, chronic urticaria; CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; UCT, urticaria control test.

TABLE 4 | Adverse events reported during omalizumab treatment.

Adverse events	*n*: 36	%
Headaches	13	36.1%
Myalgias	7	19.4%
Arthralgias	3	8.3%
Local pain and inflammation	4	11.1%
Other AEs*	9	25%

**Adverse events.*

patients evaluated, a clear predominance of the female gender was found, coinciding with what was found in previous studies (8, 18, 22, 24). The average age was 47.3 years, similar to that reported by Gaig et al. in a large population study conducted in Spain, where a higher incidence of this disease was found between 25 and 55 years (8). As in other published studies (18), patients with CSU received Omalizumab more frequently than mixed and inducible forms (25, 26). Dermographism was the most frequent physical trigger. Like other reports, factors such as cold, heat, pressure, and cholinergic urticaria were rarer (27–29).

Angioedema is considered an unfavorable prognostic factor for CU (30). Our study observed a prevalence of 39.8% ($n = 49$), comparable data in a range of 38–54% in contrast to other clinical reports (31, 32). On the other hand, mental comorbidities have been associated with CU (12, 33, 34), a finding corroborated in our study. More than a third of the patients evaluated reported symptoms related to anxiety and exacerbations associated with stress.

There are currently no reliable biomarkers to measure disease activity in CU. However, patient-reported outcome measures (PROMs) are of great importance (13, 25, 35). PROMs allow the evaluation of various aspects of the disease, such as activity, severity, and control (35). However, a systematic review of evidence in the "real life" by Bernstein et al. (36) showed low use, with UAS7 and UCT being used in only 28.6 and 3.6% of studies, respectively. In our study, 89.4% ($n = 110$) of the subjects, the activity of the disease were evaluated by the clinical interview and the UCT being the most used PROM questionnaire, reported for use in more than half of the patients.

Current guidelines recommend limiting routine laboratory tests for CSU, C-reactive protein (CRP), and complete blood count (CBC) being basic tests (1, 2, 9). In contrast, other paraclinical tests should be requested based on medical records and physical examination, particularly patients with the longer-term or uncontrolled disease (1). In our study, the most requested laboratory test was the autoantibodies anti-ANA (65%); remember the association between CU and significant autoimmune diseases (37, 38). Regarding serum concentrations of total IgE, an average of 244.7 IU/ml (SD = 397 IU/ml) was observed, similar to that reported by Saini et al. with 215.3 IU/ml (SD = 431.6 IU/ml). Patients with CSU have lower levels of total IgE in contrast to patients with asthma (39). There is little evidence to support the association between serum IgE levels and CSU; however, recent studies show that CU's low IgE levels serve as a hyporesponsive marker to Omalizumab (40–43).

In this study, most patients were treated according to the EAACI/GA²LEN/EDF/WAO guideline (23). This guideline recommends using second-generation H1 antihistamines as the first line of treatment. In cases where disease control is not achieved, it suggests increasing the dose of this medication up to four doses compared to the standard dose. We found that 45.5% ($n = 56$) of patients received second-generation anti-H1 at standard and quadruple doses (21.9%; $n = 27$) during the first consultation with the clinical allergologist. The use of immunosuppressive drugs before Omalizumab was lower than in the GLACIAL study (4.8 vs. 9.5%), as were systemic corticosteroids (16.8 vs. 57.9%) and antileukotrienes (19.2 vs. 57.5%) (44). This reduction, especially in immunosuppressants and corticosteroids, is essential because of the adverse effects commonly reported with these drugs.

Regarding the use of Omalizumab, in this study, most patients (86.9%; $n = 107$) received a dose of 300 mg every 4 weeks, similar to the studies that report the efficacy of the drug in CU administered in this therapeutic regimen (45, 46). Only 6.5% ($n = 8$) of patients were treated with 600 mg of Omalizumab every 4 weeks. More evidence is needed to show whether the 600 mg dose is more effective than 300 mg (39). In addition, the standard dose of Omalizumab may be sufficient for disease control, independent of weight and serum total IgE concentration. Omalizumab acts directly on mast cell/basophil reactivity, which would reduce the formation of hives relatively quickly rather than requiring a long-term change in serum IgE levels to a steady-state necessary for asthma control (40, 42).

Eighty-seven percent (87%; $n = 87/100$) of the patients with CSU in this study presented better disease control using Omalizumab. This result is higher than that reported in the meta-analysis by Rubini et al. of seven controlled-randomized clinical trials, where 1,312 cases showed a response rate of 36% (47). Although, our findings are closer to others "real life" studies that describe better CU remission rates with Omalizumab (18, 26, 27); a possible explanation for the observed findings in clinical trials is the use of questionnaire that measure disease activity such as the UCT or the UAS, which in our study were not constantly used. Furthermore, treatment response criteria are less stringent in real-life studies. Although comparing results between different studies is difficult because populations, dosing regimens, assessment scores, and response definitions differ from study to study. Our study reports a 38.2% ($n = 47$) of rate of early responders to Omalizumab. Similar to results of the ASTERIA I clinical study (37% of early responders) (46), although slightly lower than that reported in ASTERIA II (51%; 39). Cherrez-Ojeda et al. showed that 45.5% of the patients responded to the drug in the 1st month of treatment in their Latin American real-life study (18). This previous study reported a median duration of treatment with Omalizumab was 7.67 months, within the range found in our investigation of 6 and 12 months, as the most frequent duration in which patients received the drug.

One of the advantages of this study is the inclusion of patients with other forms of chronic urticaria other than spontaneous. We evaluated six patients (4.8%; $n = 6$) with Chronic Inducible Urticaria (CIndU), where we showed the effectiveness of Omalizumab. Although Omalizumab in these

cases is "off-label," the Colombian health system allows the formulation of this drug under the name of Chronic Urticaria without taking into account its subtype.

The use of Omalizumab in the treatment of CIndU continues to be an "off-label" use. However, there is mounting evidence of clinical reports which used this therapeutic alternative. Chicharro and Rodríguez de Argila (48) compiled case reports and case series describing the use of Omalizumab to treat CIndU, concluding that Omalizumab is a potentially effective and safe alternative in the treatment of some cases of CIndU. However, more studies are needed to evaluate the safety and efficacy of drugs such as Omalizumab, for the treatment of this condition, with a more significant number of patients and a solid prospective, double-blind, placebo-controlled methodological design.

Regarding the safety of Omalizumab, no observed severe adverse effects in this research. Headache was the most frequent adverse event, followed by myalgia, and arthralgias; adverse events equivalent to another clinical study in CU (47). Although headache is the most common neurological side effect and also noted that omalizumab led to musculoskeletal disturbances including low back pain, arthralgia, pain in the extremities, and myalgia; the mechanisms underlying the development of adverse events are unknown, these come to be given by the condition of each individual. In our study, a high frequency of the events described above was observed in relation to other studies (49). Only four patients reported local pain and inflammation at the administration site (3.2%; $n = 4$), none of the patients met criteria for anaphylaxis. Data from post-marketing studies have shown that these reactions are infrequent and anaphylaxis very rare (0.09%) (50).

We consider that the main limitations of this study include its retrospective design because we obtain information directly from patients or their medical records; this can lead to information bias. Another limitation is the small number of patients with CIndU, which does not allow conclusions about the effectiveness of Omalizumab on this condition. It was not possible to evaluate the quality of life as reported by other studies; instruments such as the Dermatology Life Quality Index (DLQI) or chronic urticaria quality of life questionnaire (CU-QoL) are little used in the Colombian health system. Although the preferred guideline for allergists participating in this study was the EAACI/GA²LEN/EDF/WAO guideline (1), it is not common to use the UAS7 to measure disease activity. Therefore the activity of the disease was measured according to clinical interview and the Urticarial Control Test (UCT) questionnaire.

CONCLUSIONS

This real-life study with Omalizumab in CU describes effectiveness and safety percentages similar to those observed in pivotal and real-life studies conducted in other regions. It confirms the presence of emotional disorders such as anxiety, depression, and sleep disturbances in patients suffering from the disease. Likewise, we corroborated the need to use objective evaluation tools for the activity and control of the disease. It is necessary for prospective clinical studies with a significant number of patients with different subtypes of CU to validate the efficacy and safety of the Omalizumab in the long term and in "real life" conditions. As well as individualize each patient through predictive factors of response to treatment to offer the best therapist option for their disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Fundación Santa Fé de Bogotá (Colombia), Fundación Valle de Lili (Colombia), and Universidad del Norte (Colombia). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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ORIGINAL RESEARCH
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Disease Impact, Diagnostic Delay, and Unmet Medical Needs of Patients With Cholinergic Urticaria in German-Speaking Countries

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Background: Cholinergic urticaria (CholU) is a common type of chronic inducible urticaria. Little is known about the burden of the disease and its unmet medical needs.

Aim: To characterize the unmet medical needs of patients with CholU.

Methods: Patients with CholU ($n = 111$) took part in a German online survey that assessed their symptoms, diagnostic delay, impact on daily life, quality of life (QoL), and their experience with physician care.

Results: Virtually all patients reported typical signs and symptoms of CholU, i.e., whealing (93.7%) and itching (91.9%), in response to typical trigger situations, such as physical activity, passive warming, or stress. Despite this, patients reported a marked diagnostic delay of 30.2 months (range from 0 to 279 months). Only 38% of the patients received a blood examination, and only 16% underwent provocation testing for diagnosing CholU, as recommended by the international guidelines. Physician contacts were common, but patient satisfaction with their disease management was low. In total, 90.1% of the patients stated to have an uncontrolled disease, resulting in a strong impact on their everyday activities, sleep, and QoL.

Conclusion: Patients with CholU exhibit many important unmet needs, and improvement in the diagnostic workup and patient care is needed, as are better treatment options.

Keywords: cholinergic urticaria, unmet medical needs, wheals, angioedema, hives, mast cells

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INTRODUCTION

Cholinergic urticaria (CholU) is a frequent skin disorder that manifests with pinpoint-sized itchy wheals and, in up to 50% of patients, with angioedema (1). CholU is a form of chronic inducible urticaria and is triggered by sweating, e.g., due to passive warming of the body or physical activity (2–4). Disease severity can range from mild symptoms in severe trigger situations, such as extensive sporting, that can be controlled by avoiding these triggers up to extensive outbreaks in everyday situations, such as climbing stairs.

Cholinergic urticaria, i.e., all forms of chronic urticaria, shows spontaneous remission, usually after several years. The aim of treatment was to achieve complete disease control either by pieces of advice in their daily life (e.g., avoiding trigger situations, using refractory phases after severe outbreaks etc.) or by providing patients with medication that completely controls the disease until this happens. Treatments for CholU, according to the international guideline for urticaria (5), include second-generation H1-Antihistamines at standard dose, with updosing to up to 4-fold in patients with an insufficient response. When antihistamines fail, treatment with omalizumab or ciclosporin is recommended (5), but these are not licensed for the use in CholU. We recently reported on the outcomes of real-life therapy for patients with CholU in German-speaking countries and demonstrated that current treatment options often fail and better therapies are needed (6, 7).

Cholinergic urticaria has a high impact on the quality of life (QoL) of the patients (4, 8) but many aspects of the disease remain poorly understood and the impact of having CholU is often underestimated. Some of the major unanswered questions on CholU are as follows: How heterogeneous are patients with CholU in their clinical manifestations and relevant triggers? How much does the disease affect patients in their everyday life and QoL? How long does it take for patients with CholU to get diagnosed? Which physicians treat patients with CholU and what diagnostic measures do they use? How many patients are in medical care and how satisfied are CholU patients with their doctor-patient relationship? Although symptoms of CholU can affect up to 20% of the population in the age group of 26–28 years (9), little is known about these questions. To address this gap of knowledge and to understand more about the unmet medical needs and the burden of CholU, we performed an online study in German-speaking countries.

MATERIALS AND METHODS

Study Design and Participants

We analyzed 111 patients who took part in an online survey study on CholU in German-speaking countries, performed by the Charité Urticaria Center of Reference and Excellence [UCARE, (10)], the Urtikaria Netzwerk e.V., and the Urtikaria Netzwerk Berlin-Brandenburg from May 2016 to August 2017. This study was approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin (#EA1/241/15) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00012387).

Patients from Germany, Switzerland, and Austria participated anonymously in the survey. The patients had to be at least 18 and had to confirm their consent before starting the survey.

In total 197 patients participated in the online survey. Of these, 111 had CholU that was confirmed by a physician and stated suitable trigger factors, and only these patients were included in our study.

The questionnaire was divided into five parts with questions on demographics, the course of the disease, impact on work and daily life, patient-doctor relationship, and treatment.

Abbreviations: CholU, Cholinergic urticaria.

In the present report, we focused on the unmet medical needs and the disease burden of patients with CholU. Results of the online survey regarding the real-life treatment situation of patients with CholU in German-speaking countries have previously been reported (6).

In our survey, we included the Urticaria Control Test (UCT) and the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-Qol). We used the UCT (Moxie, Berlin, Germany) to assess disease control in our patients (11). The UCT has four questions with five answer options each, with a score between 0 and 4 assigned to every answer option. To calculate the UCT total score, the scores for all four questions were summed up. Accordingly, the minimum and maximum UCT scores were 0 and 16, respectively, with 16 points indicating complete disease control and scores below 12 indicating poorly controlled disease.

The CholU-QoL [Moxie, Berlin, Germany; (12)] is a recently developed patient-reported outcome measure for assessing CholU-specific QoL impairment. The CholU-QoL has 28 questions and a five domain structure ("symptoms," "functional life," "social interaction," "therapy," and "emotions"). The CholU-QoL is meant to be evaluated by using its five individual domains (profile instrument) but it can also be used to determine a total score (index instrument). Points from 0 to 4 were given for the response options: not at all/no treatment, somewhat, moderately, much, or very much, respectively. The CholU-QoL domain scores and the CholU-QoL total scores are calculated by using the following formula: (Σ items/max Σ items) x 100. The linear transformation of raw scores results in minimal and the highest possible scale and total scores of 0 and 100, respectively.

The total score was not computed when >20% of the items (>5 items) were missing. The domain scores "symptoms," "functional life," "social interaction," and "emotions" were not computed when more than 25% of the items were missing in the respective domain. The domain score "therapy" was not computed when >50% of the items were missing.

Missing hours from work in the last week was evaluated, and subjective work impairment in the last week on a scale of 0 (no impairment) to 10 was also evaluated (no work possible).

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics version 23. Graphs were made with GraphPad Prism Version 6.0 and Excel Version2016. $p < 0.05$ was used to determine statistical significance.

RESULTS

Patients participating in the online survey, on average, were 38.7 years old (range: 18–78 years), and 76.6% were women.

Clinical Manifestation and Triggers

The majority of patients reported wheals (93.7%), pruritus (91.9%), or both as their main manifestation of CholU. One in three patients (35.1%) reported angioedema. Circulation

problems and dizziness occurred in 38.7 and 18.9% of patients with CholU, respectively. Only 4 patients (3.6%) experienced unconsciousness. Most of the patients (53%) stated a typical symptom duration between 30 min and 2 h. Only a few reported shorter durations (4%) and several times more than 2 h (39%).

As for trigger factors, most patients (86.5%) named the physical activity. Other common triggers included taking a warm bath, emotional stress, and feeling agitated, which were reported by 54.1, 50.5, and 47.7% of patients, respectively. Less common triggers, in 38.7, 20.7, and 13.5% of patients, respectively, were showering, spicy food, and hot food or drinks.

Diagnostic Delay and Physician-Patient Interaction

The median time between first signs and symptoms of CholU and receiving the diagnosis was 30.2 months, with a wide range of 0–279 months. In more than 60% of the patients, the diagnosis was given at least a year after the onset of the symptoms or later.

Most patients (43.2%) first consulted a dermatologist followed by a general practitioner/family physician (37.8%). Very few patients initially turned to an emergency room (3.6%), outpatient consultation of a clinic (3.6%), or a specialized urticaria clinic (2.7%).

Upon their first encounter with a physician, more than one-third of patients with CholU (38%) received a blood examination, but only 16% underwent provocation testing, the guideline-recommended approach for confirming chronic inducible urticaria (CIndU) that includes CholU (see **Table 1**).

Of note, most patients (82 of the 111; 73.9%) visited a second physician, and this was a dermatologist in half of the cases (53.7), a specialized urticaria clinic (13.4%), and a general practitioner/family physician (8%). Most patients (45%) did so on their own, whereas 44% were referred by their treating physician.

Even after the second visit, more often in a more specialized setting, the stated diagnostic procedures and treatment choices did not change dramatically. Again 38% of (31 of 82) patients

TABLE 1 | Patient-reported diagnostic workup, topics of discussion, and treatments upon the first presentation (multiple answers in each category were possible).

	1st physician	2nd physician	Current physician
Dermatologist	48/111, 43.2%	44/82, 53.7%	31/111, 27.9%
Family Doctor/ general practitioner	42/111, 37.8%	7/82, 8.5%	20/111, 18.0%
Special consultation hours for urticaria patients	3/111, 2.7%	11/82, 13.4%	6/111, 5.4%
Ambulant consultation hour of a clinic	4/111, 3.6%	6/82, 7.3%	7/111, 6.3%
Medical on-call service	0/111, 0%	1/82, 1.2%	-
Emergency room	4/111, 3.6%	3/82, 3.7%	-
Other	8/111, 7.2%	8/82, 9.8%	5/111, 4.5%
None	-	-	38/111, 34.2%
No data	2/111, 1.8%	2/82, 2.4%	4/111, 3.6%
Diagnostics			
Blood-examination	42/111, 37.8%	31/82, 37.8%	28/69, 40.6%
Allergy testing	30/111, 27.0%	28/82, 34.1%	17/69, 24.6%
Full Body examination	27/111, 24.3%	29/82, 35.4%	22/69, 31.9%
Provocation-testing	18/111, 16.2%	14/82, 17.1%	13/69, 18.8%
Other examinations	16/111, 14.4%	10/82, 12.2%	11/69, 15.9%
Topics of discussion			
Discussion about possible causes of the CholU	42/111, 37.8%	40/82, 48.8%	30/69, 43.5%
Discussion about treatment- possibilities	37/111, 33.3%	35/82, 42.7%	31/69, 44.9%
Discussion about possible progress of the CholU	32/111, 28.8%	33/82, 40.2%	33/69, 47.8%
Treatment			
Recommended treatment with a drug	46/111, 41.4%	38/82, 46.3%	37/69, 53.6%
Immediate application of a drug	34/111, 30.6%	17/82, 20.7%	15/69, 21.7%
Other*	18/111, 16.2%	11/82, 13.4%	11/69, 16.0%
No data on consultation	2/111, 1.8%	3/82, 3.7%	5/69, 7.2%
Treatment satisfaction			
Not at all satisfied	36/111, 32,4%	18/82, 22%	8/69, 11,6%
Not very satisfied	38/111, 34,2%	28/82, 34,1%	25/69, 36,2%
Satisfied	28/111, 25,2%	23/82, 28%	19/69, 27,5%
Very satisfied	5/111, 4,5%	9/82, 11%	8/69, 11,6%
No data	4/111, 3,6%	4/82, 4,9%	9/69, 13%

**Including urine tests, stool sampling and analysis, test for scabies, dental X-ray, CT of the head, ultrasound of internal organs, colonoscopy, and lung function test, referral to the specialized center.*

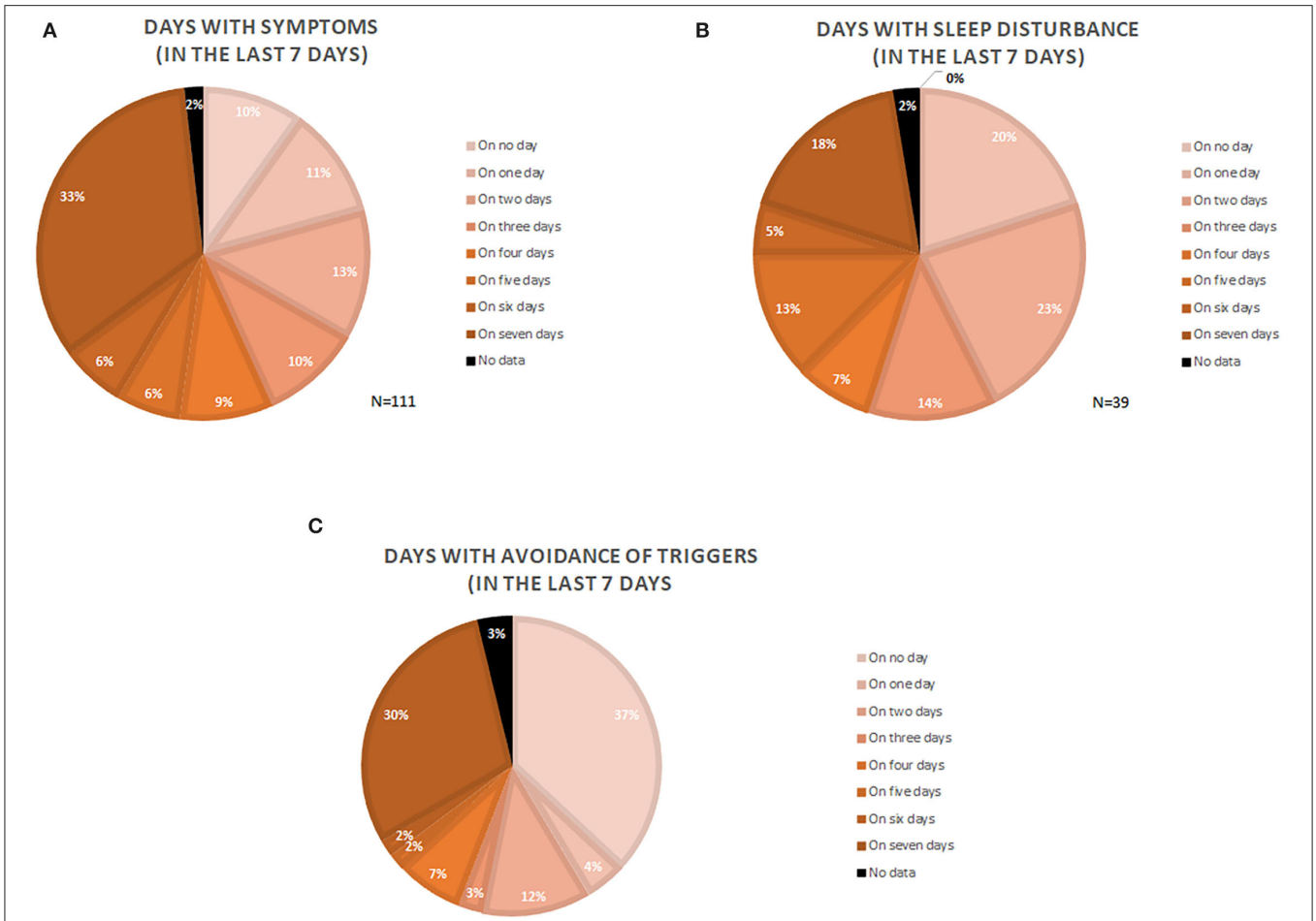

FIGURE 1 | Depiction of symptomatic days **(A)**, days with sleep disturbance **(B)**, and days where patients actively avoided trigger situations **(C)**. Numbers are given as the percentage of the analyzed patients (*N* = number of patients).

with CholU received a blood examination and 14 out of 82 patients underwent provocation testing (17%).

Of the patients who provided information on their level of satisfaction with their treatment of the first physician, 67% reported that they were not or only somewhat satisfied, whereas 30% of patients were satisfied or very satisfied.

About 30–40% of the patients were very satisfied or satisfied with their first or second physician encounter, whereas 24–30% of the patients were not at all satisfied and 32–35% of patients were only slightly satisfied.

One of three patients (34.2%) were currently not in physician care for their CholU (see **Table 1**).

Disease Activity and Control

One-third of the patients with CholU (33.3%) reported daily symptoms within the last 7 days. More than half (55%) had symptoms on more than 3 days of the week, and only 10% of patients had no symptoms during the last 7 days (**Figure 1A**).

One of three patients (35.1%) had trouble sleeping due to their CholU, and one of five patients (18%) had sleep problems due to CholU on all nights of the week (**Figure 1B**).

Every third patient (29.7%) avoided situations that could trigger symptoms on all of the 7 days of the last week, whereas 36.9% of the patients did not do this at all. More than half of the patients (55%) avoided trigger situations on 2 or more days of the week (**Figure 1C**).

Impact on Daily Activities and QoL

Nine of 10 patients (90.1%) had poorly controlled disease as reflected by a UCT score of 11 or less, and only 1% reported complete control (UCT = 16, **Figure 2**).

In our study, 45, 31, and 23% of patients, respectively, reported that their overall life quality suffered much or very much, moderately, and somewhat or not at all, during the last 4 weeks because of their CholU. As assessed by the use of the disease-specific QoL questionnaire CholU-QoL, patients, on average, showed markedly impaired QoL as reflected by a mean (±SD) CholU-QoL score of 47.5 ± 13.5. The highest impact of CholU was seen in the social interaction domain (63.1 ± 25.2), followed by the domains therapy (63.8 ± 19.2) and functioning (61.6 ± 21.5).

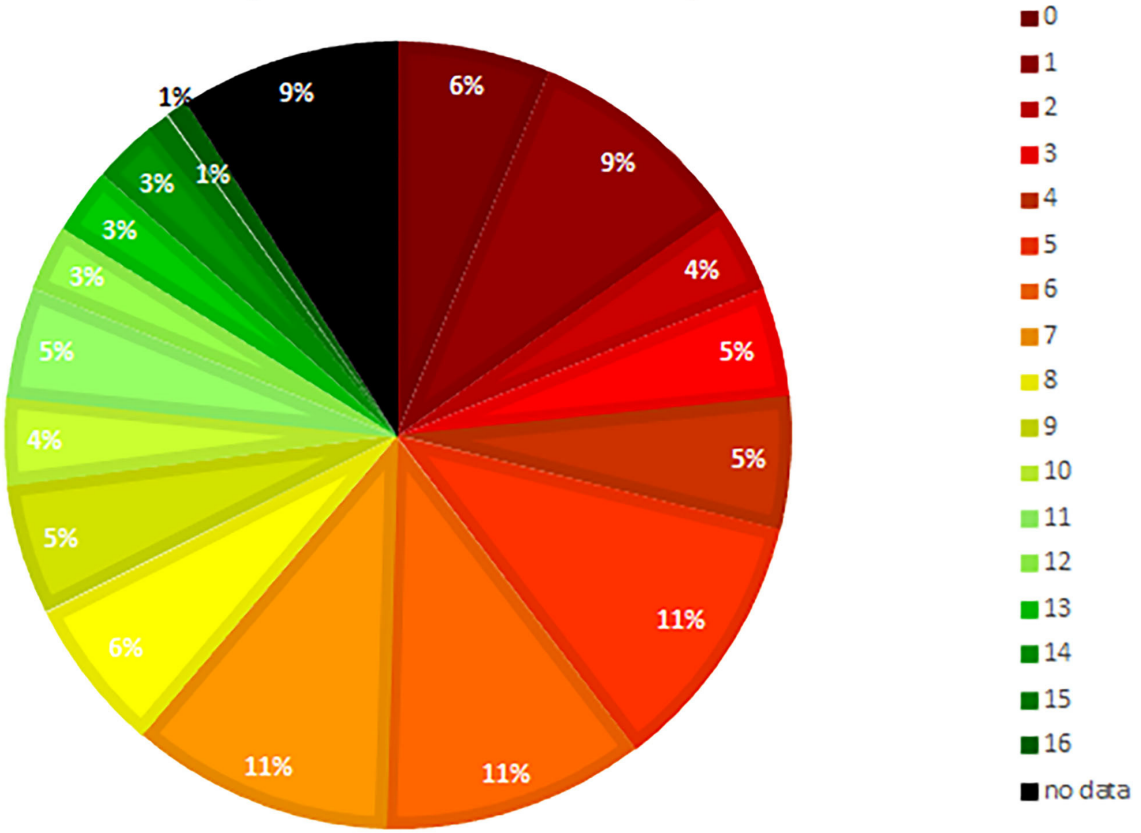

FIGURE 2 | Depiction of the distribution of the Urticaria Control Test (UCT) point results. UCT scores of more than 12 points indicate sufficient disease control. The lower the achieved points the less controlled the disease was at the time point of assessment.

Of the 111 patients, 88 (79.3%) reported to have a job. More than 50% of these patients stated that their productivity was impaired to some extent (see **Figure 3**). Moreover, 27% of the professional working patients reported that they missed work in the last week due to CholU symptoms (mean 14.7 h ± 14.0; range 1–48 h).

DISCUSSION

This study, the first on the unmet needs of patients with CholU in Germany, Austria, and Switzerland, demonstrates that patients with CholU face long delays in diagnosis, insufficient diagnostic workup, and medical treatment that many find unsatisfactory and high levels of disease activity, uncontrolled disease, and impairment of QoL.

As expected, most patients with CholU experience wheals and pruritus in response to relevant triggers, about one-third have angioedema. Severe systemic reactions that include loss of consciousness are extremely rare. All of this is in line with what has previously been reported in other patient cohorts (1, 13–15). Mild systemic signs and symptoms, such as dizziness and circulatory problems, appear to be more common than commonly held. More than half of the patients (57%) reported symptom duration of up to 2 h. A large proportion (39%) also reported symptoms of longer durations, that fit to severely affected patients that experience angioedema, since they tend to last longer. However, we cannot rule out that patients who either have a heat aggravating chronic spontaneous urticaria or patients who have both CholU and chronic spontaneous urticaria might have been included in the survey.

Physical exercise is the most common trigger of signs and symptoms comes as no surprise (2) and neither does the finding that passive warming is a frequent trigger (16). What is interesting is that emotional stress or feeling agitated, in about half of patients each, is sufficient to elicit CholU symptom development. Emotional stress and agitation had previously been reported as triggers in CholU, albeit mostly anecdotally (17, 18).

Three-quarters of the analyzed study participants were women. This unexpectedly high number of women could point to a higher disease burden in women that typically motivates patients to participate in such surveys and/or to a common fact that women incline toward earlier seek for

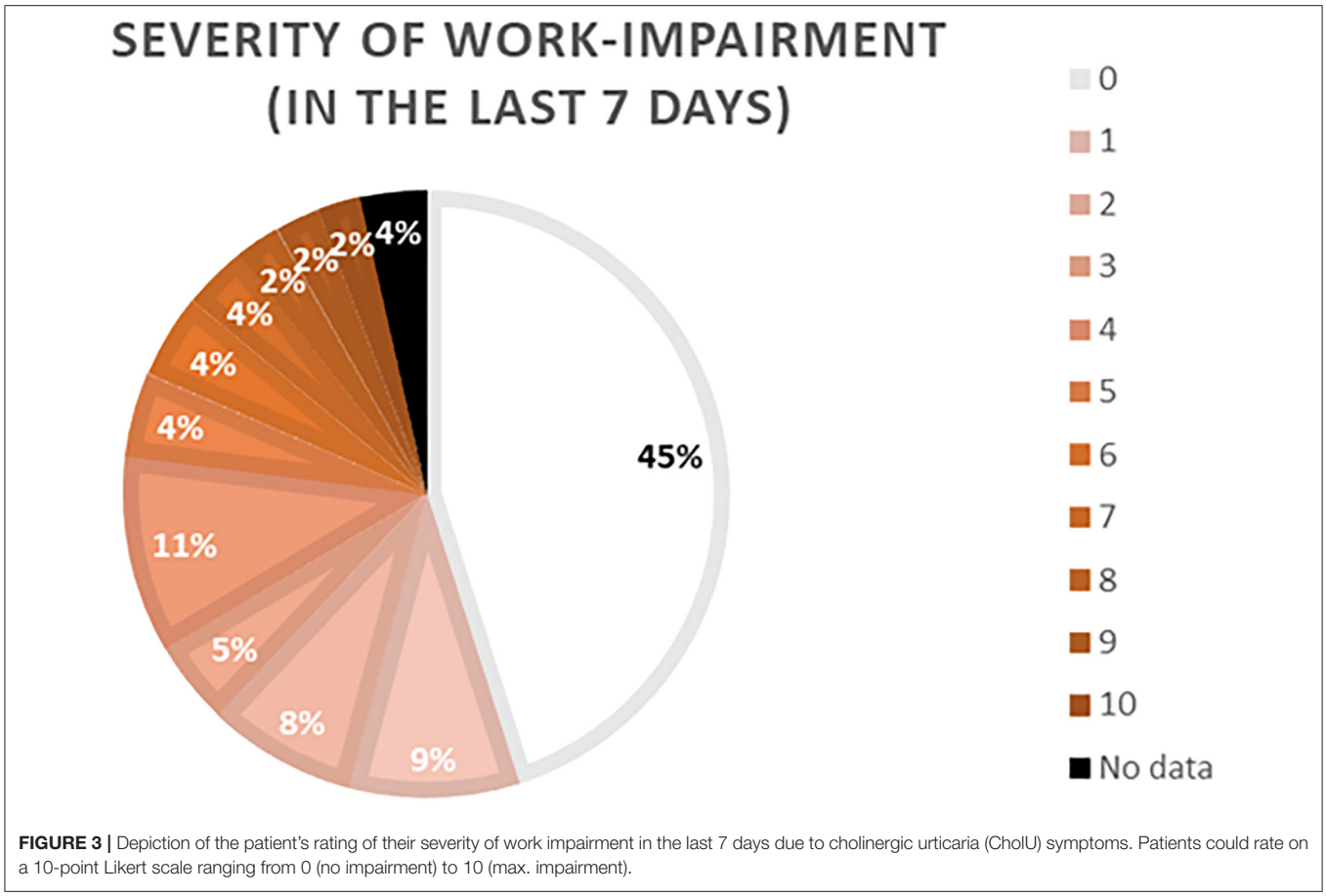

FIGURE 3 | Depiction of the patient's rating of their severity of work impairment in the last 7 days due to cholinergic urticaria (CholU) symptoms. Patients could rate on a 10-point Likert scale ranging from 0 (no impairment) to 10 (max. impairment).

medical advice/treatment (19) resulting in a physician made the diagnosis, which was an inclusion criterion.

The reason for concern is our finding that the average time for patients with CholU to receive the correct diagnosis is 2.5 years. This is concerning because not knowing what disease is responsible for their signs and symptoms can be a burden for patients and it often delays effective treatment. The long delay in diagnosis is also somewhat of a surprise since CholU, with a good history and provocation testing, is relatively easy to diagnose and many patients were first seen by a specialist (dermatologist). One reason for this long delay in diagnosis may be the fact that only one of six patients was assessed by provocation testing, the guideline-recommended test of choice in CholU (2, 5). Provocation testing for CholU is straightforward and easy to perform (20). Clearly, there is a need to increase awareness and knowledge of CholU in the physician community, especially on the diagnostic workup.

Overall, patients consulted four physicians on average because of their CholU and most patients were not satisfied with their medical care. This explains why one-third of the patients did not currently work with a physician to manage their CholU. Only about one-third of the patients were currently in specialist/dermatologist care. This explains, at least in part, our previously reported finding that half of the patients with CholU do not currently receive treatment for their condition (6).

Nine of ten patients with CholU reported poor control of their urticaria, and two reasons for this are likely. First, many patients do not receive treatment or receive treatment that does not help them control their CholU. Patients with CholU who do not respond to a standard-dosed antihistamine can benefit from updosing (21, 22), but this is not done in the conditions of many patients (6). Second, treatment options for CholU are limited. Omalizumab has been shown to benefit many patients with CholU who do respond to antihistamines at standard or high doses (23–26). However, omalizumab is off label for CIndU that includes CholU and only licensed for the use in patients with spontaneous forms of chronic urticaria. Moreover, at the time of the survey, omalizumab was a more novel treatment for patients with chronic urticaria. Of note, treatment recommendations aside from drugs (e.g., trying repetitive exercise to induce a refractory state, etc.) were only discussed with up to 16% of the patients. In our experience, such treatments can work in some patients but do not work in others and are hard to continue on a regular base. Clearly, more effective treatment options are needed for CholU, and several new therapeutics are currently in clinical development, such as lirentelimab [a mast cell-silencing anti-SIGLEC8 (27)], ligelizumab [an anti-immunoglobulin E [IgE] (28)], CDX-0159 [a mast cell-depleting anti-KIT (29)], and LEO 152020 [a histamine receptor 4 antagonist (30)].

The need for effective treatment, in patients with more severe symptoms of CholU, is high. Half of the patients experience the signs and symptoms of their CholU 5 or more days per week. One-third of patients with CholU proactively avoid trigger situations, which restrains their social activities and results in a reduced QoL. Most patients report their QoL to be moderately, much, or very much affected by their CholU. In addition, the professional productivity was impaired in more than half of the patients, resulting in an economic burden of the disease.

Limitations of this report include that data were obtained by an online survey, i.e., without verification by treating physicians. To minimize the possibility that some of the patients who participated did not have CholU, we only evaluated the responses of patients who indicated suitable trigger situations and who stated that their CholU was physician diagnosed. However, we cannot rule out that patients with other forms of urticaria (e.g., heat aggravated chronic spontaneous urticaria or with combinations of CholU and chronic spontaneous urticaria) were included. It is possible that there is a higher probability of patients with a higher disease burden and non-satisfactory treatment to participate in such an online survey, leading to an overestimation of disease burden. Moreover, we lack information about the compliance of patients with their treatment and physician advice, which could also be a reason for unsatisfactory disease control.

In summary, this report highlights the high need for better awareness and knowledge among physicians who treat patients with CholU that include specialists, such as dermatologists. The need for treatment is clearly being underestimated, and this may be because of a lack of understanding of the impact CholU has on patients. Urticaria specialists need to educate physician communities on the diagnostic workup, monitoring, and management of CholU, and the Undergraduate Creative Activities and Research Experience (UCARE) LevelUp program can help with this. Several new treatments for CholU are underway, and patients should be encouraged to participate in the ongoing clinical trials. In addition, prospective studies and further research on CholU are needed to identify and characterize pathogenic drivers and to help with the development of further treatment options.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by local Ethic Comittee of Charite - Universitätsmedizin Berlin, Berlin, Germany. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SA conducted the study and drafted the manuscript. EM was involved in data management and statistical analysis. DT-M supported with logistics and was involved with proofreading of the manuscript. EG supported patient recruitment. KW was involved in the questionnaire development, data cleaning, and statistical analysis. MM was the overall project lead, gave continuous project support, and was involved with proofreading of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/falgy.2022.867227/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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OPINION
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Chronic Urticaria: The Need for Improved Definition

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Keywords: chronic urticaria, diagnosis, opinion, revision, dissemination, epidemiology

LOOKING FOR DIAGNOSTIC CERTAINTY ON URTICARIA

The diagnosis of CU requires the presence of daily or almost daily presence of urticaria persisting for 6 weeks or longer, irrespective of whether it is spontaneous (CSU) or inducible (CIndU) in nature, compared to acute urticaria that lasts <6 weeks. Urticaria is identified by the presence of pruritic wheals or hives, accompanied by angioedema (AE) in ∼40% of cases. Up to 20% of patients present with isolated AE (1–3).

The definition of wheals or hives involves the presence of polymorphic raised skin lesions that are rounded or irregular in shape, with a pale central region and erythematous borders (although complete redness of wheals may occur), which usually persists for several hours but less than a day. These later two characteristics can sometimes help differentiate CU from vasculitis lesions, as they typically persist over 24 h and usually have a hematoma appearance (4). In addition, an uncomplicated urticaria lesion will disappear by applying pressure to the lesions whereas urticaria vasculitis lesions typically persist (1, 3, 5).

The typical histopathologic features of urticarial wheals exhibit lymphocytic infiltrates with perivascular eosinophils however, there may be mixed infiltrates of eosinophils and neutrophils, which is more often associated with chronic autoimmune urticaria.

Mast cells, which require special staining to visualize (i.e., Tryptase, CD117) are increased up to 10-fold the number found in normal skin in the reticular dermis. The presence of not only extravasated erythrocytes but also fibrinoid necrosis and leukocytoclasia are suggestive of leucocytoclastic vasculitis, which may be associated with normal or decreased complement levels (6, 7).

The definition of AE corresponds to vascular permeability in the deeper subcutis region that is typically non-pruritic but sometimes painful due to increased fluid accumulation in the interstitial space causing increased pressure and innervation of nerve fibers. Histaminergic AE which may or may not be associated with urticaria (isolated histaminergic AE), typically resolves within 72 h without treatment. Non-histaminergic AE is often bradykinin-mediated and not associated with urticaria, may persist longer than 72 h and in severe cases progress to asphyxia of the upper airway without treatment. Bradikinin-mediated AE is associated with ACE-inhibitors or different forms of hereditary or acquired AE. Histaminergic AE in contrast to non-histaminergic forms is typically not associated with a family history of AE, with gastrointestinal symptoms and is responsive to treatment with corticosteroids and antihistamines (8, 9).

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TABLE 1 | Clinical characteristics of urticaria.

	Presence	Comments
Wheals/Hives	+++	Heterogeneous in size and shapes; can be papular or macular
Duration of wheals	+	Limited to hours—evanescent
Lesions disappear when pressure applied	+++	Contrasts to vasculitis
Itching/Pruritus	++	Often intense
Angioedema	++	Can be isolated
Duration of angioedema	+	Resolves without treatment within 72 h

Table 1 summarizes clinical characteristics of urticaria that can help clinicians properly diagnose this condition.

IS CU A MATTER OF CONCERN?

The significant burden of CU has been extensively reported with a variety of validated patient reported outcome measures that demonstrate a significant impact on several aspects of life ranging from physical discomfort to personal mood changes (particularly anxiety and depression) which often interferes with interpersonal relationships, daily activities including work and school. Not surprisingly, management of CU is associated with substantial costs to our health care system due to frequent medical visits and therapies (4, 10, 11). Therefore, it is imperative to create awareness among healthcare payors and other stakeholders about the prevalence of CU and its impact on patient quality of life and the economic burden it has on society. The lack of consensus on diagnostic criteria for CU makes this task more challenging to achieve. Nonetheless, advances in the medical recognition of allergic and immunological conditions such as CU by the International Classification of Diseases (ICD)-11 committee can help overcome such barriers to ensure this condition is correctly identified by medical practitioners (12, 13).

Currently, the prevalence of CU is estimated to range from <1% to over 5% in general population (4, 11, 14) indicating that hundreds of millions of people are affected by this condition. Moreover, during the recent COVID pandemic many more individuals experienced cases of acute urticaria and there was a remarkable surge of urticarial exacerbations among patients with existing CU (15).

Registries are important for identifying existing and new cases of CU [(16), https://www.urticaria-registry.com/registry.shtml] and currently there is an ongoing voluntary, observational open registry for CU that allows any physician to provide baseline and follow-up data on their CU patient's demographics, symptom characterization, triggers, associated risk factors, comorbid conditions and treatment (17). In addition, a cross sectional registry from Latin America has been useful in obtaining retrospective data on real-life management and outcomes of CU patients (18). A multicentric study comparing CU patients from Europe and Latin America found that CU patients from Europe were less likely to present with angioedema or experience concomitant chronic spontaneous urticaria with an inducible component (CIndU). In addition, they had higher rates of controlled disease and better overall treatment access but interestingly they still had significantly impaired quality of life parameters (19). Data from registries can be used to confirm such findings.

Chronic urticaria is a heterogeneous condition and its duration varies between individuals which makes it more challenging to estimate its prevalence. A prospective evaluation of CU patients found that around 50% of those with CSU experienced remission within 1 year after onset, compared to <20% of those with CIndU. In general, patients with more severe disease and inducible triggers (CIndU) took much longer to achieve complete remission (20). A more recent report describes that up to 80% of patients with CSU may achieve remission over 1 year but >10% may suffer a more prolonged time course of up to 5 years (3). This variability in disease remission can be explained by several factors and comorbidities that have led to the categorization of patients into specific clinical phenotypes based on the presence or absence of certain inflammatory cells or autoantibodies predicting a good or poor response to high dose antihistamines or biologics. These phenotypes have subsequently been linked to endotypes that have improved our understanding of the underlying immunopathomechanisms of this complex condition and have led to the development of more targeted therapies that could potentially improve the management of CU patients refractory to current treatment options. Current CU guidelines represent living documents that will continuously be modified as our knowledge about CU continues to broaden (5, 21).

Limitations were exposed along the present document, about the absence of a consensus on diagnostic criteria, while its strength is the proposal of practical parameters for an undoubtful identification of CU.

CONCLUSIONS

The health and economic burden of CU is substantial and should not be trivialized. The significant impact of CSU on patients requires that physicians and other health care providers understand how to properly identify and manage this condition. An expert consensus on diagnostic criteria for CU is urgently required to improve the reliability of global epidemiologic data.

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All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Differential Diagnosis of Urticarial Lesions

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Urticaria is a mast cell-dependent disease, characterized by the presence of wheals, angioedema, or both in the absence of systemic symptoms. It is a common disease worldwide, with an important health burden especially in chronic situations, that last more than 6 weeks. Although urticaria is usually a straightforward diagnosis, some diseases presenting with urticarial lesions must be excluded, particularly urticarial vasculitis and auto-inflammatory syndromes. In these settings additional atypical features are often present (long-lasting lesions, bruising, fever, malaise, arthralgia), allowing the clinician to suspect a diagnosis other than urticaria. The authors propose an approach based on these atypical features, the presence or absence of systemic symptoms and on skin histopathology as well as some blood parameters.

Keywords: urticaria, angioedema, urticarial syndromes, autoinflammatory syndromes, chronic spontaneous urticaria

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INTRODUCTION

Urticaria is characterized by mast cell-dependent wheals, angioedema, or both in the absence of systemic symptoms. Urticaria can be acute or chronic (recurrent signs and symptoms for more than 6 weeks), in the latter case spontaneous and/or inducible (1). Chronic spontaneous urticaria (CSU), the most common form of chronic urticaria (CU), presents with transient wheals, angioedema or both, without any definite triggers. Wheals are pruritic, pink or pale swellings of the superficial dermis that, by definition, resolve in <24 h. Wheals may be round or polycyclic and have various sizes, or may be pale, eventually with an "orange peel" appearance, surrounded by erythema and can affect any area of the body usually in an asymmetric distribution. Angioedema is characterized by swellings that involve the deeper dermis and the subcutaneous or submucosal tissue. Lesions tend to have less precise limits, usually have a normal skin color and are more frequently painful than pruritic. Angioedema can last longer than 24 h but resolves completely over a few days.

Acute urticaria is a common, usually self-limited entity. Although mainly idiopathic, the most commonly identified causes of acute urticaria are infections, followed by drugs, food and hymenoptera venom allergy (2). Food constituents can behave either as allergens (proteinic molecules as tropomyosin from seafood, ovalbumin from egg) or pseudoallergens (non-proteinic molecules like salicylates, benzoic acid). Physical activity can also induce acute urticaria as in exercise-induced urticaria. Oral allergy syndrome represents a mucosal allergic contact urticaria in people sensitized to common pollens, due to IgE cross-reactivity between homologous pollen allergens and various plant foods. It is the most prevalent food allergy, and, even though symptoms are usually mild, self-limiting and localized to the oropharyngeal mucosa, they may sometimes become generalized and life-threatening, with cutaneous manifestations including urticaria (3).

Chronic urticaria has a prevalence of 0.5%−3% and typically persists for months to years. CSU has no obvious cause, but autoimmunity or autoallergy plays an important role in most

TABLE 1 | Clinical entities with acute and chronic urticarial lesions.

Systemic symptoms \ Clinical history	Acute	Chronic
Present	Anaphylaxis Maculopapular drug exanthem Viral exanthem Erythema multiforme Sweet's syndrome	HUV/HUVS Hypereosinophilic syndromes Cryopyrin-associated periodic syndromes Schnitzler syndrome Adult-onset Still disease Gleich syndrome
Absent	PLE	Maculopapular cutaneous mastocytosis Bullous pemphigoid EAC Autoimmune progesterone dermatitis Urticarial dermatitis NUV

EAC, Erythema annulare centrifugum; HUV, hypocomplementemic urticarial vasculitis; HUVS, hypocomplementemic urticarial vasculitis syndrome; NUV, normocomplementemic urticarial vasculitis; PLE, polymorphic light eruption.

cases and external triggers, like drugs, infections or stress, can exacerbate it. Inducible urticaria includes a heterogeneous group of conditions elicited mainly by physical stimuli (cold, heat, light, pressure, etc.) or by exercise (cholinergic urticaria). Patients usually identify the trigger although it is important for the physician to confirm it and establish thresholds of reactivity (4). Inducible urticaria can also present with concomitant systemic manifestations, that can occasionally be life-threatening, namely in cold-induced or cholinergic urticaria (5).

DIFFERENTIAL DIAGNOSIS OF URTICARIA

The diagnosis of urticaria is usually straightforward, but several mimickers need to be considered in case of an atypical clinical history or physical examination (6) (**Table 1**). The distinction between wheals and urticarial lesions can be useful in determining when to suspect another diagnosis. Atypical urticarial lesions can be infiltrated and long-lasting (>24 h), coexist with other elementary skin lesions (papules, vesicles, hemorrhages), resolve with hypo/hyperpigmentation or scaling, may have a more symmetric distribution and angioedema is usually absent (4). The presence of systemic symptoms (fever, malaise, arthralgia) is also unusual and should discourage a diagnosis of urticaria. There are several systemic disorders that can present with urticarial lesions, including urticarial vasculitis, connective tissue diseases, hematologic diseases and autoinflammatory syndromes. All these conditions may be considered as differential diagnosis of urticaria (7). Angioedema is associated with CSU in more than 50% of the cases (8), often aggravating the disease burden (9), but when it occurs alone and particularly with associated systemic symptoms, the hypothesis of a bradykinin-mediated angioedema needs to be considered (10).

When first evaluating a patient with a presumable diagnosis of urticaria, the acute and chronic subtypes may not be discernable. In both settings, other diagnosis may have to be considered, therefore, an approach based on the particular aspects of the lesions and presence or absence of accompanying systemic symptoms and the number of previous episodes seems to be the best clinical strategy.

Differential Diagnosis in Acute Urticaria

A first episode of urticarial lesions without any accompanying symptoms is not always acute urticaria. When some of the previously mentioned atypical characteristics are present, other diagnosis should be considered (**Figure 1**).

Polymorphic Light Eruption

Polymorphic light eruption usually occurs in spring and consists of symmetrically distributed itchy, polymorphic, erythematous skin lesions that appear after sun exposure and persist for several days (11).

Maculopapular Cutaneous Mastocytosis

Maculopapular cutaneous mastocytosis is characterized by multiple hyperpigmented macular or maculopapular lesions that urticate within a few minutes when rubbed (12).

Bullous Pemphigoid

Bullous pemphigoid usually begins with a non-specific pruritic rash, occasionally with an urticarial appearance, but lesions tend to persist for days and may progress to bullae. It may be similar to some urticarial dermatoses in pregnancy, e.g. *pemphigoid gestationis*.

Erythema Annulare Centrifugum

Erythema annulare centrifugum is characterized by solitary or multiple erythematous, ring-shaped and polycyclic plaques that slowly spread peripherally and may show a characteristic slight scaling behind the advancing edge.

Autoimmune Progesterone Dermatitis

Autoimmune progesterone dermatitis is triggered by hypersensitivity to progesterone. Variable skin lesions, resembling wheals or eczema, aggravate cyclically in the premenstrual period (11).

Urticarial Dermatitis

Urticarial dermatitis occurs mostly in elderly patients and presents with highly pruritic eczematous and urticarial lesions, simultaneously or sequentially. It is difficult to treat and may be idiopathic or represent the initial presentation of several skin diseases, namely bullous pemphigoid or drug eruptions (13–15). All these clinical entities can also present as recurrent dermatosis and participate in the differential diagnosis of both acute and chronic urticarial lesions.

Otherwise, in the setting of acute urticarial lesions accompanied by systemic symptoms, the clinician should always consider some differential diagnosis. Anaphylaxis with acute urticaria occurs after exposure to an allergen, such as food, medications or insect venom, which trigger the release

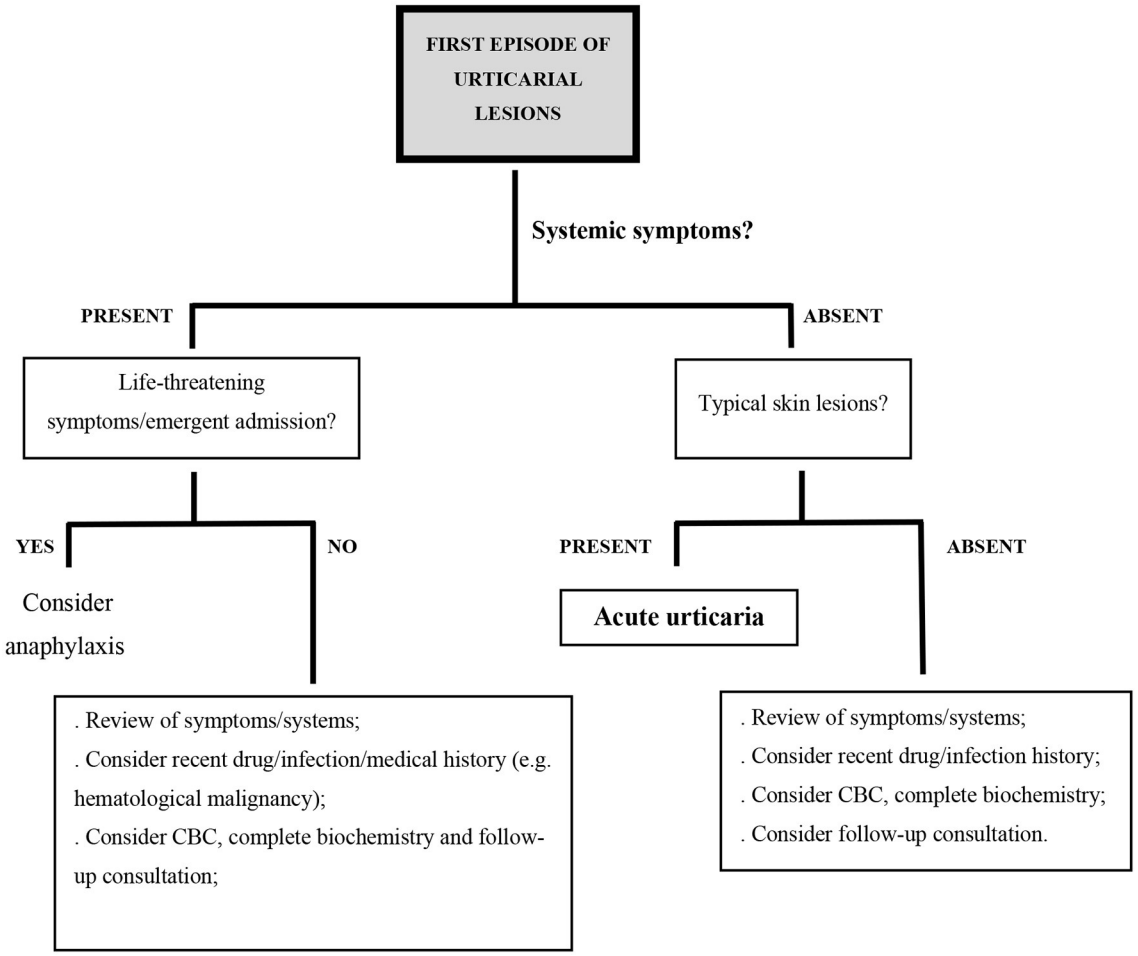

FIGURE 1 | Proposed diagnostic algorithm in the setting of acute urticarial lesions; CBC, complete blood count.

of vasoactive mediators from mast cells and basophils, often *via* an IgE-mediated pathway. Anaphylaxis is likely when there is an acute onset of generalized wheals and/or angioedema accompanied by respiratory symptoms, reduced blood pressure, syncope, gastrointestinal symptoms, incontinence or uterine cramps (16). Acute urticaria present for hours or days is not likely to evolve into anaphylaxis.

Maculopapular Drug Exanthem

Maculopapular drug exanthem is a T-cell mediated reaction that can occur within a few days to 3 weeks of the onset of almost any drug. There is usually a symmetrical eruption of confluent red macules and urticarial papules that begin on the upper trunk and progress distally, persist for several days and evolve into desquamation, sometimes accompanied by systemic symptoms. Viral exanthem may also present as a macular, maculopapular, urticarial, or vesicular reaction that lasts a few days and may be associated with mucosal lesions, fever or other systemic symptoms. Erythema multiforme is an acute eruption of dull red, macular, papular or urticarial lesions with a target appearance. Lesions are preferentially distributed on distal extremities and tend to appear in successive crops for a few days, slowly enlarge, and fade in 1–2 weeks. Erythema multiforme major is usually accompanied by mucosal erosions and systemic symptoms such as fever. On the other hand, urticaria multiforme, an entity sometimes difficult to distinguish from erythema multiforme, is a benign cutaneous hypersensitivity response seen in pediatric patients characterized by the acute and transient onset of urticarial lesions with a dusky quality.

Sweet's Syndrome

Sweet's syndrome (acute febrile neutrophilic dermatosis) is characterized by fever and acute onset of painful, erythematous papules, plaques or nodules, often with a pseudovesicular aspect, that persist for days to weeks.

Differential Diagnosis in Chronic Urticaria

If a patient reports intermittent crops of wheals for a period longer than 6 weeks, often with angioedema, the diagnosis of CU is likely. However, when accompanied by systemic symptoms or presenting with atypical characteristics, additional diagnoses must be ruled out. Systemic symptoms should alert to the

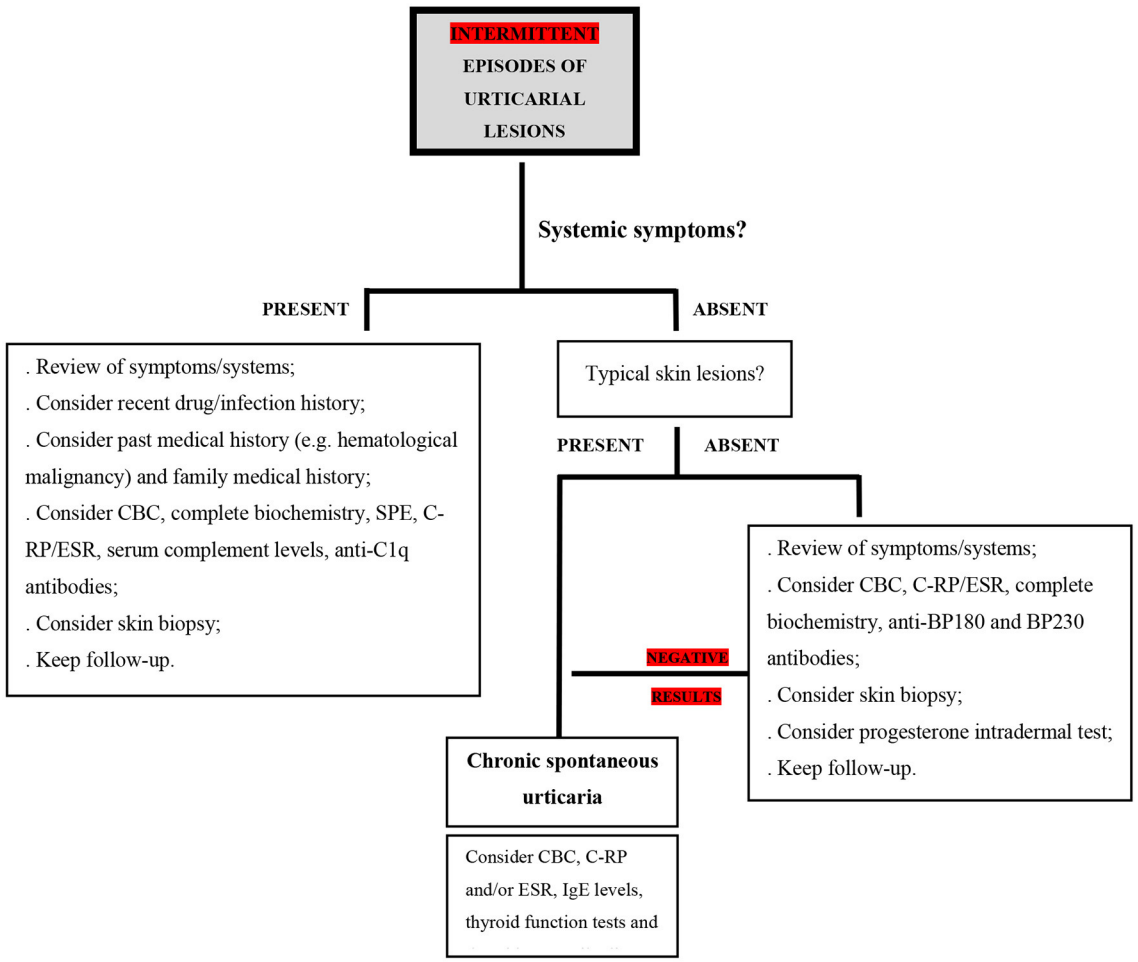

FIGURE 2 | Proposed diagnostic algorithm in the setting of intermittent urticarial lesions; CBC, complete blood count; C-RP, C-reactive protein; ESR, erythrocyte sedimentation rate; SPE, serum protein electrophoresis; IgE, immunoglobulin E; BP180, BP 230 - bullous pemphigoid antigens BP230 and BP180.

possibility that an urticarial rash is not urticaria but rather a systemic syndrome with urticaria-like skin lesions (7). Also, these need to be suspected in patients who are refractory to standard CU treatment (**Figure 2**).

Urticarial Vasculitis

Urticarial vasculitis (UV) is characterized by recurrent urticarial lesions that remain fixed for more than 24 h and have histopathologic findings of leukocytoclastic vasculitis (17). Skin lesions slowly change in size and shape, can be painful, and often resolve with bruising or post-inflammatory hyperpigmentation (18). UV can also present with angioedema, purpura, extracutaneous manifestations related to systemic vasculitis such as arthralgia, lymphadenopathy, abdominal pain, ocular and renal manifestations or dyspnea/cough. It is usually idiopathic, but it can be associated with drugs, infections, malignancy or autoimmunity (17, 19). The diagnosis is ultimately based on cutaneous histopathology, but suggested laboratory studies include a complete blood count, serum creatinine, C-reactive protein (C-RP), erythrocyte sedimentation rate (ESR), urinalysis, complement studies (C1q, C3, C4), anti-C1q antibody assays and tests for underlying connective tissue disease or viral infection. The levels of complement divide UV into normocomplementemic (NUV), hypocomplementemic (HUV) or hypocomplementemic urticarial vasculitis syndrome (HUVS) (19). About 80% of all UV patients have NUV (19) which can be difficult to distinguish, on a clinical or even histopathological level, from severe forms of CSU (20, 21). HUV and HUVS are the most severe forms of UV and are often associated with longer disease duration and underlying disorders (17). Anti-C1q antibodies are found in about 55% of HUV patients, but they are not specific and may be observed both in patients with primary and secondary vasculitis (18).

Hypereosinophilic Syndromes

Hypereosinophilic syndromes constitute a heterogeneous group of disorders, characterized by a persistent and marked blood eosinophilia for more than 6 months, associated with evidence of eosinophil-induced organ damage, in the absence of other causes of hypereosinophilia, e.g., parasitosis. Cutaneous manifestations

are common and nonspecific and generally consist of urticarial lesions, very itchy erythematous papules and nodules or eczematous lesions. Mucosal ulcerations are also possible (7). Cutaneous histopathology often shows dermal eosinophilic infiltration with typical flame figures.

Mast Cell Activation Syndrome

Mast cell activation syndrome (MCAS) is a recently described entity that may include primary (associated with clonality), secondary (a response to environmental triggers by normal mast cells) and idiopathic etiologies and can have cutaneous, gastrointestinal, cardiovascular, respiratory, and neurologic involvement. Cutaneous and subcutaneous manifestations include urticaria and angioedema that can be accompanied by anaphylaxis, flushing, nausea, vomiting, diarrhea, hypotension or tachycardia. MCAS remains a controversial diagnosis and has not been generally accepted. Some authors consider that the term MCAS should only be used in the idiopathic setting. However, some of the patients diagnosed with an idiopathic form are latter diagnosed with a clonal mast cell proliferative disease. Lastly, and even though some diagnostic criteria for MCAS have been proposed, this remains a complex topic and there are no definite diagnostic criteria identified (22).

Autoinflammatory Urticarial Syndromes

Autoinflammatory urticarial syndromes are rare and debilitating chronic diseases that can present with recurrent urticarial lesions with neutrophilic rich infiltrates on cutaneous histopathology, neutrophilic leukocytosis and elevated inflammation markers such as C-RP, ESR and serum amyloid A (SAA) (6, 18, 23). Lesions are usually flat erythematous wheals that last up to 24 h, are distributed mainly on the trunk and/or extremities and do not respond to H1-antihistamines. Pruritus may be absent, and lesions can be painful. These disorders are often diagnosed with a delay of several years (6) and may be hereditary or acquired. Cryopyrin-associated periodic syndromes are hereditary autoinflammatory diseases characterized by episodes of fever, urticaria-like rash, fatigue, headaches, arthralgia, arthritis, myalgia, sensorineural hearing loss, ocular inflammation, and/or bone lesions. They often manifest in early childhood. Inflammation is caused by an inappropriate activation of the innate immunity and overproduction of the proinflammatory cytokine interleukin-1 (18). Schnitzler syndrome is an acquired autoinflammatory disease that usually starts later in life and is characterized by recurrent fever, urticarial lesions, arthralgia, arthritis, myalgia, lymphadenopathy, hepatosplenomegaly and monoclonal gammopathy (mostly IgM class). About 15% of patients develop a lymphoproliferative disorder (23). Its pathophysiology remains unclear, but it is assumed to be IL-1 mediated (18, 23, 24). Anti-IL1 drugs can effectively control the disease but if left untreated, chronic inflammation may cause amyloidosis (18, 23). Adult-onset Still disease is a rare systemic inflammatory disease and usually manifests as a triad of high fever, arthralgia and an erythematous evanescent rash that accompanies the fever spike. Urticarial eruptions displaying neutrophilic infiltrates in histopathology occur in about 22% of the cases. IL-1 has also been implicated in its pathogenesis and, along with other acute inflammatory parameters, serum ferritin is usually significantly elevated. Neutrophilic urticarial dermatosis has also been reported as the presenting feature in systemic juvenile idiopathic arthritis, a closely related entity (25). Gleich syndrome (episodic angioedema with eosinophilia) is characterized by cyclic episodes of angioedema, wheals, fever, characteristic weight gain and dramatic eosinophilia (26).

If an autoinflammatory disease is suspected, testing for elevated inflammatory markers, serum protein electrophoresis to rule out monoclonal gammopathy in adults, urinalysis to screen for proteinuria due to secondary renal amyloidosis and skin biopsy to look for neutrophil-rich infiltrates are indicated. If a hereditary autoinflammatory disease is suspected, testing for mutations in the relevant genes should also be considered.

DIFFERENTIAL DIAGNOSIS OF ANGIOEDEMA WITHOUT WHEALS

Angioedema without wheals represents a distinct clinical pattern and evokes several differential diagnoses (**Table 2**). Early diagnosis is essential since effective treatment depends on the main subtype and the main mediator responsible for increased vascular permeability (26, 27).

Mast Cell-Mediated Angioedema

Mast cell-mediated angioedema is triggered by histamine and other mast cell mediators. It responds well to H1-antihistamines, glucocorticoids and adrenaline. Around 10% of CSU patients have angioedema without wheals (28) and in this setting, angioedema can last up to 72 h (6) and commonly starts on the head or neck in the early morning hours (27). Mast cell-mediated angioedema may also occur in acute urticaria or during anaphylaxis. IgE-independent mechanisms of mast cell activation may also be involved in angioedema caused by drugs such as vancomycin or fluoroquinolones *via* Mas-related G protein-coupled receptor X2 (MRGPRX2) or non-steroidal anti-inflammatory drugs *via* alterations in arachidonic acid metabolism.

Bradykinin-Mediated Angioedema

Bradykinin-mediated angioedema is triggered by bradykinin that promotes vasodilatation and increases vascular permeability. After phosphorylation of endothelial cadherins induced by bradykinin, adhesions between endothelial cells are opened, therefore causing plasma leakage with edema of the dermis and subcutis (angioedema), but no wheals. This type of angioedema responds poorly to standard CU medications, lasts up to 3–5 days and may cause a life-threatening swelling of the larynx and oropharynx and edema of gastrointestinal tract with occlusive symptoms, that often mimic a surgical abdominal emergency (27, 28).

Drugs, particularly angiotensin-converting enzyme inhibitors (ACEi) and less frequently angiotensin II receptor antagonists (ARA-II), dipeptidyl peptidase 4 (DPP-IV) inhibitors and sacubitril, involved in kinin degradation, have been associated with bradykinin-mediated angioedema (29). ACEi-associated angioedema is relatively common and may occur months, or even

TABLE 2 | Differential diagnosis in patients with angioedema.

Subtype of angioedema	Mast cell-dependent angioedema	Bradykinin-mediated angioedema			
		Hereditary		Non-hereditary	
		Types I – II	Normal C1-INH	Drug-induced	Acquired C1-INH deficiency
Associated urticaria	Frequent	No	No	No	No
Hereditary	No	Yes	Yes	No	No
Systemic symptoms	Not in CSU If acute, possible anaphylaxis	**Life-threatening oropharyngeal swellings Pseudo-occlusive abdominal crisis**			
Laboratory		Low C4, C1-INH	Genetic studies		Low C4, C1-INH
Culprits drugs/diseases	Possible NSAID, …	No	No	ACEi, ARA-II DPP-IVi sacubitril	Lymphoma Auto-immune diseases

C1-INH, complement component 1 esterase inhibitor; CSU, chronic spontaneous urticaria; C4, complement component 4; ACEi, angiotensin-converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; DPP-IVi, dipeptidyl peptidase 4 inhibitors; NSAID, non-steroidal anti-inflammatory drugs.

years, after onset of the drug. It usually resolves slowly after drug withdrawal, but some patients may have recurrent angioedema for months after ACEi withdrawal (30).

Hereditary Angioedema

Hereditary angioedema can begin early in life or only after adolescence/early adulthood and is mainly due to autosomal dominant mutations in C1 inhibitor (C1-IHN) gene. Quantitative or functional C1-INH deficiency is associated with consumption of complement (low C4), but also uncontrolled activation of kallikrein and kininogen, which results in bradykinin overproduction. Angioedema attacks occur either spontaneously or triggered by minor stimuli like trauma or stress and may be life-threatening. Hereditary angioedema can occur with normal C1-INH, due to mutations in other genes involved in bradykinin overproduction, e.g. factor XII (Hageman Factor), plasminogen gene, angiopoeitin-1 gene and kininogen-1 gene, but there are still many unclassified cases of hereditary angioedema (31). Angioedema due to acquired C1-INH deficiency is often accompanied by a lymphoproliferative or autoimmune disorder that leads to continuous activation of the classic complement pathway with consequent depletion of C1-INH (32). Any patient with recurrent angioedema without wheals nonresponsive to standard CU treatment, not taking ACE inhibitors, should be screened for complement deficiency. If C4 level is low, C1-INH quantification and function need to be determined (27).

Angioedema also needs to be distinguished from other conditions characterized by swellings, especially when standard angioedema treatments fails. Granulomatous cheilitis is characterized by intermittent lip swelling at an initial stage, followed by persistent swelling of the lips, occasionally extending to the face due to granulomatous inflammation of unknown cause (26). In cellulitis and erysipelas there is acute inflammation of dermal and subcutaneous tissue due to a bacterial infection and the area involved becomes bright red, swollen, painful and hot usually with high fever and accompanying systemic symptoms. Wells syndrome (eosinophilic cellulitis) presents with a swelling resembling cellulitis (11). Autoimmune hypothyroidism, dermatomyositis and Sjögren's syndrome may present with periorbital swelling resembling angioedema of the eyelids (26). Allergic contact dermatitis, particularly related with hair dye allergy, may be misdiagnosed as facial angioedema. Initial clinical differentiation from angioedema may be challenging, but the swelling in contact dermatitis slowly spreads in the direction of gravity and clinical signs reflecting epidermal changes, like vesicles, scale and crusting, are present and regress faster if treated with glucocorticoids. Patch testing is required to confirm hypersensitivity to *p*-phenylenediamine and related chemicals used in hair dyes (30). Photoallergy, either from exposure to systemic drugs or from contact with photoallergens (non-steroidal anti-inflammatory drugs or sunscreens) usually appears several hours to days after exposure. It presents as a dermatitis, sometimes with important edema, and can be misdiagnosed as angioedema (33).

CONCLUSION

A significant diagnostic challenge lies on the differentiation of common urticaria from urticarial syndromes or other dermatologic conditions that present with urticarial lesions and/or angioedema. Adding to the substantial value of a comprehensive clinical history and evaluation of skin lesions, skin biopsy, always supported by the clinician's perspective, may be of extreme value in these clinical settings. Looking for serum inflammatory parameters, like C-RP and ESR, leukocytosis, or other more clinically oriented biomarkers (C1q, C3, C4, ferritin, protein immunofixation, specific IgE, tryptase, ferritin) may also contribute to solve the puzzle of the differential diagnosis of urticarial lesions.

AUTHOR CONTRIBUTIONS

AM and MG contributed equally to manuscript writing. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Urticaria in Pregnancy and Lactation

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Chronic urticaria (CU) is a mast cell-driven chronic inflammatory disease with a female predominance. Since CU affects mostly females in reproductive age, pregnancy is an important aspect to consider in the context of this disease. Sex hormones affect mast cell (MC) biology, and the hormonal changes that come with pregnancy can modulate the course of chronic inflammatory conditions, and they often do. Also, pregnancy-associated changes in the immune system, including local adaptation of innate and adaptive immune responses and skewing of adaptive immunity toward a Th2/Treg profile have been linked to changes in the course of inflammatory diseases. As of now, little is known about the effects of pregnancy on CU and the outcomes of pregnancy in CU patients. Also, there are no real-life studies to show the safety of urticaria medications during pregnancy. The recent PREG-CU study provided the first insights on this and showed that CU improves during pregnancy in half of the patients, whereas it worsens in one-third; and two of five CU patients experience flare-ups of their CU during pregnancy. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for urticaria recommends adopting the same management strategy in pregnant and lactating CU patients; starting treatment with standard doses of second-generation (non-sedative) H1 antihistamines, to increase the dose up to 4-folds in case of no response, and to add omalizumab in antihistamine-refractory patients; but also emphasizes the lack of evidence-based information on the safety and efficacy of urticaria treatments during pregnancy. The PREG-CU study assessed treatments and their outcomes during pregnancy. Here, we review the reported effects of sex hormones and pregnancy-specific immunological changes on urticaria, we discuss the impact of pregnancy on urticaria, and we provide information and guidance on the management of urticaria during pregnancy and lactation.

Keywords: urticaria, pregnancy, lactation, treatment, autoimmunity, immunological changes, mast cells, hormones

INTRODUCTION

Chronic urticaria (CU) is a chronic inflammatory disorder, which presents with the sudden and unpredictable appearance of wheals, angioedema, or both for longer than 6 weeks (1). CU is a female dominant disease with a higher diagnosed incidence (0.18 vs. 0.11%) and prevalence (0.62 vs. 0.37%) of females vs. males (2). Recently a meta-analysis showed that chronic spontaneous urticaria (CSU) has a point prevalence of 1.3 and 0.8% in women vs. men and chronic inducible urticaria (CIndU) shows a female: male ratio of 2:1 to 3:1 (3). From the results of the recent AWARE study, which focused on worldwide management patterns of antihistamine-refractory CU, it is also clear that rates of female CU are higher than those of males, i.e., 72% for CSU and 69.8% for CIndU (4). CU is not only more common in females but also more severe, with higher rates of high disease activity, angioedema, poor prognosis, refractoriness to treatment, and longer disease course (5–9). The lack of female predominance in children younger than 15 years (3) suggests a disease-modifying role for female hormones in CU. Female sex hormones can influence inflammatory diseases including autoimmune conditions in many different aspects. They are considered risk factors of disease onset and are held to contribute to the activity and progression of autoimmune diseases (10, 11).

From the clinical experience, change in hormone levels, for example across menstrual cycle or during pregnancy, with the onset of menopause, or as a result of using hormonal contraceptives or hormone replacement therapy, some changes in disease activity might be observed. Further, because CU affects mostly women in reproductive age, it is important to understand the consequences of hormonal changes within the menstrual cycle, because of hormonal contraception and during pregnancy for CU disease course and severity. Robust data on this is scarce, but a recent multicenter study revealed that CU tends to improve during pregnancy in half of the patients and worsen in one third of them (**Figure 1**). Worsening of urticaria was associated with having a mild disease before pregnancy and not being on treatment before pregnancy (12). These findings stress the importance of proper clinical and laboratory diagnosis as well as treatment of CU for patients willing to get pregnant and also a personalized follow-up during pregnancy. Therefore, optimal management of urticaria during pregnancy is vital to ensure the best outcome for the mother and the baby, however, medications' potential risks must be balanced against the consequences of untreated disease.

In this review, we are going to focus on the effect of sex hormones on urticaria, disease activity changes during

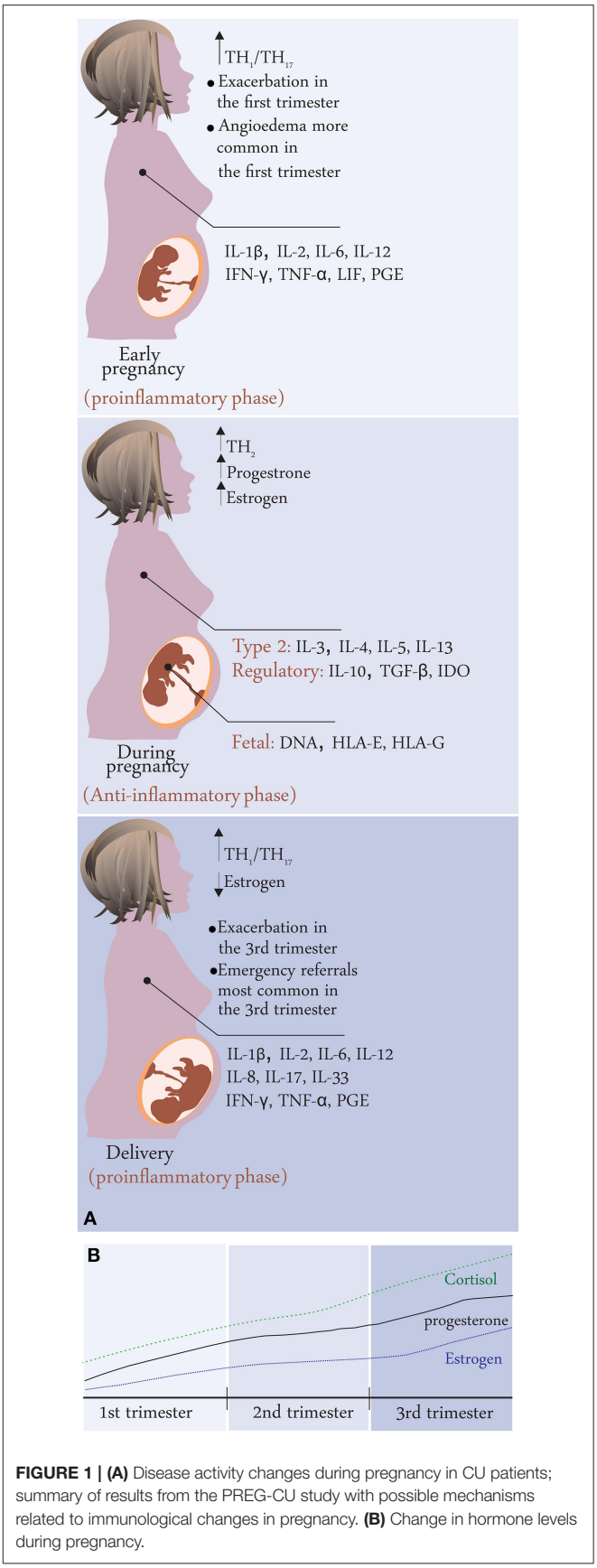

FIGURE 1 | (A) Disease activity changes during pregnancy in CU patients; summary of results from the PREG-CU study with possible mechanisms related to immunological changes in pregnancy. **(B)** Change in hormone levels during pregnancy.

Abbreviations: AAbs, Asymmetric antibodies; AFP, Alpha-fetoprotein; AH, Antihistamine; APCs, Antigen-presenting cells; ASST, Autologous serum skin test; Breg, Regulatory B-cells; CIndU, Chronic inducible urticaria; CSU, Chronic spontaneous urticaria; CU, Chronic urticaria; DCs, Dendritic cells; ERs, Estrogen receptors; FDA, Food and drug administration; Foxp3, Fork head box protein 3; GCs, Glucocorticosteroids; hCG, Human chorionic gonadotrophin; LIF, Leukemia inhibitory factor; MCs, Mast cells; NK cells, Natural killer cells; PIBF, Progesterone-induced blocking factor; PLLR, Pregnancy and lactation labeling rule; PRs, P4 receptors (progesterone receptors); TLR, Toll-like receptor; TPO, Thyroid peroxidase; Tregs, Regulatory T-cells; uMCs, Uterine mast cells; VEGF, Vascular endothelial-derived growth factor; MMP, Matrix metalloproteinase.

pregnancy, and management of urticaria during pregnancy and lactation.

HORMONAL AND IMMUNOLOGICAL CHANGES DURING PREGNANCY

A number of important hormonal changes that modulate the immunological milieu take place during pregnancy. Some of these changes may influence CU during this period as highlighted below.

Hormonal Changes

In addition to the emergence of the pregnancy-specific hormone human chorionic gonadotrophin (hCG), several other hormones are upregulated during pregnancy such as progesterone (P4), estrogens, cortisol, prolactin, leptin, vitamin D, and alpha-fetoprotein (AFP).

HCG is a placental glycoprotein hormone, that appears first during pregnancy and serves as pregnancy confirmation, peaks during the 9th−12th week of pregnancy, followed by a gradual decline until delivery, even though hCG levels during pregnancy remain high. Its major function is to maintain P4 synthesis by the corpus luteum (13). HCG promotes maternal immune tolerance and helps to ensure fetal survival (14). The hormone is able to convert naïve T cells into regulatory T cells (Treg) (15); can modulate dendritic cells (DCs) into tolerogenic antigen-presenting cells (APCs) (16, 17) and stimulate IL-10 production by B cells (18). HCG application was shown to *in vivo* boost the number of Treg cells and prevent abortion in mice (14) and is also injected intrauterine in IVF protocols for women with a history or implantation failure (19).

Progesterone (P4), is a member of the steroid hormone family and plays a crucial role in maintaining pregnancy, in addition to HCG (14). During the initial stages, it is secreted by the corpus luteum and, later on, by the placenta. P4 modulates the immune system *via* intracellular P4 receptors (PR) expressed by epithelial cells, eosinophils, macrophages, lymphocytes MCs, and DCs (20), and by the upregulation of progesterone-induced blocking factor (PIBF) and glycodelin A (a cell-surface glycoprotein expressed in endometrium/decidua, amniotic fluid, and maternal serum, with immunosuppressive properties) (14). P4 contributes to gestational tolerance by suppressing innate immunity *via* different mechanisms such as blocking the cytolytic action of NK cells, inducing tolerogenic DCs, and promoting Th2 polarization by preferential apoptosis of Th1 subset and increasing Th2 cytokine production (20, 21). Furthermore, P4 stimulates Treg cells by inducing Fork Head Box Protein 3 (FoxP3) expression in naïve T-cells at the feto-maternal interface, in murine pregnancies (21). P4 plays a crucial role in maintaining gestational tolerance by suppressing innate immunity and promoting Th2 polarization (20). The maternal P4 level continues to rise until about 10–12 weeks of gestation (corpus luteum), then returns to its baseline level and again starts to rise around the 32nd week of pregnancy (2nd peak-secreted by the placenta) to be maintained until conception (22). P4 levels drop during lactation (23). Occasionally, CSU-like cutaneous eruption has been reported due to excess serum P4, called progesterone hypersensitivity. The reasons for increased serum P4 include pregnancy or exposure to exogenous progesterone or increased level during the menstrual cycle (luteal phase; 3–10 days before the onset of menstruation) (24).

Estrogens, also belonging to the steroid hormone family, are of three major types, estrone (E1), estradiol (E2), and estriol (E3). Among them, E2 constitutes the major fraction in reproductive females (both pregnant and non-pregnant) and accounts for most of the classic estrogenic-induced effects. In contrast, E3 is exclusively secreted in pregnant females, by the fetoplacental unit, and comprises almost 90% of the pregnancy estrogen (20). During pregnancy, estrogen levels rise steadily until delivery due to placental secretion. Estrogens act *via* estrogen receptors (ERs) expressed by B and T lymphocytes, macrophages, and DCs and affect both innate and acquired immunity (14). It is generally accepted that estrogens play a role in the development of adaptive immunity such that low levels of estrogen promote pathogenic Th1/Th17 pathway while high levels (as during pregnancy) promote Th2/Treg responses. E3 downregulates innate immunity by programming DCs to become tolerogenic and anti-inflammatory (23). Many researchers have depicted the harmful role of exogenous estrogen mimickers, called endocrine-disrupting chemicals (EDCs), which act by disrupting the endocrine milieu. These substances are present in several daily use products such as plastic water bottles or food containers, which may be systemically absorbed by ingestion. Recently, the negative impact of EDCs, particularly Bisphenol A and phthalates, is being recognized on human pregnancy and fetal development by interfering with the developing embryonic epigenome (24). Rarely, premenstrual urticarial eruption has been reported in women with estrogen hypersensitivity. In such cases, removal of the exogenous estrogen results in remission e.g., discontinuation of estrogen-containing oral contraceptives or use of estrogen antagonists (leuprolide or tamoxifen) (25).

Cortisol, synthesized in the adrenal cortex and released into circulation after various physical and psychological stimuli; has strong anti-inflammatory effects. During pregnancy, maternal cortisol levels rise continuously to facilitate fetal development, followed by an abrupt drop post-partum (26). Cortisol exerts its anti-inflammatory effect by multiple pathways such as reducing the circulating levels of pro-inflammatory cytokines such as IL-2, IL-3, IL-6, IFN-γ, and TNF-α, activating tolerogenic Treg cells by enhancing the expression of high-affinity IL-2 receptor (CD25), inducing the apoptosis of T cells, and reducing the number of B cells in spleen and lymph nodes, thereby reducing IgG production (23). These effects may explain, in part, the improvement of some immunological disorders during pregnancy.

Prolactin, a polypeptide hormone, is largely produced by the lactotrophic cells of the pituitary gland and several extra-pituitary sources like mammary epithelium, ovaries, and placenta, under the influence of dopamine. Prolactin levels increase slightly during gestation with exponential rise during delivery and lactation, contrasting the abrupt reduction of sex hormones (E2, E3, and P4) post-delivery (27). Prolactin stimulates the immune system and causes aberrant activation by aiding the maturation

of naïve Th0 cells to effector CD4 and CD8 cells, impairing the clonal deletion of auto-reactive B cells, and reducing the threshold for activating anergic B cells. Thus, hyperprolactinemia has been associated with several autoimmune disorders and might explain disease flare or relapse during breastfeeding (28). The effects of prolactin on CU during pregnancy remain largely unexplored, but Sabry et al. (29) reported significantly higher serum prolactin levels in a subset of CU patients (positive autologous serum skin test, ASST) and its association with disease severity. In contrast, Soliman et al. (30) did not find any relationship between serum prolactin levels and urticaria activity.

Leptin, secreted by adipocytes, primarily regulates energy metabolism, but its impact on the immune system is increasingly being recognized. Leptin promotes inflammatory responses by activating the JAK-STAT, PI3K, and MAPK pathways as its receptor mimics the IL-6 receptor (31). A recent review has highlighted the cross-talk between mast cells and adipocytes in certain situations like obesity, where adipose tissue-resident MCs release pro-inflammatory cytokines like TNF-α, under the influence of leptin, and worsen the inflammatory state (32). During pregnancy, leptin levels rise to counter the hypermetabolic state and modulate the feto-maternal immune system. The recent findings that the placenta is a relevant source of leptin and its trophoblastic effects further strengthen this view (33). Several authors have reported higher serum levels of leptin in patients with CU (34, 35), but, as of yet, pregnant CU patients have not been studied.

Vitamin D, a steroid hormone, plays an important role in modulating the immune system during pregnancy. The placenta is one of the major sites of extra-renal vitamin D synthesis and produces considerable amounts during pregnancy. Vitamin D promotes antibacterial innate immune responses and suppresses inflammatory adaptive immunity *via* negative effects on NK cells, T, and B cells (36). The effect on T-cells include a shift from Th1 to Th2 phenotype, *in vitro* suppression of Th17 axis and IL-17 secretion, and inducing the conversion of naïve T-cells into tolerogenic Treg cells, while antibody production by B-cells is suppressed by inhibiting the differentiation of plasma cells and memory cells (23). Furthermore, placental vitamin D contributes to the development of localized fetal-maternal immune tolerance (37). Vitamin D deficiency may negatively affect several immune-mediated disorders, such as psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, tuberculosis, sepsis, and systemic lupus erythematosus (23, 38). A recent systematic review concluded that adult patients with CU are at a higher risk of developing Vitamin D deficiency, and its supplementation may provide therapeutic benefit in this subset (39).

Alpha-fetoprotein (AFP) is another pregnancy-specific glycoprotein hormone secreted by the yolk sac and fetal liver. This hormone peaks between weeks 12 and 16 of pregnancy, and gradually declines thereafter. AFP may have immune regulatory effects, but conclusive evidence is lacking (40).

Immunological Changes

The human immune system is designed to recognize and eradicate possibly harmful foreign, i.e., non-self antigens. During pregnancy, paternal antigens that are expressed by the fetus are recognized as foreign, but the maternal immune system protects the fetus through several immunological changes briefly discussed here.

Changes in Innate Immunity

Innate immunity refers to the inborn, non-specific, immediate host defense against any antigen, which does not require a previous sensitization. During pregnancy, the innate immune system and its effector cells change considerably, and this adaptation is important rather locally, primarily aimed at uterine vascular remodeling for fetal development. Among the various components of innate immunity, uterine NK cells (uNK) constitute the most important population. The important changes pertaining to innate immunity are briefly discussed below.

Dendritic Cells

Dendritic cells (DCs) are vital APCs and act as a conduit between innate and adaptive immunity. During pregnancy, P4, E2, and hCG stimulate most of the uterine/decidual DCs to become tolerogenic and secrete the anti-inflammatory cytokine IL-10, thus creating a favorable local environment for the growing fetus (14). This is supported by a study by Segerer et al. (41) and Wan et al. (42), who reported significant up-regulation of IL-10 secretion by human DCs when stimulated *in vitro* by pregnancy hormones. Additionally, sex hormone-primed decidual DCs demonstrate impaired up-regulation of MHC-II and other co-stimulatory molecules, thereby reducing their ability to secrete proinflammatory cytokines (43). Interestingly, these effects are restricted to uterine DCs expressing sex-hormone receptors, whereas bone marrow or spleen-derived DCs are spared, which may possibly explain how the pregnant immune system tolerates a semi-allogenic fetus while protecting it from infections at the same time. The exact mechanism of this selective sparing remains unclear, but it reinforces the pleiotropic nature of DCs and their alluring ability to respond depending on the situation (44).

Monocytes/Macrophages/Neutrophils

Monocytes or macrophages, also important APCs, contribute to immune responses by phagocytosis and the production of cytokines. Decidual CD14+ monocytes secrete anti-inflammatory cytokines such as IL-10 and TGF-β and become tolerogenic under the influence of galectin-1 and macrophage inhibitory protein-1 (45). Uterine decidual macrophages also demonstrate prominent anti-inflammatory polarization during pregnancy, under the influence of Th2 cytokines (IL-4, IL-5, IL-10, IL-13) and high glucocorticoid concentrations, with converting from an inflammatory M1 phenotype to a non-inflammatory M2 phenotype (46). P4 further inhibits toll-like receptor (TLR)-4 mediated activation of macrophages, thereby suppressing innate immune response to prevent fetal rejection during normal pregnancy (47).

Mast Cells

The rising level of estrogen during pregnancy activates uterine mast cells (uMCs) *via* estradiol receptors, and they promote their degranulation to release histamine, which aids proper blastocyst

implantation (by tissue remodeling) and placental development (48). The pro-secretory role of estrogen is further confirmed as specific ER antagonist tamoxifen inhibits MC degranulation both *in vitro* and *in vivo* (49). Elevated histamine levels also induce pregnant myometrial contractions *in-vivo*, and this may possibly explain the increased number of pre-term deliveries reported in females with systemic mastocytosis (50).

During pregnancy, the number of uMCs increases, and there is a shift from tryptase and chymase positive MCs (MC_{TC}) to only tryptase positive (MC_T) phenotype (48). These MC proteases (tryptase and chymase) activate matrix metalloproteinase (MMP)2 and MMP9 to mediate extracellular matrix degradation and facilitate delivery (51). Interestingly, the role of MCs in delivery is further corroborated by significant rise of pre-term deliveries in women with asthma, another MC-mediated disorder (52). Besides histamine and proteases, uMCs also release VEGF and galectin-1 (a glycan-binding protein), which support uterine neovascularization, fetal spinal artery (SA) remodeling; and placental development, fetal growth, respectively, (51, 53). uMCs collaborate with uNKs for SA remodeling, as evidenced by worsened SA remodeling in the simultaneous absence of both cell lines, compared to isolated deficiency (54). Recent evidence suggests that Mcpt5, secreted by uMCs and uNKs, is essential for proper SA remodeling in pregnant mice (55). Additionally, MCs secrete pro-inflammatory cytokines (IL-2, IL-12, TNF-α, and IFN-γ) in the early and late stages of pregnancy, and anti-inflammatory cytokines (IL-4, IL-10) during mid-pregnancy, to maintain the Th1 and Th2 dynamics during early/late and mid-pregnancy, respectively, necessary for a successful outcome (48). In addition to sex hormones, regulatory T-cells (Tregs) also promote IL-9 mediated proliferation of uMCs and angiogenesis at the murine feto-maternal interface to prevent early abortion (41, 56). Thus, there is a complex interplay between MCs, sex hormones, and immune cells during pregnancy, which may influence urticaria, as it is primarily a MC-mediated disorder.

Natural Killer Cells

NK cells, specifically the uterine variant (uNKs) constitute the major fraction of uterus lymphocytes in early pregnancy (∼70%) and are responsible for maternal uterine vasculature remodeling and fetal survival (14). uNK cells differ from peripheral NK both structurally (differential expression of genes and receptor repertoire) and functionally (uNKs have lower cytotoxic activity compared to peripheral NKs) (14) Thus, the major function of uNKs is uterine vasculature remodeling and spinal artery formation, mediated primarily by the proangiogenic factor VEGF (57). Additionally, these cells secrete IFN-γ, a prominent anti-viral cytokine for fetal protection (58). However, there is confusion regarding the origin of uNK cells- whether they are recruited from peripheral NK cells into uterus, or they expand *in-situ* after pregnancy is established (14). Decidual NK cells increase in number under the influence of P4, IL-15, TGF-β, and stem-cell factor (SCF). P4 also promotes uNK cell recruitment in the pregnant uterus *via* secretion of osteopontin (59). Notably, a recent study has highlighted the role of decidual stromal cells in uNK proliferation in early pregnancy, by secreting IL-24, in an autocrine fashion (60).

Cytokines

Cytokines are polypeptides secreted by both innate and adaptive immune cells, which maintain a particular microenvironment, e.g., inflammatory or tolerogenic. The feto-maternal interface demonstrates a pro-inflammatory cytokine profile [IFN-γ, TNF-α, IL-1, IL-6, 1L-17, and the IL-6 family leukemia inhibitory factor (LIF)] during implantation and delivery, and an anti-inflammatory/tolerogenic profile (IL-10 and TGF-β) during the 2nd and 3rd trimester (61).

Changes in Adaptive Immunity

Adaptive immunity refers to the acquired and specific host defense system against previously exposed antigens, primarily involving T and B lymphocytes.

T Lymphocytes

Normal pregnancy reflects a pro-inflammatory Th1/Th17 profile at its early and late stages, essential for fetal implantation and onset of labor, respectively. Major adaptation occurs mid-gestation, involving a shift from the pro-inflammatoryTh1/Th17 spectrum toward Th2 immunity, thus creating a tolerogenic environment to ensure the survival of the semi-allogenic fetus (14, 23). E2 plays a major role in skewing immunity toward Th2 at the fetal-maternal interface along with depressing the inflammatory Th1 axis (20).

Although a conspicuous Th2 immunological shift occurs during pregnancy, absolute dominance of Th2 cytokines does not occur as evidenced by successful pregnancies in mice deficient in Th2 cytokines such as IL-4,5,9, and 13 (62). Recently, researchers have demonstrated up-regulation of soluble receptor antagonists of pro-inflammatory cytokines such as soluble IL-6 Ra, TNFRA and IL-1Ra, and expansion of Treg cells, in addition to Th2 cytokines, in healthy human pregnancies (63).

Apart from conventional T cells, CD4+ Treg cells are also involved in creating an anti-inflammatory milieu by "regulating/depressing" the immune system *via* cytokines like IL-10 and TGF-β and inhibition of decidual effector T-cells by silencing their chemokine genes. The concentration of Treg cells fluctuates during pregnancy and reaches its peak in mid-gestation, under the influence of P4, E2, and fetal antigens, to suppress the maternal immune system and prevent fetal rejection. The important contribution of Treg cells (CD4+CD25+) is further corroborated by worse pregnancy outcomes in their absence (64). A healthy pregnant uterus demonstrates increased endometrial expression of Foxp3, the major transcription factor of Treg cells, and its reduced expression has been associated with infertility (65). In addition to Treg cells, γδ T-cells (a minor fraction accounting for <5% of circulating T-lymphocytes) also increase in the feto-maternal interface and contribute to the local anti-inflammatory state by secreting IL-10, TGF-β, and PIBF (63).

B Lymphocytes

B lymphocytes are classically associated with antibody production; however, they also perform other roles such as

antigen presentation and modulation of T-cell function. Notably, two types of antibodies (Abs) are produced- natural antibodies (autoreactive and cause autoimmune diseases- harmful for pregnancy) and asymmetric antibodies (AAbs) (needed for a successful pregnancy by reducing alloreactive responses). In normal pregnancy, natural Ab significantly reduces during the 3rd trimester to induce labor, while AAbs remain elevated during the entire pregnancy. Serum hCG regulates natural Ab production, while AAbs are controlled by P4 (66, 67).

Similar to Treg cells, Breg cells also increase during pregnancy, under the influence of hCG. These cells secrete IL-10 and inhibit Ab production by the B-cells, thus minimizing the chance of autoimmune disorders and graft (fetus) rejection (68).

Other Changes

Pregnancy-induced immunologic tolerance may increase maternal susceptibility toward various bacterial and viral infections. These infections might trigger inflammation and tissue destruction and stimulate auto-reactive T cells as a "bystander phenomenon", and possibly worsen some autoimmune disorders (69).

Another interesting consequence of this altered immune status is the maternal gut microbiome remodeling, characterized by expansion of *Enterobacteriaceae* sp., which may facilitate metabolic and immunological adjustments for a successful pregnancy outcome (70). Although several authors have reported an association between chronic urticaria and gut microbial dysbiosis, studies are lacking in pregnant women (71, 72).

Recently, the concept of feto-maternal microchimerism has gained importance, which states that the maternal immune system acquires a state of immunological tolerance by means of transplacental feto-maternal cross-talk (transfer of genetically heterogeneous fetal material into maternal circulation) (63). Triche et al. (73) have shown HLA disparity between a mother and fetus is essential for a normal pregnancy, while feto-maternal HLA matching (class I and class II) has resulted in spontaneous abortion and pre-eclampsia.

The hormonal and immunological changes during pregnancy are summarized in **Table 1** and **Figures 2**, **3**.

DISEASE ACTIVITY CHANGES DURING PREGNANCY

During pregnancy, disease activity of chronic inflammatory disorders are subject to change due to the changes in immune responses such as decrease in Th1-type and Th17-type cytokines (that promote allograft rejection and may compromise pregnancy), increase in Th2-type cytokines (that inhibit the Th1 responses, promote allograft tolerance and therefore may improve pregnancy success) as well as an increase in T reg cells which dampen all the T helper responses and provides tolerance for fetal alloantigens and could induce fetoallograft tolerance through the production of IL-10 and TGF-β (75–77). As a result, Th2-type autoimmune disease get worsen and Th1/Th17-type autoimmune disease improve; i.e., rheumatoid arthritis (RA), multiple sclerosis, Graves' disease, and Hashimoto thyroiditis improve while systemic lupus erythematosus (SLE) and systemic sclerosis (SS) worsen during pregnancy (75). A favorable Treg–TH17 balance, the reduction in pro-inflammatory γδ T cells, and an increase in the soluble receptors that buffer the biological effects of TNF and IL-1 have been suggested to be the leading factors that contribute to pregnancy-related improvement of RA (63, 78, 79). Contrary to improvement in RA, lupus has been reported to deteriorate during pregnancy; however, the renal and skin lupus are differently affected by pregnancy; lupus nephritis deteriorates while skin lupus ameliorates during pregnancy. The worsened kidney function has been reported to be associated with renal inflammation and higher IFN-γ and IL-10 levels in the kidneys. IFN-γ by stimulating secretion of IgG antibodies and IL-10 by inducing B-cells to produce autoantibodies, which finally result in increased glomerular IgG deposition (80). In contrast, IL-10 was found to be increased and IFN-γ was decreased in the skin lesions of multiparous lupus-prone mice highlighting the role of IL-10 as a suppressor on skin lupus by possibly suppressing T-lymphocyte driven autoimmunity (81).

On the other hand, due to the increase in Th2 immune responses, an increased disease activity is anticipated in allergic disorders. That is, asthma exacerbations have been reported to range from 13 to 52% during pregnancy and most exacerbations occur in the second or beginning of the third trimester (82). Atopic dermatitis worsened during pregnancy in 52% in one study which also reported that most of the worsening occurred by 20 weeks of gestation (83) and in 61.0% in another (84).

Although CU is a very common and female-dominant disease that favors the reproductive age group, there is only one study that evaluates the effects of pregnancy on CU or the effects of CU on pregnancy outcomes, which is performed by the UCARE network (12, 85). In this study, 288 pregnant patients with CU from 21 centers/13 countries were asked to answer an a-47-item questionnaire which included questions on the exacerbations, angioedema attacks, emergency referrals, the overall course of CU during pregnancy, the course of urticaria after giving birth as well treatments before and during pregnancy, outcomes of pregnancy, and treatments given during breastfeeding. The study included both CSU and CIndU patients (CSU 66.9%, CIndU 12.8%, CSU + CIndU 20.3%) who experienced pregnancy within the last 3 years, and whose CU started before pregnancy (**Figure 4**). Disease activity before pregnancy was almost equally distributed among the patients (35.7% reported their disease activity as mild, 34.2% as moderate, and 29.7% as severe before pregnancy, respectively). Of 288 patients, 51% rated their CU as improved, 29% as worse, and 20% as unchanged during pregnancy. Two in five (43.5%) experienced acute CU exacerbations during pregnancy which most commonly occurred exclusively in the 3rd trimester (27.6%) or the 1st trimester (22.8%). Emergency referrals for CU were also most common in the 3rd trimester and angioedema occurrence was most common in the first trimester. The reason for the increase of disease activity during the first and third trimesters was explained by the predomination of Th1 immune responses and pro-inflammatory signals that promote MC activation in CU patients.

TABLE 1 | Hormonal and immunological changes during pregnancy.

Name of hormone/type of immunity	Change during pregnancy	Role
Progesterone (P4)	The maternal progesterone level continues to rise till about 10–12 weeks of gestation (corpus luteum), then returns to its baseline level and again starts to rise around the 32nd week of pregnancy (2nd peak-secreted by placenta) to be maintained until conception	P4 plays a crucial role in maintaining gestational tolerance by suppressing innate immunity and skewing the adaptive immunity toward the anti-inflammatory Th2 axis (20)
Estrogens	Estrogen concentration rises continuously until term, as it is primarily secreted by the fetoplacental unit	High concentration (as during pregnancy) favors the anti-inflammatory Th2/Treg responses (c.f. low concentration promotes the inflammatory Th1/Th17 pathway). It further depresses the innate immunity by programming DCs to become tolerogenic and anti-inflammatory (23)
Cortisol	The cortisol level maintains a steady rise during pregnancy and drops abruptly post-delivery	It exerts its anti-inflammatory effect by several modalities- reducing the levels of pro-inflammatory cytokines in circulation, activating tolerogenic Treg cells, inducing apoptosis of effector T-cells, and reducing the number of antibody-secreting B-cells (74)
Prolactin	Prolactin concentration slightly increases during gestation with the exponential rise during delivery and lactation period (c.f, sex hormones abruptly reduce after delivery). Secreted by the pituitary gland	It stimulates the immune system and causes its aberrant activation, and is associated with several autoimmune disorders (28)
Leptin	Its concentration rises to counter the hyper-metabolic state during pregnancy. Placenta is the 2nd source of leptin after adipose tissue	This hormone acts as a pro-inflammatory cytokine by activating the JAK-STAT, PI3K, and MAPK pathways (31)
Vitamin D	Placenta acts as the major extra-renal source of Vitamin D during pregnancy	Acts as an immunomodulator by promoting antibacterial innate immunity and suppressing inflammatory adaptive immunity (23)
HCG	Secreted by the placenta, its level peaks from 9th to 12th week, followed by a gradual decline until delivery	Its major role is stimulating the corpus luteum to secrete P4 (up to 10th/12th week). May have additional role in promoting maternal tolerance to ensure fetal survival (14)
AFP	Secreted by the yolk sac and fetal liver, this hormone peaks between 12 and 16 weeks, and gradually decline subsequently	Immunoregulatory role is currently under research (40)
Innate immunity	Uterine/decidual DCs secrete more IL-10 (anti-inflammatory cytokine)	Uterine DCs (professional APCs) become more tolerogenic and create a favorable local environment for the survival of the semi-allogenic fetus (14).
	Decidual CD14+ monocytes secrete more IL-10 and TGF-β. Macrophages change phenotypes from pro-inflammatory M1 to anti-inflammatory M2	A local (uterine) anti-inflammatory milieu is created, which facilitates the survival of fetus and prevents its rejection by hostile maternal immunity (46).
	Activation and degranulation of mast cells under influence of sex hormones	Histamine, released from MCs is necessary for fetal implantation and placental development. It may have a role in pregnancy CSU as histamine is its primary mediator (48). Additionally, VEGF secreted by uMCs aid in uterine vascular remodeling and fetal spinal artery development (14).
	Decidual NK cells increase in number and secrete VEGF (pro-angiogenic factor) and IFN-γ (anti-viral cytokine).	Plays an important role in the development of placenta, uterine vascular remodeling, and spinal artery formation. Additionally, protects the growing fetus from viral infections (14).
	Pro-inflammatory cytokines (IL-6 IL-1, TNF-α, IFN-γ, LIF) increase during 1st trimester and term, while anti-inflammatory cytokines (TGF-β, IL-10) predominate during 2nd and 3rd trimesters	Pro-inflammatory cytokines are necessary for fetal implantation and delivery, while anti-inflammatory cytokines (mid-gestation) create a tolerogenic local environment for the survival of semi-allogenic fetus (61)
Adaptive immunity	Pro-inflammatory Th1/Th17 profile (early and late stages) shifts toward anti-inflammatory Th2/treg axis (midgestation)	Early and late inflammatory milieu necessary for fetal implantation and labor, respectively. Midgestation anti-inflammatory tolerogenic profile ensures the survival of non-self fetus in the hostile maternal environment (14)
	Increase in CD4+ Treg cells and γδ T-cells at the feto-maternal interface, which peak during mid-gestation	These cells further suppress local adaptive immunity by secreting anti-inflammatory IL-10, TGF-β, and PIBF, to ensure fetal survival and prevent its rejection (63)
	Natural ABs (auto-reactive and harmful for pregnancy) significantly reduce during 3rd trimester, while asymmetric Abs (beneficial for pregnancy) remain elevated through pregnancy.	Drop in natural Abs induce labor and delivery, while asymmetric Abs protect the fetus by mitigating alloreactive responses (66)
	Regulatory B-cells (Breg) increase in number, under the influence of hCG	Secretion of anti-inflammatory IL-10 and reducing Ab production by B-cells, thus reducing the chance of fetal rejection and autoimmune disorders (68)

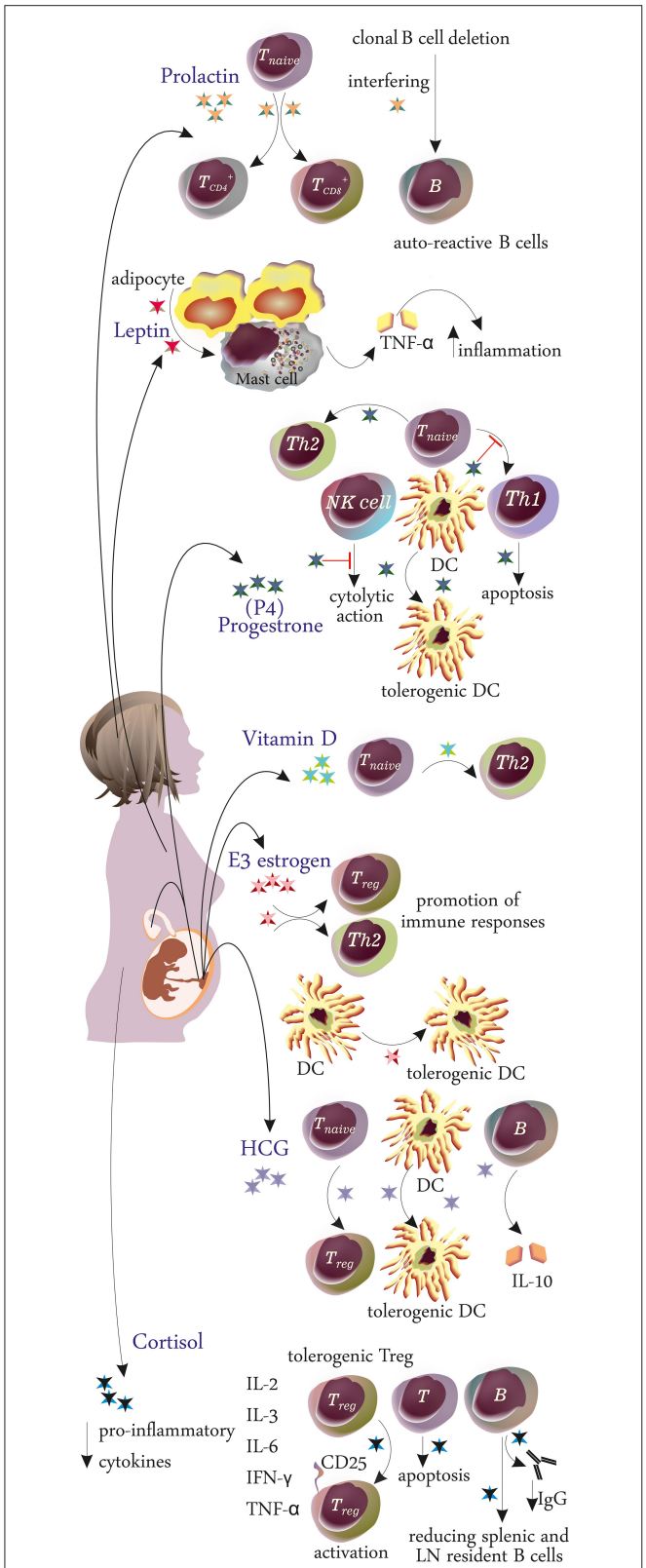

FIGURE 2 | Effects of various hormonal changes on the immune system during pregnancy.

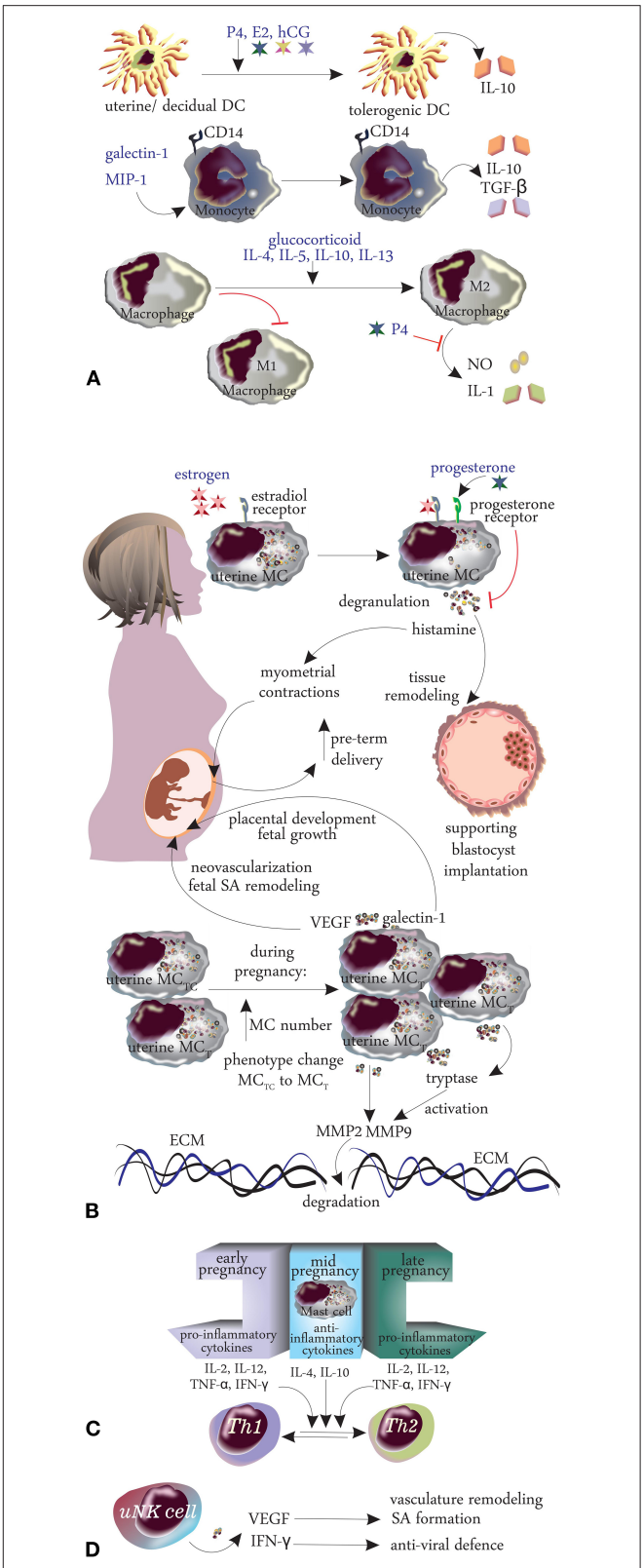

FIGURE 3 | Changes in innate immunity during pregnancy. **(A)** Dendritic cells, monocytes, macrophages, mast cells. **(B)** Cytokines. **(C)** TH1/TH2 shift. **(D)** Natural killer cells.

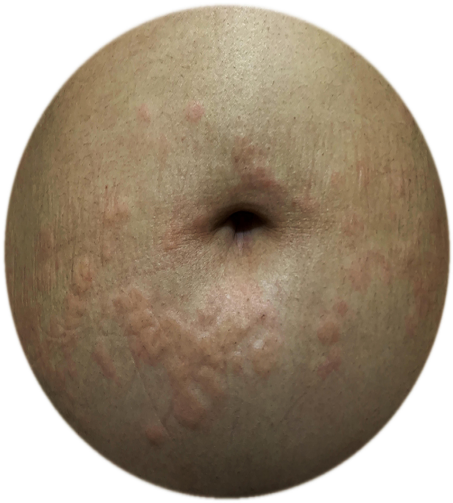

FIGURE 4 | A pregnant CU patient with exacerbation of urticaria in the third trimester; urticarial plaques around the umbilicus.

These results were found similar to pregnant patients with mastocytosis who also showed exacerbation during the 1st or 3rd trimester (48).

The rate of emergency referrals (9.8%) and rate of angioedema (17.4%) during pregnancy were lower than the reported rates in non-pregnant CU patients (compared to 14.8 and 33.5%; and 40.3 and 45% in ASSURE and AWARE studies, respectively) (86, 87).

While the risk factors determined in the univariate analysis for CU worsening during pregnancy were having no angioedema and having mild disease activity before pregnancy, receiving no treatment before pregnancy, receiving treatment during pregnancy, having CIndU, worsening of CU during the previous pregnancy; after adjusting for cofounders, having mild disease before pregnancy and receiving treatment during pregnancy were left as the relevant risk factors for CU worsening during pregnancy.

After delivery, half of the patients (50%) whose urticaria improved during pregnancy reported worsening of CU after giving birth, while half (52%) with worsening of CU during pregnancy showed no change in their CU activity after giving birth. As an explanation to disease activity changes after birth, the authors proposed that the subsiding of Th2 skewing in the post-partum period results in the worsening of Th1 and Th17 autoimmune disorders and improvement in Th2-driven disorders (75) and concluded that CU patients with a dominant immune profile of Th1/Th17 might experience increased disease activity after birth, while CU patients with a Th2-linked autoallergic profile might show improvement.

As there were also patients who displayed disease activity increase during the second trimester and also patients whose urticaria had a worse course during pregnancy; the authors hypothesized that these patients might have the type 1 autoimmune (autoallergic) type of CSU.

MANAGEMENT OF URTICARIA DURING PREGNANCY

The management of CU depends on four major steps; (1) Disease activity assessment and monitoring (2) Education of patients (3) Control of triggering factors such as physical factors, NSAIDs and stress (4) Pharmacotherapy

Even though CU is a common disease in the reproductive female population, there is a lack of information on the safe use of recommended treatments and outcomes of pregnancy in pregnant CU patients. In the recent, already mentioned PREG-CU study, which evaluated the treatment patterns during pregnancy and lactation as well as the outcomes of pregnancy in 288 pregnant CU patients. The study evaluated the treatments before and during pregnancy, pregnancy trimesters which the treatments were received, outcomes of pregnancy, and treatments given during breastfeeding with a questionnaire. The results of the study showed that 81.4% of CU patients continued to use their medication when they decided to become pregnant. During pregnancy 60% of the patients used regular medication for CU with half of them (48.8%) did so during the whole pregnancy. During pregnancy, standard-dose sg-AHs (35%), standard-dose first-generation AHs (fg-AH) (7.6%), higher than standard-dose sg-AHs (5.6%), and omalizumab (5.6%) were the most commonly used treatments, respectively. Most commonly used AHs were cetirizine (37.4%), loratadine (14.6%); and levocetirizine and fexofenadine (7.3%; each). The outcomes of pregnancy in patients with CU were similar to the normal population: a preterm birth rate of 10.2% and newborn medical problems rate of 7.9%. No risk factors were found to be associated with preterm birth and newborn medical problems (88). Eight of 10 CU patients breastfed their babies and 54.3% of them used medication for CU while breastfeeding. Of them, 63.4, 14.1, and 6% used a standard-dosed sg-AH, higher than standard-dosed sg-AH and omalizumab; respectively.

The EAACI/WAO/EDF International guideline for the management of urticaria recommends to start treatment with standard doses of second-generation (non-sedative) H1 antihistamines (sg-AH), to increase the dose up to 4-folds in case of no response to standard doses of sg-AHs and if there is no response in 2–4 weeks to add on omalizumab as the third step (1). The recommended treatment in omalizumab-resistant cases is cyclosporine-A (1). The guideline recommends adopting the same approach in the management of pregnant and lactating patients but also emphasizes the lack of evidence-based information on the safety of urticaria treatments.

For getting information on the safe use of medications during pregnancy, we have been using the letter category system of the Food and Drug Administration (FDA). Based on data derived from human and animal studies, this system has classified the reproductive safety of medications in five risk categories (A, B, C, D, and X). However, in 2015 a new system called "Pregnancy and Lactation Labeling Rule" or PLLR is implemented given to the oversimplified or sometimes misleading nature of the pregnancy risk category system (89). The new PPLR format summarizes data on pregnancy, lactation, and exposure registries and includes a new section for men and women with reproductive potential.

With this new system, physicians will be able to evaluate benefits vs. risks while counseling pregnant and nursing patients who need to take medication. This new system required that FDA drug submissions on or after 30th June 2015 be in the new PLLR format. The drugs which were approved between 30th June 2007 and 29th June 2015 should have transitioned to the new PLLR format by 30th June 2019 (90). However, it is not known if the foreseen FDA drug labels have been transitioned to the new PLLR format.

H1 Antihistamines

The key elements of pharmacotherapy of CU are H1 antihistamines and antihistamines are among the most frequently prescribed medications during pregnancy. Approximately 15% of pregnant women use antihistamines during pregnancy, particularly during the first trimester (91). Despite associations of first- and second-generation H1AHs with birth defects have been reported in older reports, detailed analysis of the findings from these reports did not show a meaningful association between antihistamines and major congenital anomalies (92, 93).

Loratadine and cetirizine are the antihistamines of choice based on the data on their safety and the recommendations in the urticaria guidelines (1, 94–98). Compared with loratadine, the use of desloratadine during pregnancy did not increase the risk of adverse pregnancy outcomes (99) and a study from Denmark showed that use of fexofenadine during pregnancy did not increase the risk of major birth defects or spontaneous abortion compared with cetirizine (100).

The use of chlorpheniramine or diphenhydramine as first-generation H1 antihistamines is not recommended as the first-line treatment due to their various side effects. They have not been associated with adverse fetal outcomes in prospective cohort trials (97). The use of H1 antihistamines during the first trimester was not found to be associated with an increased risk of major malformations or other adverse pregnancy outcomes (91). **Table 2** shows the pregnancy categories of H1-antihistamines. The safety of higher than approved doses of antihistamines has not been evaluated in pregnant patients, therefore potential risks and benefits have to be discussed with the patient before implementing it.

Montelukast

Although the use of leukotriene antagonists for the treatment of CU is not recommended by the international guidelines due to insufficient level of evidence (1), in case of intention to use during pregnancy, it will be useful to know that montelukast has been assigned pregnancy category B and no increase in major malformations were reported with the use of this medication during pregnancy (101).

Omalizumab

Omalizumab is a recombinant IgG1 anti-IgE monoclonal antibody which is recommended in the treatment of antihistamine resistant CSU (1). Animal data on omalizumab (reproduction studies in cynomolgus monkeys) showed no maternal toxicity when administered throughout late gestation, delivery and nursing, subcutaneously in doses up to 75 mg/kg (12-fold the maximum clinical dose) as well as no impaired male or female fertility, embryotoxicity or teratogenicity and no adverse effects on fetal or neonatal growth (102). The Xolair Pregnancy Registry (EXPECT) which was designed to compare the maternal and neonatal outcomes of asthma patients treated with omalizumab ($n = 250$) or conventional drugs but not omalizumab ($n = 1{,}153$) during pregnancy. The prevalence of major congenital anomalies (8.1 vs. 8.9%), live births (99.1 vs. 99.3%), premature birth (15.0 vs. 11.3%) was similar between omalizumab treated and the conventional treatment groups (103). Given that this study includes only asthmatic patients and is an observational study, it is difficult to draw definitive conclusions for the safety of omalizumab in pregnant CU patients, however, there are several case reports on the safe use of omalizumab during pregnancy in CU patients (104).

Of note, omalizumab has a very long life of elimination half-life (26 days), and omalizumab exposure of the neonate would persist for weeks after birth. This may also translate to the exposure of the fetus to omalizumab which has been given to the patient even she was not aware of her pregnancy (of note: elimination of a given drug totally from the body takes 4–5 half-lives; in case of omalizumab this would take $26 \times 5 = 130$ days).

Another point to remember is that although all IgG subtypes can cross the placenta, IgG1 has the greatest transplacental transfer. It is expected that the lowest omalizumab exposure occurs during the first trimester of pregnancy and the greatest during the third trimester (105).

In 2019, European Medicine Agency updated the European Public Assessment Report and stated that omalizumab might be considered for use in pregnancy (82). In antihistamine refractory, severe CU patients, omalizumab may be a reasonable choice of treatment; however, the benefit-risk ratio should be reconsidered in every pregnant case individually and should be discussed with the patient in detail.

Cyclosporine-A

Cyclosporine-A is the treatment recommended by the guidelines for CSU cases who do not respond to omalizumab treatment for 6 months. It is classified as category "C" in the FDA letter category system for pregnancy.

Bar Oz et al. reported in their meta-analysis which included 15 studies with 410 transplant patients that cyclosporine-A is not a major human teratogen but is associated with a trend toward increased risk of congenital malformations in the babies of transplant recipients and increased rates of prematurity (106).

Due to its side effects such as hypertension and nephrotoxicity which can potentiate gestational complications such as preeclampsia, cyclosporine-A is generally not recommended in pregnancy. It should be preserved for very severe cases only after other treatments have failed (107).

Systemic Steroids

The use of systemic glucocorticosteroids (GCS) in CSU is limited only during exacerbations for short periods by the guidelines (1). GCS are generally not considered to be teratogenic but

TABLE 2 | Considerations for pregnancy and lactation for the medications used in the treatment of chronic urticarial.

Medication	FDA pregnancy labeling and lactation rule	Pregnancy considerations	Lactation considerations
Cetirizine	Pregnancy category B PLLR is available (https://pdf.hres.ca/dpd_pm/00035506.PDF)	May be used for the treatment of CU during pregnancy	Excretion in breast milk is considered low. High doses may cause drowsiness in infant
Loratadine	Pregnancy category B	May be used for the treatment of CU during pregnancy	Excretion in breast milk is considered low.
Chlorpheniramine	Pregnancy category B PLLR is available (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206323Orig1s000Lbl.pdf)	Not recommended by the guidelines; however, may be used for the treatment of CU during pregnancy if individually preferred	Occasional doses are acceptable. High doses might cause effects in infant or decrease the milk supply
Hydroxyzine	PLLR is available. In product monograph contraindicated in early (first trimester) pregnancy (http://eci2012.net/wp-content/uploads/2015/03/Atarax-En-Monograph-100902.04-Jan-2015.pdf)	Not recommended by the guidelines; however, may be used for the treatment of CU during pregnancy if individually preferred	Small doses may not cause any adverse effects in infants. High doses may cause drowsiness in infant or decrease the milk supply
Diphenhydramine	Pregnancy category B	Not recommended by the guidelines; however, may be used for the treatment of CU during pregnancy if individually preferred	Excretion in breast milk is considered low. May cause drowsiness in newborn
Montelukast	Pregnancy category B	Not recommended by the guidelines; however, may be used together with antihistamines if individually preferred	Excretion in breast milk is considered low
Omalizumab	Pregnancy category B PLLR is available (https://www.novartis.ca/sites/www.novartis.ca/files/xolair_scrip_e.pdf)	Recommended to use only in antihistamine refractory severe CSU cases after outweighing risks over benefits	Excretion in breast-milk is considered very low
Systemic corticosteroids	Pregnancy category B (for prednisolone & methyl-prednisolone) No adequate and well-controlled studies in pregnant women Should be used only if the potential benefit justifies the potential risk to the fetus	Recommended to use only for the treatment of CU exacerbations in the lowest effective dose for the shortest duration (use ≤20 mg/day)	Excretion in breast milk is considered very low
Cyclosporine	Pregnancy category C No adequate and well-controlled studies in pregnant women Should be used only if the potential benefit justifies the potential risk to the fetus	Avoidance recommended; only to be considered in very refractory CSU cases; requires monitoring for adverse events	Excretion in breast milk is considered low. Detectable in infant's blood

PLLR, pregnancy and lactation labeling rule.

has been linked to growth retardation if fetal exposure (a median of 20 mg/day) happens during intrauterine development (108). Even though an increased risk of ∼3-fold for oral clefts has been shown (109), the US National Birth Defects Prevention showed no increased risk of oral clefts with the 1st trimester use of GCS in a case-control study (110). It should be remembered that GCS use in pregnancy may lead to maternal side effects such as hypertension, gestational diabetes, and preeclampsia, and these can lead to poor pregnancy outcomes (i.e., intrauterine growth restriction, macrosomia, intrauterine fetal demise). Therefore, if possible, the use of GCS should be avoided in pregnancy, but if it must be used, it should be prescribed for severe cases at the lowest effective dose (≤20 mg/day prednisone) for a limited period (111, 112). Use of GCS during exacerbations of CU as short courses of 1–5 days with minimally effective dose is unlikely to cause pregnancy complications. With a short half-life and effective metabolization by 11-β-hydroxy-steroid present in the placenta, prednisone should be the steroid of choice (FDA category B). Fetal exposure is found ∼10% of the maternal plasma level (113–115).

MANAGEMENT OF URTICARIA DURING LACTATION

Antihistamines

Hence the transfer rate to breast milk is minimal, second-generation antihistamines are safe to use during lactation (116). Cetirizine, loratadine, and fexofenadine are the best studied antihistamines (117, 118). Higher doses of terfenadine and loratadine showed very minimal transmission to the milk (114, 119). In refractory cases of CU who are nursing their babies,

higher doses of second-generation antihistamines might be safely used since the transfer rate to breast milk is minimal (114). First-generation antihistamines might lead to infant irritability and drowsiness (120) and are better not used during lactation.

Systemic Steroids

GCS are considered to be safe to use during lactation by The American Academy of Pediatrics. They recommend the use of minimal effective dose for the possible shortest duration and to prefer prednisone or prednisolone over other GCS options (121). Since low amounts of prednisolone can transfer to breast milk, delaying breastfeeding for 4 h after maternal GCS ingestion to avoid plasma level peaks occurring 1 h after ingestion is recommended (122, 123).

Montelukast

Montelukast is safe to use during breastfeeding given its very low levels in breastmilk. Since it is approved for use even in infants as young as 6 months of age, amounts ingested during breastfeeding by the infants are not expected to cause any adverse effects (124). A task force of respiratory experts reported that the use of these medications during breastfeeding is probably safe (125).

Omalizumab

With a molecular weight of 145,058 Da, omalizumab is a large protein molecule and, likely, omalizumab transfer to the milk and, therefore the level in milk, is very low. It is partially destroyed in the gastrointestinal system of the infant and systemic absorption by the baby is probably minimal (126). Pregnant and nursing asthmatic patients have been followed in the EXPECT pregnancy registry for several years; 154 infants of these mothers were breastfed while their mothers were on omalizumab treatment. The results of this study showed that there is no difference in serious adverse events among the infants who received or did not receive omalizumab (102, 103). A case report of a CU patient who was treated with omalizumab during pregnancy and nursery showed that only 1/10,000 to 1/1,000 of omalizumab in the maternal serum is transferred into breast milk (127).

Cyclosporine-A

Cyclosporine-A transfers to the milk <1% of the mother's weight-adjusted dosage. It does not cause adverse effects on infant's growth, development, or kidney function. However, if cyclosporine-A is used during lactation, infants should be monitored for the serum levels of cyclosporine-A to rule out toxicity (128).

The considerations for pregnancy and lactation for CU medications are shown in **Table 2**.

CONCLUSION

Managing a pregnant patient with CU is often a challenge for treating physicians. Our review provides information on the hormonal and immunological changes across pregnancy and their potential relevance for CU, and we present what is known about the impact of pregnancy on CU. We also provide information on treatment options for pregnant patients with CU.

CU may improve, stay the same or worsen during pregnancy. This information as well as the fact that no treatment could end up with emergency referrals and worsening of the disease therefore requirement of more treatment should also be discussed with the patient.

For sure the ideal situation during pregnancy and lactation is "no pharmacologic therapy", especially during the first trimester, however, it is almost impossible for a CU patient to have no disease activity during pregnancy. Therefore, treatment with the aim of zero or minimal disease activity with the least treatment should be commenced during pregnancy. The potential side effects of the medications should be balanced against the risks of inadequately treated disease for the mother and the fetus. These considerations should be discussed with the patient who is weighing the potential benefits of relief from the treated disease vs. the potential risks of the medication and an informed and shared decision should be made.

Currently, there is for sure, lack of sufficient information on the management of CU during pregnancy and questions remain to be answered are which treatments are safe to use during pregnancy, how CU manifests during pregnancy, which CU patients show amelioration or deterioration during pregnancy and are there biomarkers to show how CU will progress during pregnancy and lactation? To answer these questions, prospective studies with large patient populations which will determine patient characteristics both in the clinical level and in the molecular level are needed.

USEFUL LINKS

ENTIS (European Network of Teratology Information Service) https://www.entis-org.eu/ UK Teratology information service (UKTIS) https://medicinesinpregnancy.org

German: https://www.embryotox.de/;French: http://www.lecrat.fr/; Dutch: https://www.lareb.nl/ Organization of Teratology Information Specialists https://mothertobaby.org/

For pregnancy registry studies for the relevant drug (https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries).

For lactation database visit the Drugs and Lactation Database (LactMed) [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK501922/.

AUTHOR CONTRIBUTIONS

EK: concept. EK and MM: design. EK and IP: data collection or processing and writing. EK, IP, AZ, AK, DE-A-K, MC, and MM: analysis or interpretation and approval. EK, IP, AZ, and AK: literature search. DE-A-K: figures. All authors contributed to the article and approved the submitted version.

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Efficacy and safety of omalizumab therapy in urticaria vasculitis

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Urticarial vasculitis (UV) is a small-vessel leukocytoclastic vasculitis characterized by different clinical manifestations ranging from long-lasting urticarial lesions to severe and potentially life-threatening multi-organ involvement. Omalizumab (OMA), anti-IgE recombinant humanized IgG1 monoclonal antibody, has been successfully used to treat few cases of severe and/or refractory UV. In this study we report our experience on 6 patients with refractory normocomplementemic UV successfully treated with anti-IgE therapy (OMA), suggesting that this biological therapy may be a safe and effective therapeutic option in UV.

KEYWORDS

urticarial vasculitis, omalizumab, anti IgE, therapy, biological agent

Introduction

Urticarial vasculitis (UV) is a rare immune-complex mediated small-vessel leukocytoclastic vasculitis, characterized by long-lasting urticarial lesions, persisting more than 24 h. Clinical manifestations may range from itchy and/or burning skin lesions to severe and potentially life-threatening multi-organ involvement, having a substantial impact on patients' life expectancy and quality of life. On the basis of complement levels, UV is classified into two different forms: normocomplementemic (NUV) and hypocomplementemic (HUV). Moreover, the latter form is mainly associated with multi-organ involvement and with the presence of anti-C1q antibodies in more than half of the patients (1). Although most of the forms of UV are defined as idiopathic as the cause of the disease is not identified, some of them can be also associated with autoimmune and/or infectious and/or malignant diseases and can resolve following treatment of the underlying condition. Several drugs or vaccines, including recently those for COVID-19, have been identified as potential triggers for UV (1–3). The therapeutic approach to this disease is currently challenging due to the lack of large randomized controlled trials and approved therapies. Corticosteroids are among the most effective drugs for the treatment of both skin and extracutaneous manifestations, although their long-term administration may lead to serious dose-dependent side effects. In such cases immunosuppressive or immunomodulatory therapies such as azathioprine, cyclophosphamide or cyclosporine may improve disease control and reduce the dosage of corticosteroids. However, side effects, especially in the case of prolonged administration, and/or lack of efficacy often require discontinuation of the treatment (2, 4).

Thus, due to the evident limitations of the current treatment of UV, it is important to identify novel effective and safe therapeutic approaches for patients with diagnosis of UV, able to improve their quality of life and life expectancy. Several biological agents such as etanercept, infliximab, canakinumab, anakinra, rituximab, tocilizumab have been proposed as alternative therapeutic options in severe and/or treatment-refractory UV patients, even though the evidences on their efficacy and safety in the treatment of this condition are currently limited to a few case reports (2, 4).

Omalizumab (OMA) is a recombinant humanized IgG_1 monoclonal antibody directed to IgE-specific epitopes within the C3 (FcεRI binding) region of circulating IgE, that reduces IgE/FcεRI binding on mast cells and basophils with consequent down-regulation of cell activation. After being approved in the USA and Europe for the treatment of antihistamine refractory chronic spontaneous urticaria (CSU), severe allergic asthma and severe chronic rhinosinusitis with nasal polyps, its efficacy and safety has been widely demonstrated in real-life experience. Based on the markedly positive impact of OMA in CSU, the use of this drug has been reported in some cases of severe and/or refractory UV either idiopathic or associated with autoimmune diseases (2, 4, 5).

In the Immuno-allergology Unit of Azienda Ospedaliero-Universitaria Pisana (AOUP) 6 patients with diagnosis of severe and/or refractory UV (F/M 5:1) with mean age of 62 years (range 43–74) were treated with OMA at dosage of 300 mg every 4 weeks, according to our experience in CSU (6). Written informed consent for off-label therapy was obtained from all the patients (University Hospital internal protocol, AOUP). Demographic and clinical characteristics were collected, including co-morbidities and current and previous pharmacological treatments for UV. According to the improvement in skin (long-lasting wheels, itch, burning, pain) and systemic (arthralgia, asthenia, abdominal pain, fever and lymphadenopathy) symptoms in response to OMA treatment, the patients were classified as responders, partially responders or not responders and any adverse side effects were recorded. The levels of IgE in the sera of UV patients were also measured before staring OMA treatment.

As reported in Table 1, in all the 6 patients evaluated the results of the immunohystochemistry analysis of skin biopsies were consistent with the diagnosis of UV, mainly revealing a lymphocytic/mononuclear infiltrate. Four out of the 6 patients reported systemic symptoms, including arthralgia, asthenia, abdominal pain, fever and lymphadenopathy, without ocular, renal, or cardiovascular involvement. According to the levels of complement components (C3 and C4), all UV evaluated were classified as NUV and none of them had anti-C1q antibodies. All of the patients had co-morbidities such as infectious diseases and/or malignancies and/or autoimmune diseases, however their UV were un-responsive to the pharmacological treatment for the underlying diseases. Before OMA treatment, all the patients had previously received oral corticosteroids, 5 of them also immunomodulatory and/or immunosuppressive drugs (see Table 1). Only one patient underwent previous biological therapies with anakinra and canakinumab due to severe and refractory disease. Reliever or daily administration of second generation H_1-antihistamines were maintained in all the patients during the treatment with OMA. In 4 out of the 6 patients evaluated, a complete resolution of skin symptoms was achieved since the 1st OMA injection. As reported in Table 1, one patient was a partial responder (according to the improvement of skin symptoms) and this was observed after the 3rd injection. In most of our cohort, the improvement of both skin and systemic symptoms was observed since the 1st injection. Among the six patients evaluated, only one did not achieve any improvement in skin symptoms before the 4th OMA injection. She partially improved her long-lasting skin lesions from the 4th to the 6th injection and she was not responder anymore from the 7th injection. According to the clinical history of this patient, the discontinuation of OMA treatment was decided after the 10th injection.

During the OMA treatment some common mild/moderate side effects such as headache were reported and in one case a maculo-papular rash occurred after the 4th injection.

In our experience, OMA, used at dosage of 300 mg every 4 weeks, proved to be a safe and effective therapeutic option in severe and/or refractory UV, for which no drugs are currently approved. Thus, the possibility to treat severe and/or refractory UV with manageable drugs such as OMA, that improves the quality of life of these patients, is an important goal for physicians managing UV patients. Few reports have already described the efficacy of OMA in treatment of different forms UV. However, the dosage of OMA and the interval between injections are not concordant among these clinical reports. This is probably due to the heterogenicity of the patients in terms of co-morbidities and/or clinical manifestations and/or laboratory data.

Even though the precise mechanisms of action of this biological agent are still to be clarified, we can postulate that its efficacy in UV treatment is probably due to its ability to reduce circulating IgE, and their binding to membrane of mast cells and basophils, that finally leads to downmodulation of cellular activation and/or inflammatory cells chemotaxis and/or immune complex formation (7).

A limit of our study is that it was a single arm open-label designed and further designed randomized double blind placebo control clinical studies are required. We have to take into account that in further studies large sample groups with different clinical phenotypes of UV should be included. On the whole our report suggests that OMA might be a promising option in the treatment of UV. The major improvement observed during OMA treatment was at skin level and was observed since the 1st injection. It could be interesting to modify dosage and administration

TABLE 1 Demographic and clinical characteristics of patients with normocomplementemic UV.

Pt	Sex	Age, yrs	Comorbidities	UV onset, yrs	UV duration, yrs	Systemic symptoms	Baseline IgE levels (U/ml)	Skin lesional biopsies	Previous therapies	OMA 300 mg/4 wks, injections (n°)	Response after (wks)	Skin symptoms improvement (after wks)	Systemic symptoms improvement (after wks)	SE
1	F	43	HP infection, Hashimoto thyroiditis, IGT, liver disease	7	31	Yes	461	Lympho-monocytic	CS, CsA, AZA	10	16	Partial improvement (16), but no improvement (25)	No improvement	None
2	F	48	HP infection, Hashimoto thyroiditis	27	20	Yes	138	Lympho-monocytic	CS, HCQ	7	4	Complete resolution (4)	Complete resolution (4)	None
3	F	67	GERD, ACD, liver disease, osteopenia	53	10	Yes	177	Lymphocytic	CS, HCQ, CsA, LEF, CLH, AZA, MMF, MTX, anakinra, canakinumab	38	4	Complete resolution (4)	Partial improvement (4)	Headache
4	F	72	Asthma, DM2, AHT, liver disease	65	4	Yes	161	Granulocytic	CS, CsA, MTX, HCQ, MMF, DP	22	4	Complete resolution (4)	Complete resolution (4)	None
5	M	74	Latent TBC, MGUS, neoplatic disease, COPD, AHT, BPH	68	3	No	42	Lymphocytic/ granulocytic	CS	11	12	Partial improvement (12)	–	None
6	F	66	Neoplastic diseases	62	0.6	No	358	Granulocytic	CS, CLH	4	4	Complete resolution (4)	-	Maculo-Papular rash

Pt, patient; F, female; M, male; yrs, years; HP, Helicobacter pylori; IGT, impaired glucose tolerance; GERD, gastroesophageal reflux disease; ACD, allergic contact dermatitis; DM2, diabetes mellitus type 2; AHT, arterial hypertension; TBC, tuberculosis; MGUS, monoclonal gammopathy of undetermined significance; COPD, chronic obstructive pulmonary disease; BPH, benign prostatic hyperplasia; UV, Urticarial vasculitis; C3, complement C3; C4, complement C4; CS, corticosteroids; CsA, cyclosporine; AZA, azathioprine; HCQ, hydroxicloroquine; LEF, leflunomide; CLH, colchicines; MMF, mycophenolate mofetil; MTX, methotrexate; DP, dapsone; OMA, Omalizumab; wks, weeks; no, number; SE, side effects.

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frequency of this biological drug in partially or not responders UV patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FP, DG, SB, ID, VR, PM, and IP made substantial contributions to conception and design, acquisition of data, interpretation of data, reviewed it critically for important intellectual content, given final approval of the version to be published, and agree to be accountable for all aspects of the work related to its accuracy or integrity. FP, DG, and IP drafted the article.

Conflict of interest

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Comorbidities of Chronic Urticaria: A glimpse into a complex relationship

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Chronic Urticaria (CU) is a chronic inflammatory, predominantly mast cell-driven disease, characterized by the development of wheals and/or angioedema for more than 6 weeks. It affects approximately 1%–5% of the total population worldwide and imposes a substantial burden on health-related quality of life, significantly affecting patients' daily life. The economic impact on the health system is also not negligible, with an estimated cost per patient per year of approximately 2.000 $ in the United States. Although the underlying pathophysiology is not fully explored, autoimmune mechanisms have been proposed, including type I ("autoallergy" by means of autoantibodies to self-antigens) and type IIb (autoimmunity). Atopic, autoimmune, and psychiatric disorders are prevalent comorbidities in both children and adults with Chronic Spontaneous Urticaria (CSU). Although malignancies, cardiovascular diseases and other comorbidities have also been reported as associated diseases in patients with CSU, data remain scarce. It is still unknown whether the aforementioned comorbidities share common pathophysiological mechanisms with specific endotypes of CSU. The current review aims to overview current data on comorbidities of CU, and furthermore to comment on the potential linked pathways underlying these diseases.

KEYWORDS

chronic urticaria, comorbidities, chronic spontaneous urticaria, psychiatric disorders, atopic diseases, autoimmune diseases

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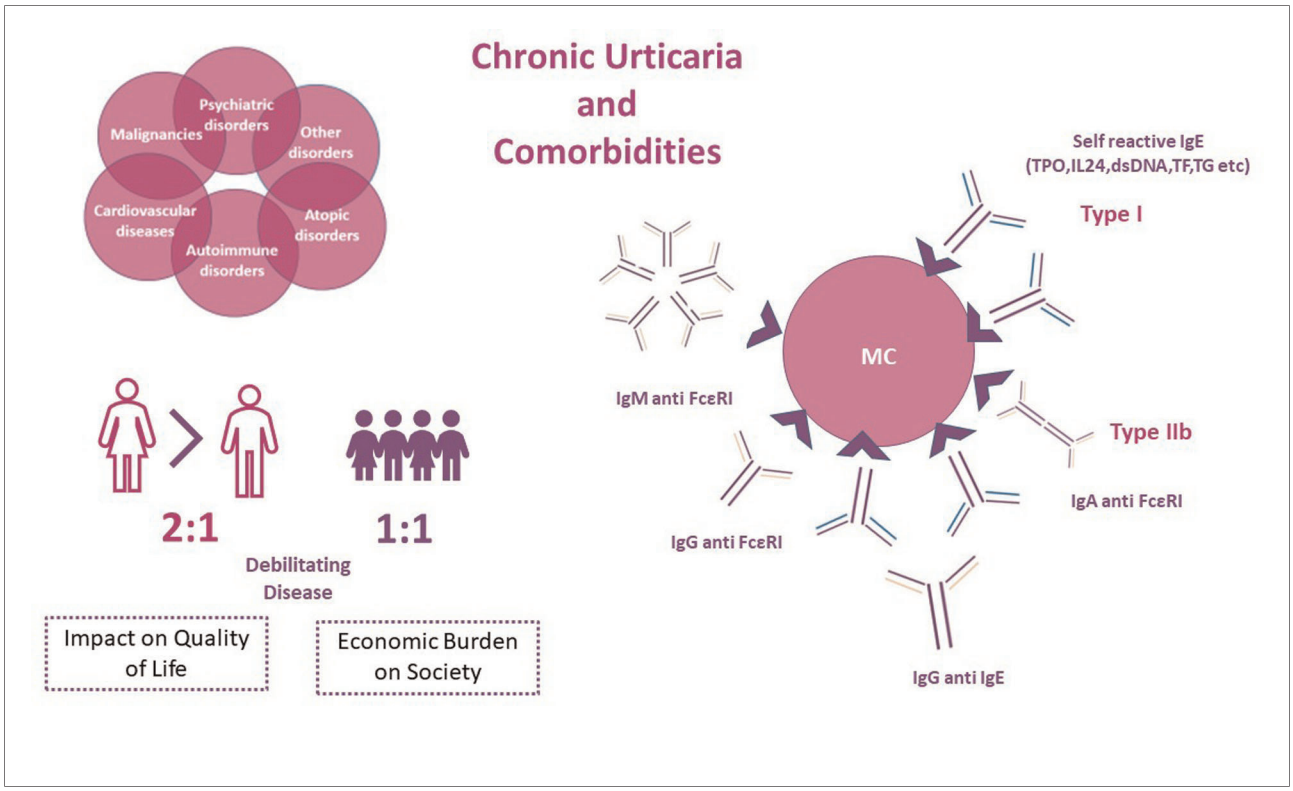
Graphical abstract



Introduction

Chronic Urticaria (CU) is a predominantly mast cell-driven disease presenting with recurrent wheals, angioedema, or both for more than six consecutive weeks (1, 2). The disease is further classified into Chronic Inducible Urticaria (CIndU) and Chronic Spontaneous Urticaria (CSU), based on the presence or absence of specific causative triggers respectively (2), while 10%–30% of the patients with CU present both the spontaneous and inducible type (3).

CU is one of the most common skin disorders, with an estimated global prevalence ranging from 1% to 5% (4–6), both in children and adults, while data support an increasing prevalence worldwide, despite substantial regional disparities.(4) Females are slightly more affected compared to males (7, 8), with an increased point incidence of 0,18% vs. 0,11% and prevalence of 0,62%–1.3% vs. 0,37%–0.8% respectively (9). Such discrepancies are not present in the pediatric population (boys 1, 1% vs. girls 1, 0%) (4).

While CU affects all age groups, it is more frequent in patients aged 30–50 years (10), and thus influences mostly young and middle-aged women (11), compromising not only the quality of life but also work productivity and emotional well-being (12, 13). The socioeconomic burden is also substantial with an estimated cost per patient per year of 2,047$ in the United States and total direct and indirect costs accounting for 244$ million per year (14).

CSU is considered a chronic inflammatory skin disease and mast cells (MC) are undoubtedly the key effector cells, while various other cells and mediators are involved (15). The crucial role of basophils in CSU has recently been explored, revealing new aspects of CSU pathomechanisms (16). Blood basophil counts in patients with CSU inversely correlate with urticaria severity, and basopenia *per se* is linked with poor response to omalizumab treatment (17–19). Moreover, basophil infiltration has been detected in urticarial skin lesions, indicating a possible migration of these cells to the skin (20). Omalizumab administration has been associated with increased blood basophil counts and surface activation markers (21, 22). Based on this observation and omalizumab kinetics regarding rapid downregulation of FcϵRI on the surface of basophils, Takimoto- Ito et al. hypothesized that activated basophils in CSU patients migrate to the skin. In contrast, inactive ones remain in the bloodstream. Upon omalizumab administration and urticaria resolution, levels of activated basophils increase in the blood, further highlighting basophils' role in CSU (16).

Although the underlying mechanisms of CSU remain largely unclear an autoimmune basis was first proposed in 1962 (23) and during the last decade two different endotypes have been described and classified as type I and Type IIb autoimmune mechanisms (24–27). In type I autoimmunity or "autoallergy", activation of mast cells is driven by an IgE mediated reaction against an endogenous allergen (autoantigen) such as thyroid peroxidase (TPO), interleukin-24, double- stranded DNA, tissue factor, thyroglobulin etc (28–31). In type IIb, IgG autoantibodies, and to a less extent IgM and IgA autoantibodies, are directed against IgE or its high affinity receptor (FcϵRI) resulting in activation of MCs (28, 32–35). The presence of MC activating autoantibodies can be identified by the autologous serum skin test (ASST), basophil tests (BTs) and immunoassays (32). Low total IgE levels and elevated IgG against TPO are present in type IIb autoimmune CU and are inversely correlated in patients belonging to this endotype (32) Coexistence of IgG and IgE autoantibodies against the same endogenous antigen has also been reported (36). Multiple other triggers can activate MCs resulting in different, yet unexplored, non-autoimmune endotypes of CU (37). Apart from high (FcϵRI) and low affinity (FcϵRII) IgE receptors in the surface of MCs, numerous other receptors are capable of activating MC, such as Mas-Related GPR family member X2 (MRGPRX2) for substance P, eosinophilic peroxidase and major basic protein, C5a receptor for anaphylatoxins, CRTh2 for Prostaglandin D2(PGD2), cKit for stem cell factor (SCF), cytokine receptors like IL-4Rα, IL5R, and TSLP-R, Toll-Like Receptors (TLRs) for pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Moreover, inhibitory receptors like Siglec-8 and CD200R exist on the surface of MCs (38–40). Endothelial cells and the coagulation system have also been implicated in CU pathogenesis (40), as well as the dysregulation of intracellular signals within mast cells and basophils (37, 41). Moreover, aggregation and stacking of highly lipophilic IgE molecules can result in crosslinking of FcϵRI in the absence of antigen binding (42).

Pruritus, pain and burning sensation of wheals and angioedema can result in anxiety, stress, sleeplessness, poor self-esteem, shyness, anger, and social isolation (43, 44). Furthermore, patients' quality of life is further compromised by the coexistence of CU with a broad spectrum of comorbidities, such as sleep disorders, anxiety, depression, other psychiatric disorders, autoimmune diseases, atopic diseases, cardiovascular disorders, and less frequently malignancies (9, 45–47) (**Figure 1**).

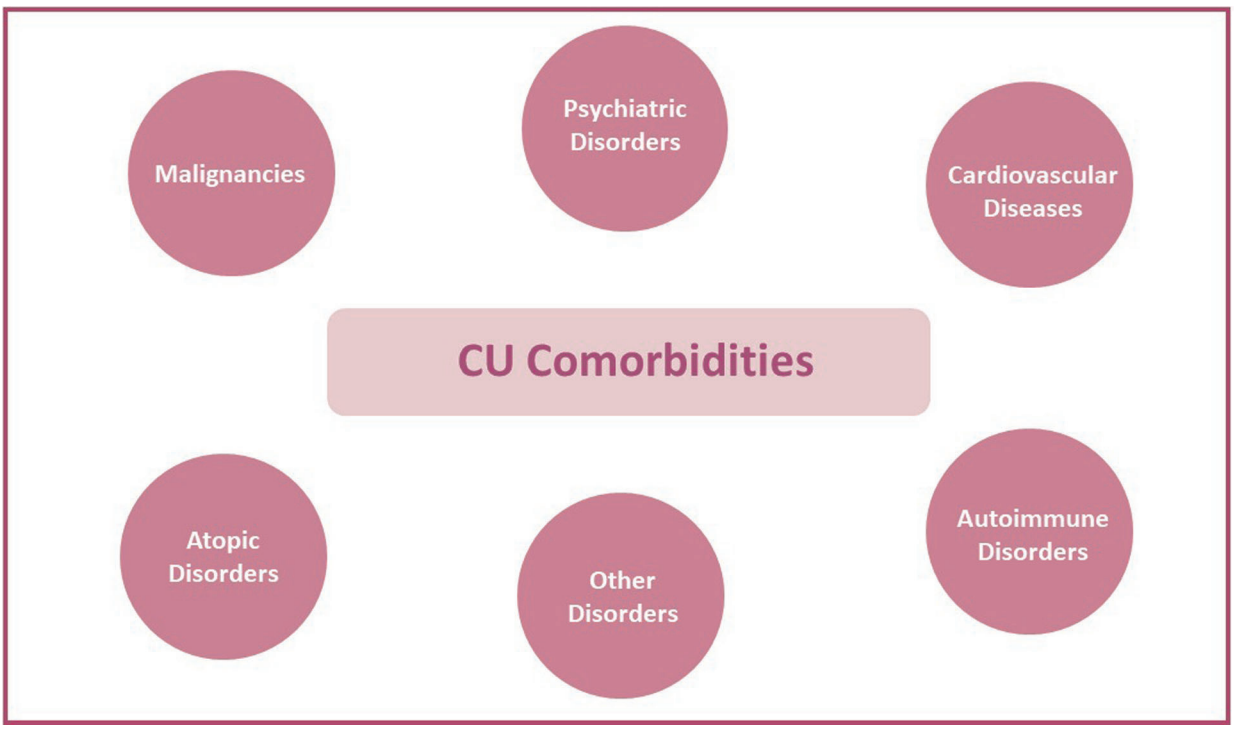


FIGURE 1
Chronic Urticaria frequently presents with various associated diseases (comorbidities). The robust link between atopic diseases, autoimmune diseases, psychiatric disorders and Chronic Urticaria is well established. A less clear relationship between malignancies, cardiovascular disorders of other comorbidities in patients with Chronic Urticaria exists.

The above-mentioned data on CU pathophysiology and the underlying immune pathways has raised the interest for a more holistic approach of CU; to this end, both epidemiological data and possible common pathophysiological mechanisms linked to CU comorbidities are of major interest. In the present review we aim to overview data on the complex interplay between CSU and associated comorbidities, apart from CIndUs, and comment on their potential relationships in terms of underlying mechanisms.

CSU and autoimmunity

CSU as an autoimmune-autoreactive skin disorder *per se*, often coexists with a variety of other autoimmune diseases (37). Overall, approximately 30% of CSU patients present with at least one autoimmune disorder, while 2% may have two or more autoimmune disorders, with Hashimoto's disease and vitiligo presenting more frequently as co-existent diseases (48).

Thyroid diseases have been reported as the most prevalent autoimmune diseases in up to 50% of CSU patients, depending on the study population (32, 49–51). Other autoimmune diseases as vitiligo (prevalence >3%), pernicious anaemia (>5%), rheumatoid arthritis (>1%), psoriasis (>1%), celiac disease (>1%) and insulin-dependent diabetes mellitus (>1%) have also been reported in CSU patients (50, 52, 53). From another perspective, the prevalence of CSU is higher, in patients suffering from Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, autoimmune thyroid diseases, and celiac disease compared to the general population (49, 52).

It has been recently acknowledged that the type IIb autoimmune CSU, as assessed by positive ASST, BHRA and/or BAT and identification of specific IgG antibodies against FcεRI/IgE, is highly related with other autoimmune diseases (48).

Thyroid diseases

IgG autoantibodies against thyroid peroxidase (TPO) have been identified in up to 50% of CSU patients, with 5-to-7-fold increased risk of presenting anti-TPO antibodies in CSU patients compared to controls, while increased levels of IgE antibodies against TPO have also been detected in those subjects (49, 54). Thyroid dysfunction disorders, such as hypothyroidism and Hashimoto's thyroiditis, are also reported more significantly in CSU adult patients than healthy controls (49).

First, Rumbyrt et al. suggested that the inflammation in the thyroid gland can lead to a generalized inflammatory response with a subsequent complement activation along with activation of mast cells, mainly through anaphylatoxins receptors (55). Moreover, the recognition of IgE antibodies against TPO as a cause of Type I autoimmune CSU has further enhanced the link between thyroid dysfunction and CSU (25, 56). In line, although a causative role of IgG antithyroid autoantibodies on the occurrence of CSU has not been demonstrated (57–59), IgE antithyroid autoantibodies have been implicated in the formation of immune complexes, and activation of complement system, potentially facilitating activation of MCs and subsequent clinical expression of CSU (49).

Although conflicting evidence exists, especially in euthyroid patients with CSU, data support the efficacy of levothyroxine or other thyroid drugs on CSU morbidity, potentially by reducing inflammatory thyroid pathways mediating mast cell activation (49).

Other autoimmune diseases

In a large registry-study from Denmark including more than 12.000 CU patients, rheumatoid arthritis was reported as the most prevalent autoimmune comorbidity (1.7%), while thyroiditis (0.3%), vitiligo (0.1%) and Systemic Lupus Erythematosus (SLE) (0.3%) were also identified, although to a lower extend. Of note, it cannot be excluded that the high prevalence of RA might be attributed to the high prevalence of the disease *per se*, in relation to the other autoimmune diseases. At the day of the diagnosis, rates of vitiligo and SLE were significantly higher than in the control group (OR = 5.43 1.78–15.35 and OR = 4.72 2.36–7.4 respectively). During the follow up, an increased risk for RA occurrence was observed [Hazard Ratio = 1.8 (1.4–2.3)] (51). This could potentially be attributed to the systemic inflammation facilitated by MCs, while the role of MC's activating autoantibodies might be more relevant in CU patients with autoimmune thyroid diseases, vitiligo and SLE (51).

Additionally, it is well known that Urticarial rash is common in patients with Systemic Lupus Erythematosus (SLE), ranging from 0.4%–27.5% in adults and in 4.5%–12% in children as shown in the meta-analysis by Kolkhir et al. Data on the vice versa relationship is scarce. It has been proposed that the underlying pathogenetic mechanism associating both diseases might include the activated complement and coagulation system, linking inflammation and autoimmunity (60).

Autoimmune diseases in paediatric population

The prevalence of autoimmune diseases in children with CU is diverse, ranging from 0%–16% (61, 62). A prospective study in Canada, evaluating the prevalence of autoimmune diseases in children with CSU, demonstrated an increased prevalence of autoimmune diseases, such as hypothyroidism, lupus, juvenile

rheumatoid arthritis, and type I diabetes compared to the general paediatric population (2.10% vs.0.13%, 0.52% vs.0.005%, 1.05% vs. 0.053% and 1.57 vs. 0.19% respectively) (63). Nevertheless, the overall prevalence of autoimmune diseases in children with CSU was relatively low (<5%), thus evaluation for autoimmune diseases is proposed only when a suggestive clinical history and/or laboratory findings are present (63). Moreover, autoimmune hypothyroidism was observed in older children with CSU and with increased CD63 levels, a well-established marker of IgG-mediated autoimmunity, potentially attributed to the impact of epigenetic changes, due to environmental factors, on the development of inflammation and autoimmunity with increasing age (63).

In respect to the prevalence of atopic diseases in children with CSU, studies have shown an increased occurrence compared to autoimmune diseases while in adults respective rates are either similar or even lower (49, 51, 63, 64). Moreover, in agreement with recent finding linking autoimmune type IIb endotype with higher prevalence of other coexisting autoimmune diseases in adults, elevated levels of CD63, may propose such a relationship in children as well (48, 63, 65).

A systematic review reported that positive ASST, identifiable antinuclear antibodies (ANA) and thyroid biological abnormalities were present in 36.8%, 6.4% and 10.4% of children <12 years with CSU respectively (66), supporting further the presence of a type IIb autoimmune endotype in children. The lower rates of thyroid function abnormalities are in line with the observation that autoimmune mechanisms are evolving and may manifest several years after the initial diagnosis (66). However, whether children with positive ASST and ANA need to be screened for autoimmune diseases is a matter of debate (67, 68).

The importance of identifying autoimmune comorbidities in patients with CU

Specific endotypes of CSU are linked to comorbid autoimmune diseases, and thus early diagnosis and therapeutic intervention of associated diseases may be beneficial in the multidisciplinary therapeutic approach as suggested by EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI Guidelines (2, 48). In the era of precision medicine, knowledge of a patient's profile, shaped not only by CU *per se* but also by the various coexisting diseases, may lead to targeted, personalized interventions (69, 70). As new therapeutic options are developing, identifying the presence of comorbid autoimmune diseases is of importance, since they can interfere with CSU activity, duration, natural course, and response to treatment (69, 71). Thus, in the updated CU 2022 guidelines the measurement of IgG anti-TPO and total IgE in all CSU patients is strongly supported to identify autoimmune thyroiditis and to untangle the underlying endotype (2, 32).

CU and atopic diseases

Atopic diseases have been commonly reported in CU patients. The results from the Scandinavian arm of the AWARE study, showed that atopic diseases are the most frequent comorbidities in a cohort of 158 adult patients with CU. In specific, asthma was reported in 19.6% of the patients, allergic rhinitis in 16.5%, atopic dermatitis in 6.3% and food allergy in 8.2% (11). Higher rates of sensitization -approximately 40%- to at least one inhalant or food allergen have been reported by Zuberbier et al. in a general German population with CU (72), while allergic rhinitis and asthma were among the five most common comorbidities among CU patients in a large Korean study (73). In agreement, Ghazanfar et al. found that atopic diseases like rhinoconjuctivitis and atopic dermatitis are overrepresented among CU patients with an increased risk of developing atopic diseases following CU diagnosis (HR = 3.09, CI 2.0–4.8 for atopic dermatitis and HR = 1.4, 0.75–2.55 for rhinoconjuctivitis) (51).

With regards to the pediatric population, a personal history of atopic dermatitis in children has identified as a risk factor for subsequent CSU development, (OR 2.92, 95% CI 1.64–5.18, $p < 0{,}001$) in a pediatric population (74). In addition, in a recent systematic review evaluating comorbidities and interventions in children younger than 12 years with CSU, including 522 patients with CU (or CSU), atopic diseases were found in 28.1% of the population with a reported prevalence of 15.4% for asthma, 13.8% for allergic rhinitis and 9.4% for atopic dermatitis respectively (66). In agreement, Lachover-Roth et al. in a retrospective study of 250 children with CSU showed that atopic diseases were significantly more prevalent in children with CSU than in the general paediatric population, with one out of three children suffering an atopic comorbidity (17.2% atopic dermatitis, 16% allergic rhinitis, 13.2% asthma and 3.2% food allergy) (75). Allergic sensitization, as assessed by total IgE has been identified in almost 30% of children with CU, irrespective of relevant clinical symptoms (76). Moreover, 24 out of 77 children with CU were described as atopic with presence of allergen specific-IgE to at least one allergen. Importantly, total levels of IgE were positively associated with disease duration. ($r = 0.262$, $p = 0.021$) (77). In CU adults, high IgE levels correlated with disease severity and duration, but not the clinical course of the disease (64, 78).

Despite the robust epidemiologic association between atopic diseases and CU, both in adults and children, no causal relationship has been established so far, thus therapeutic interventions for allergy-associated symptoms have no effect on the natural course or severity of CSU and vice versa (75, 79). Nevertheless, a TH2 endotype in CSU patients, especially children, with atopic diseases

along with high IgE levels, which in turn are associated with type I autoimmunity or "autoallergy" and IgE autoantibodies detected in CSU patients, has been suggested (26, 34, 42, 75).

CU and psychiatric disorders

Psychiatric and mental disorders are quite frequently reported among CU patients, in the literature (80–83). A recent systematic review and meta-analysis reported that almost one out of three CU patients have at least one underlying psychiatric disorder (84). Sleep-wake disorders, followed by anxiety and mood disorders, including depression are frequently identified (pooled prevalence 36.7%, 30.6% and 29.4% respectively). Trauma and stressor related disorders, somatic symptom and related disorders, obsessive- compulsive and related disorders and substance-related and addictive disorders were also reported. Regarding CU severity, duration, and mental functioning, no association has been demonstrated. Konstantinou et al. conclude that none of the studies included in the systematic review clearly stated whether psychiatric disorders pre-existed or follows CU diagnosis (84).

Data from the Danish National Patient Registry ($n = 12.185$ CU patients) found that CU patients were at increased risk of presenting depression, while a marginally increased risk for presenting psychosis was observed over time [HR adjusted = 1.38 (0.99–1.93) in CU patients] (51). Affective disorders (27.0%) were frequently in adults with CU in a cross-sectional study in Germany; of interest, in pediatric CU patients somatoform disorders were the most frequently reported comorbidities (7.7%), following rhinitis (24.7%) and asthma (20.2%) (9). Recently, Lachover-Roth et al. found a prevalence of 2.8% with respect to psychiatric disorders in a retrospective study of children with CSU ($n = 380$); depression, anxiety, bipolar disorders, and schizophrenia were identified (75).

Anxiety disorders are also prevalent in CSU patients compared to healthy controls (9.6% vs. 5.7%, $p < 0.001$), with a strongest association observed between anxiety, younger and higher socioeconomic status subjects (85). Moreover, anxiety can negatively correlated with social functioning (86).

Both anxiety and depression were negatively correlated with Quality of Life assessed by Chronic Urticaria Quality of Life Questionnaires (CU-QoL) (87).

Although a number of studies reports increased frequencies of depression and anxiety among CU patients (48,1% and 38% respectively) other reports show lower levels (11); discrepancies are potentially attributed to selection bias, heterogenous population and diagnostic criteria regarding diagnosis of psychiatric disorders (11).

Suicidal ideation is also reported in patients with CU (84). Picardi et colleagues (88) reported a 18.8% prevalence of suicidal ideation in CU patients, while Mehta et al. (89) and Sorour et al.(90) reported a 12% and 19.9% prevalence respectively.

The underlying pathogenetic mechanisms are unclear, although a potential interplay between the immune and central nervous system has been reported (91). A "brain-skin connection" may contribute to inflammatory skin diseases like CU, with stress causing aggravation of urticaria (92, 93). Moreover, a causal relationship between stress and inflammatory disorders, including CU, has been reported (94, 95). It has been postulated that chronic inflammation can dysregulate the immune and the central nervous system, resulting in mental disorders (96). The role of substance P, through neurogenic inflammation in acute stress has been described (97). Substance P is produced by a variety of inflammatory cells and is implicated in the release of histamine and serotonin from mast cells (98). In accordance, in a study evaluating patients with CSU and depression levels of Substance P were higher in CSU with depression than those without, but no dissimilarity was observed between CSU and healthy controls (99).

As CU has a debilitating effect on quality of life and productivity, data are inconclusive on whether psychiatric disorders affect or are affected by CU (84). Albeit case series have reported that pharmacological interventions with anti-depressants and anti- anxiety drugs may have a beneficial impact on CU (100, 101).

It is advised that CU patients be evaluated for phycological disorders and be treated accordingly.

CU and malignancies

The association between CU and malignancies remains controversial (37). The first implication of a causal relationship between CU and cancer was described in 1942, when the removal of a rectal carcinoma in a 70-year-old male was associated with CU remission (102). Since then anecdotal cases of urticaria linked to malignancies have been reported in the literature (103).

Neoplasms have been reported to promote both chronic spontaneous and inducible urticaria in a systematic review, suggesting a linkage. The most frequently reported cancers in CSU patients are carcinomas (68%) with 24% of all cases being papillary carcinomas of the thyroid gland (103). In agreement, Napolitano et al., in a retrospective population-based study of 1,493 patients with CU, reported that CU was associated with cancer in 0,007% of the population, while CSU in those patients is (a) antihistamine resistant, (b) resolves after chemotherapy, or tumor removal, (c) can reoccur upon cancer relapse and (d) presents 2 to 8 months before malignancy diagnosis (103, 104). In accordance, a large registry study from Taiwan reported an increased risk of cancer in patients with CU (standardized incidence ratio 2.2;

95% CI 2.0–2.3). The risk was even higher for hematologic malignant tumors (SIR = 4.1, 95% CI, 3.1–5.4) and non-Hodgkin lymphomas (SIR = 4.4,95% CI, 3.0–6.1) (105). Moreover, two additional cases of urticaria remission after colorectal cancer removal are also reported in the literature, suggesting that urticarial lessons may manifest as a paraneoplastic phenomenon (106, 107). The incidence rates of CSU were statistically significantly higher for neoplasms (adjusted HR 1.14, 95% CI 1.02–1.27) in a population-based study in Italy (108). Non hematological neoplasms were among the most common comorbidities in a large Korean population-based study with the likelihood of occurrence 1.37 higher than in patients without CU. Stomach, thyroid and liver cancer were the most common neoplasms in CU patients while thyroid, liver and prostate in the CSU subgroup (73). In contrast, data from a Swedish registry showed no association between cancer and CU (109).

As urticaria and cancer are common diseases in the general population, they can incidentally coexist, although the immediate CU resolution following cancer remission and the reoccurrence upon relapse suggests causality (104). Neoplasms may induce immune dysregulation and activate coagulation and complement system, while the release of tumor-derived antigens detected by IgE can cause cross-linking of high-affinity IgE receptors in mast cells' surface, inducing degranulation (110–113).

Despite the reported cases in the literature, the overall rate is quite low among CSU patients and hence, the international EAACI/GA^{2}LEN/ EuroGuiDerm /APAAACI guidelines suggest not to routinely screen for malignancies as potential underlying causes of CU (2, 114).

A careful clinical examination and history are essential for this rare relationship to be exposed in a cost -effective way.

CU and hypertension, hyperlipidemia, metabolic syndromes, and cardiovascular disorders

The relationship between CU and cardiovascular diseases is unclear. A retrospective population-based cohort study in Denmark found no association between CU and cardiovascular diseases (115). On the contrary, a prospective study showed that systemic hypertension was associated with urticaria persistence (hazard ratio, 0.71; 95% CI 0.53–0.95; $p = 0.02$) (110), while hypertensive and lipoprotein metabolic disorders were among the more frequent reported comorbidities (43.5% and 32.1% of CU adult population respectively) in a recently published cross-sectional German study (9), and in a Swedish registry based-study (12% and 17% respectively) (116).

Metabolic syndrome was reported in 29.8% of patients with CU compared to 17.8% in a matched control group ($p = 0,001$) in a Korean cohort study and was independently correlated with uncontrolled urticaria, as assessed by total urticaria activity score. Larger waist-circumference, as a marker of obesity, was more prevalent in subjects with CU, and significantly associated with IgE, Eosinophilic Cationic Protein (ECP) and Tumor Necrosis Factor-a (TNF-a) levels (117), while a postive association between CU and obesity was shown in a large population-based Italian study (adjusted HR 1.40,95% CI 1.17–1.67) (108). Moreover, hyperlipidemia has been identified as a risk factor for CU development (OR 1.97 95% CI: 1.85–2.09) (118).

The Scandinavian arm of the AWARE study also reported a prevalence of obesity and hypertension at 7% and 1.9%, respectively, among an adult CU population with half of the patients being overweight (BMI > 25) (11).

Similarly, a pediatric cohort with CU from Spain, Italy, Germany, France, and the UK manifested significantly higher BMI compared to the control group (119).

CU is a chronic inflammatory disease presenting with low grade systemic inflammation (37). Hence, although an increased ratio of cardiovascular diseases derived from atherosclerosis could be partially explained by the inflammation stage in CU patients, data by Egeberg et al. report otherwise (115). The relatively short duration of CU may not be sufficient to increase the risk of presenting cardiovascular diseases (8, 120). However, alterations in lipid metabolism and co-occurrence of obesity can result in immune system dysregulation and presentation of autoimmune diseases (121, 122), with a subsequent activation of mast cells resulting in CU clinical presentation. Nevertheless, this hypothesis is far from well-established and further studies are needed to unravel the potential relationship between urticaria, hyperlipidemia, obesity, and cardiovascular diseases.

CU and other comorbidities

Although less common, a variety of other associated diseases have been reported in patients with CU.

Osteoporosis and diabetes mellitus were found in 2.9% and 2.3% of 12.185 CU patients respectively (51). It is speculated that corticosteroid use plays a significant role as, despite current guidelines recommending against their use, they are still prescribed by physicians (2, 123, 124). The same study reported increased risk of having or achieving mastocytosis and anaphylaxis in the CSU group. However, the adjusted HR decreased when the diagnosis of these diseases within the first year were excluded, supporting a possible misdiagnosis before patients were referred to specialized centres (51). Drug allergy has also been identified to co-occur with CU with a likelihood of 4.68 times higher than in patients without CU (73).

Inflammatory diseases were the most prevalent comorbidities identified in a population-based study in

Taiwan, with peptic ulcer (4.83%), hepatitis B or C (1.64%) and periodontitis (2.82%) presenting more frequently. In patients with persist CU, an increasing prevalence of inflammatory diseases was observed, indicating a possible link between inflammation and endurance of CU (125).

Back pain, acute upper respiratory infections, non-inflammatory disorders of the vagina, spondylosis, and gastritis were among other rare disorders detected by using the anonymized research database of the Institute for Applied Health Research in Berlin, including insured individuals with a diagnosis of CU (9).

Additionally, a systematic review assessing the relationship between CSU and Vitamin D levels revealed that Vitamin D levels in 12 out of 14 included studies were significantly lower in CSU patients compared to controls (34.3%–89.7% of CSU patients and 0%–68.9% in controls). No causal relationship was identified, although supplementation of vitamin D for 1–3 months might have a beneficial effect in CU course (126). In accordance, a systematic review assessing comorbidities in children with CU found low vitamin D levels in 69.1% of the children (66); however data from other studies are not confirmatory (64).

Conclusion

CU presents with a wide range of associated comorbidities. Autoimmune, psychiatric, and atopic diseases are the most frequently reported associated diseases among CSU patients. Although the link between specific comorbidities and CU is solid, the potential interplay, regarding the nature of co-occurrence, is a recently explored era. The existing data cannot provide evidence in order to elucidate whether those diseases circling CU coexist independently with it or if a causal relationship, deriving from shared pathogenetic mechanisms, exists. Besides, if this is the case, a further unanswered question would be whether therapeutic interventions regarding comorbidities could interfere with CU's clinical course and vice versa. Therefore, prospective well-designed studies addressing the impact of various comorbidities on CU course and severity, as well as the impact of therapeutic interventions of comorbidities in both CU activity and natural course, are of urgent need. As we are marching into the era of personalized medicine, patients with CU should be recognized as a multimorbid group, and management should involve recognizing and treating any comorbid disorders in addition to urticaria management.

Author contributions

All authors contributed equally to the manuscript preparation. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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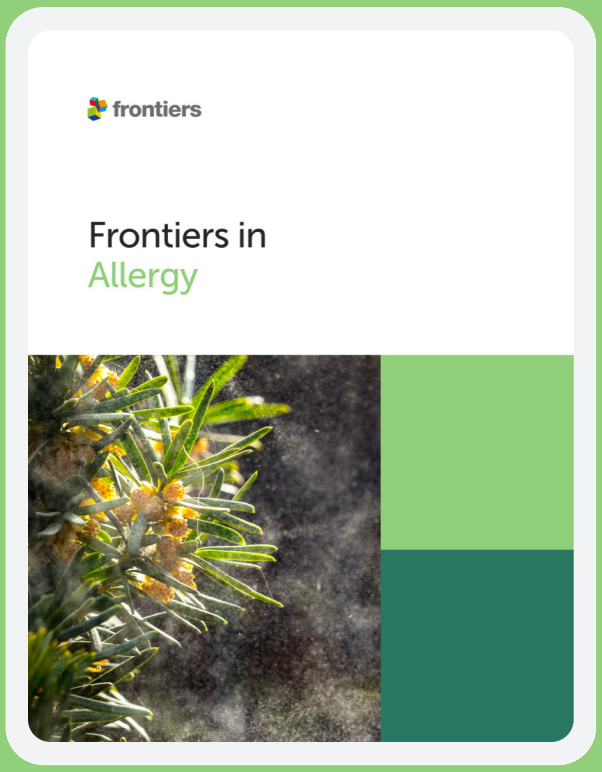

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